# Heterocyclic sulfones. Part IV.[1–3] A novel synthesis of pyrrole and fused heterocyclic sulfones

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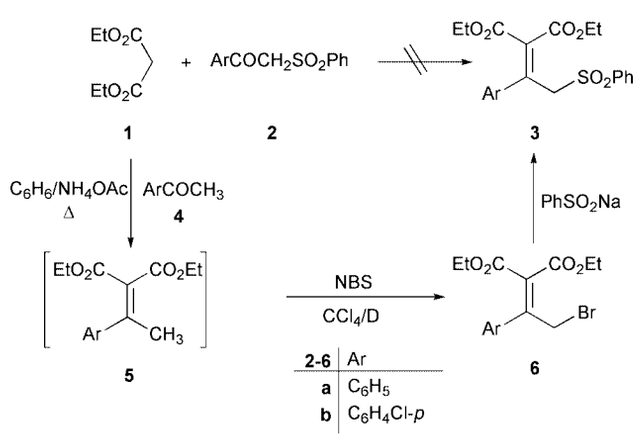
The applicability and synthetic potency of the novel reagents diethyl 2-aryl-3-(phenylsulfonyl)propene-1,1-dicarboxylate **3** are reported. Compounds **3** are shown to be key precursors in heterocyclic sulfones syntheses. Chemical and spectroscopic evidence for the structure of the newly synthesized compounds are described.

## Introduction

In view of the diverse biological and physiological activities of sulfones,[1–7] and in connection with our previous efforts directed towards the simple synthesis of heterocyclic ring systems,[8–13] we designed a specific simple programme aimed at the development of convenient synthetic approaches to heterocyclic sulfone systems of expected potential bioresponses, utilizing the novel reagents **3** as unique key precursors. The newly synthesised sulfone derivatives appear to be promising for further chemical transformations as well as biological activity evaluations.

## Results and discussion

Our attempts to prepare the key precursors diethyl 2-aryl-3-(phenylsulfonyl)propene-1,1-dicarboxylates **3** *via* condensation of equimolar amounts of diethyl malonate **1** with the appropriate arylsulfonylacetophenone **2** utilizing a variety of acidic or alkaline conditions failed. In our hands, the precursor **3** could be prepared stepwise. Thus, diethyl 2-aryl-3-bromopropene-1,1-dicarboxylates[3] **6** reacted with equimolar amounts of sodium benzenesulfinate in ethanolic solution to furnish the target reagents **3** (Scheme 1).




**Scheme 1**

Compounds **3** proved to be highly reactive towards various reagents and underwent numerous chemical transformations, resulting in the construction of a wide range of heterocyclic sulfone systems. Thus, compounds **3** could be brominated when equimolar amounts of **3a**,**b** and bromine in dry benzene were boiled under reflux to afford the corresponding diethyl 2-aryl-3-bromo-3-(phenylsulfonyl)propene-1,1-dicarboxylates **7**. Treatment of **7** with the appropriate primary aromatic amine in ethanolic triethylamine solutions afforded the corresponding ethyl 1,4-diaryl-2-hydroxy-5-(phenylsulfonyl)pyrrole-3-carboxylates **8**. The latter reaction yields the corresponding ethyl 2-aryl-5-oxo-1-(phenylsulfonyl)-5*H*-benzo[*d*]pyrrolo[2,1-*b*]-[1,3]oxazine-3-carboxylate **11**, in one pot, if anthranilonitrile **9** is used. Similarly, the pyrrolo[2,1-*b*]thieno[2,3-*d*][1,3]oxazines **13** are obtained on treatment of **7a** with the appropriate ethyl 2-aminothiophene-3-carboxylate **12** (Scheme 2).

Compound **3a** reacted with an arylidenemalononitrile **14** to yield the corresponding ethyl 4-aryl-3-cyano-2-hydroxy-6-phenyl-5-(phenylsulfonyl)benzoate **16**. Compounds **16** are assumed to be formed *via* addition of **3** to the activated double bond in **14** to yield the Michael adducts **15** which intramolecularly cyclised and aromatised *via* loss of HCN to give the final isolable ethyl benzoate derivatives **16**. Compound **16a** could be prepared *via* an independent route involving the condensation of **3a** with benzaldehyde and subsequent addition of malononitrile to the so-formed benzylidene derivative **17** (Scheme 3).

Compound **3a** readily coupled with equimolar amounts of arenediazonium chlorides to yield the hydrazone corresponding compound **18**. Furthermore, on boiling of the hydrazone **18** in ethanolic sodium acetate solution, the corresponding pyridazine **19** could be obtained.

Ethyl 1-benzoyl-4-phenyl-5-(phenylsulfonyl)pyridine-3-carboxylate derivative **20** was obtained in good yield from the reaction of **3a** with benzoyl isothiocyanate in boiling dry 1,4-dioxane. Compound **20** reacted further with either chloroacetonitrile or ethyl chloroacetate in the presence of $K_2CO_3$ to yield the corresponding ethyl thiazolo[3,2-*a*]pyridine-6-carboxylate derivatives **21**.

Compound **3** reacted with equimolar amounts of trichloroacetonitrile in ethanolic NaOAc solutions to produce exclusively the corresponding ethyl 4-aryl-6-(trichloromethyl)-pyridine-3-carboxylate derivatives compounds **22**. The trichloromethyl group in compounds **22** proved to be highly reactive towards nucleophilic reagents. Thus, compound **22** reacted readily with equimolar amounts of hydrazine hydrate

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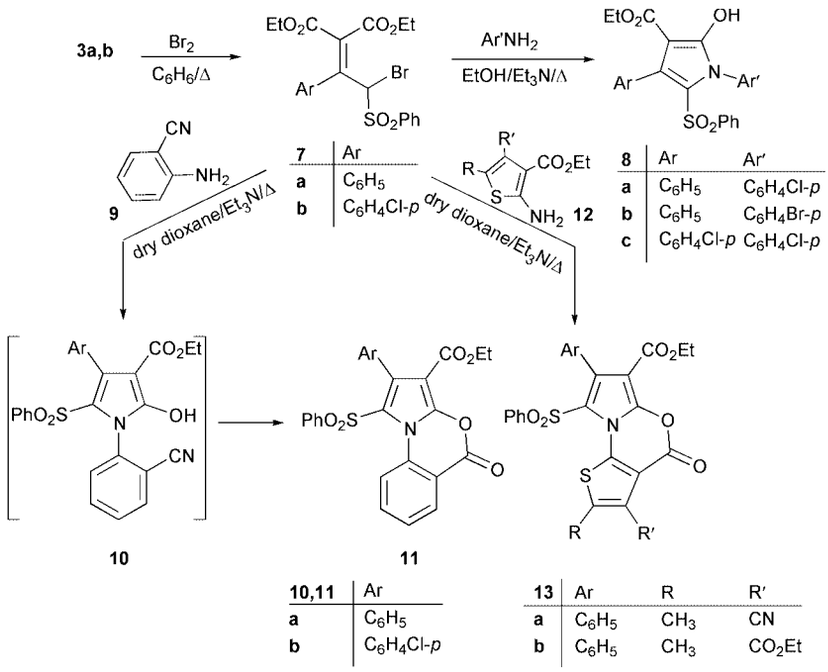


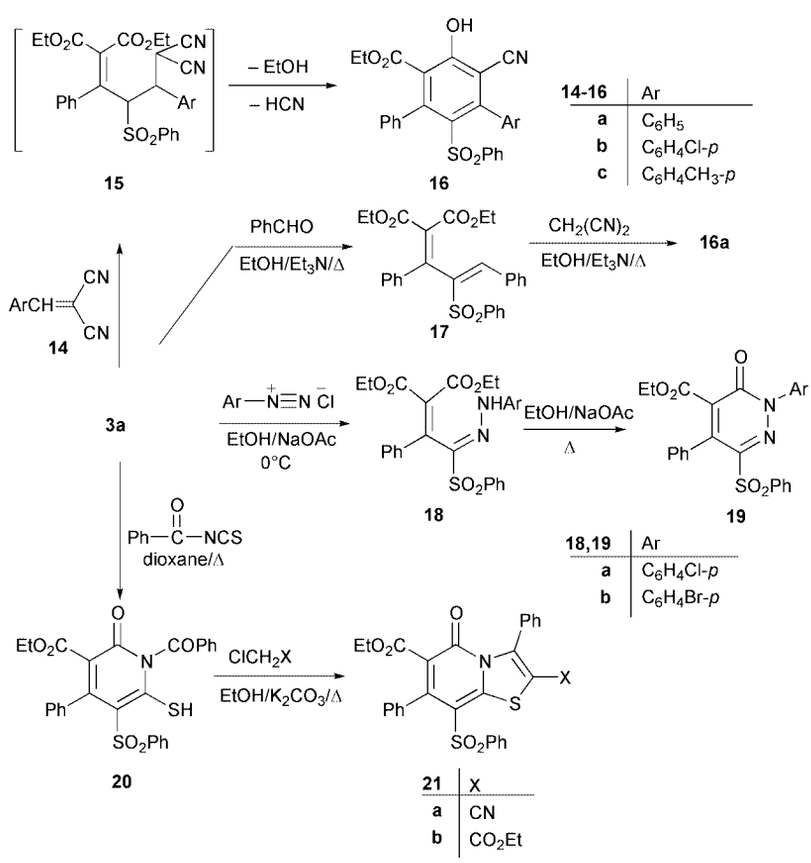
| 7 | Ar |
|---|---|
| a | $C_6H_5$ |
| b | $C_6H_4Cl$-*p* |

| 8 | Ar | Ar′ |
|---|---|---|
| a | $C_6H_5$ | $C_6H_4Cl$-*p* |
| b | $C_6H_5$ | $C_6H_4Br$-*p* |
| c | $C_6H_4Cl$-*p* | $C_6H_4Cl$-*p* |

| 10,11 | Ar |
|---|---|
| a | $C_6H_5$ |
| b | $C_6H_4Cl$-*p* |

| 13 | Ar | R | R′ |
|---|---|---|---|
| a | $C_6H_5$ | $CH_3$ | CN |
| b | $C_6H_5$ | $CH_3$ | $CO_2Et$ |

**Scheme 2**



| 14-16 | Ar |
|---|---|
| a | $C_6H_5$ |
| b | $C_6H_4Cl$-*p* |
| c | $C_6H_4CH_3$-*p* |

| 18,19 | Ar |
|---|---|
| a | $C_6H_4Cl$-*p* |
| b | $C_6H_4Br$-*p* |

| 21 | X |
|---|---|
| a | CN |
| b | $CO_2Et$ |

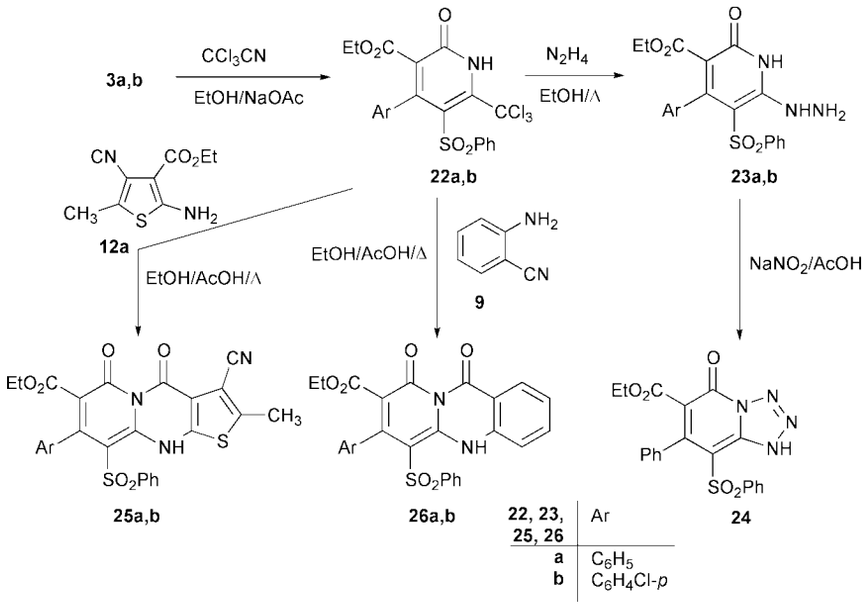
**Scheme 3**

in ethanol under reflux to give the corresponding ethyl 6-hydrazinopyridine-3-carboxylate derivatives **23**. Compound **23a** could be successfully cyclised into the corresponding ethyl 1,5-dihydro-5-oxo-7-phenyl-8-(phenylsulfonyl)tetrazolo[1,5-*a*]-pyridine-6-carboxylate **24** upon treatment with an equimolar proportion of $NaNO_2$ in glacial acetic acid (Scheme 4).

Treatment of compounds **22** with ethyl 2-amino-4-cyano-5-methylthiophene-3-carboxylate[14] **12a** in absolute ethanol solution containing glacial acetic acid under reflux furnished the corresponding ethyl 8-aryl-4,6-dioxo-9-(phenylsulfonyl)-10*H*-pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidine-7-carboxylates **25**. Similarly, ethyl pyrido[2,1-*b*]quinazoline-8-carboxylates **26** could be obtained upon treatment of **22** with anthranilonitrile **9**.

## Experimental

All mps were measured on a Büchi apparatus and are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer and are reported in wavenumbers ($cm^{-1}$). $^1H$ NMR spectra were obtained on a Varian Gemini




**Scheme 4**

200 MHz spectrometer (int. standard: TMS). Chemical shifts are expressed as $\delta$ (ppm). Mass spectra were recorded on a GCMS-QP 1000 EX mass spectrometer operating at 70 eV. Microanalytical Data were performed by the Microanalytical Unit, Cairo University. Compounds **6a**,**b** have been prepared according to our previously reported methodology.[3,13] Solid products were dried in a vacuum oven at 60 °C before crystallisation.

### Synthesis of diethyl 2-aryl-3-(phenylsulfonyl)propene-1,1-dicarboxylates 3a,b (general procedure)

To a solution of **6a**,**b** (0.02 mol) in ethanol (50 ml) was added sodium benzenesulfinate (3.04 g, 0.02 mol). The reaction mixture was refluxed for 3 h and the solvent was triturated with cold water (20 ml), whereby the solid product was collected by filtration, washed thoroughly with water, dried, and crystallised from an appropriate solvent.

**Diethyl 2-phenyl-3-(phenylsulfonyl)propene-1,1-dicarboxylate 3a.** Yield 5.2 g (65%), mp 110–111 °C (from ethanol) (Found: C, 62.5; H, 5.4; S, 7.9. $C_{21}H_{22}O_6S$ requires C, 62.67; H, 5.51; S, 7.96%); $\nu_{max}$ 3000–2950 ($CH_2$), 1715, 1700 (2 CO); $\delta_H$ (DMSO-$d_6$) 1.08–1.30 (6H, m, 2 × $CH_3$), 3.80–4.28 (4H, m, 2 × $CH_2$), 4.66 (2H, s, $CH_2$), 6.90–7.85 (10H, m, ArH); *m*/*z* 324 (100%), 402 ($M^+$, 18%).

**Diethyl 2-(*p*-chlorophenyl)-3-(phenylsulfonyl)propene-1,1-dicarboxylate 3b.** Yield 5.9 g (68%), mp 117–118 °C (from ethanol) (Found: C, 57.8; H, 4.7; Cl, 8.0; S, 7.5. $C_{21}H_{21}ClO_6S$ requires C, 57.73; H, 4.84; Cl, 8.11; S, 7.33%); $\nu_{max}$ 3000–2960 ($CH_2$), 1712, 1700 (2 CO); $\delta_H$ (DMSO-$d_6$) 1.05–1.25 (6H, m, 2 × $CH_3$), 3.70–4.22 (4H, m, 2 × $CH_2$), 4.65 (2H, s, $CH_2$), 6.95–7.74 (9H, m, ArH).

### Synthesis of diethyl 2-aryl-3-bromo-3-(phenylsulfonyl)propene-1,1-dicarboxylates 7a,b (general procedure)

To a solution of **3a**,**b** (0.02 mol) in dry benzene (50 ml), was added dropwise bromine (3.20 g, 0.02 mol). The reaction mixture was refluxed for 3 h and the solvent was then evaporated *in vacuo*. The residue was triturated with ethanol, whereby the solid product was collected by filtration, dried, and crystallised from an appropriate solvent.

**Diethyl 3-bromo-2-phenyl-3-(phenylsulfonyl)propene-1,1-dicarboxylate 7a.** Yield 5.6 g (59%), mp 146–147 °C (from ethanol) (Found: C, 52.3; H, 4.2; Br, 16.5; S, 6.4. $C_{21}H_{21}BrO_6S$ requires C, 52.39; H, 4.40; Br, 16.60; S, 6.66%); $\nu_{max}$ 1718, 1705 (2 CO); $\delta_H$ (DMSO-$d_6$) 1.05–1.33 (6H, m, 2 × $CH_3$), 3.85–4.45 (4H, m, 2 × $CH_2$), 5.61 (1H, s, CH), 6.95–7.90 (10H, m, ArH).

**Diethyl 3-bromo-2-(*p*-chlorophenyl)-3-(phenylsulfonyl)propene-1,1-dicarboxylate 7b.** Yield 6.2 g (60%), mp 151–153 °C (from ethanol) (Found: C, 48.8; H, 3.9; Br, 15.4; Cl, 6.7; S, 6.2. $C_{21}H_{20}BrClO_6S$ requires C, 48.90; H, 3.91; Br, 15.49; Cl, 6.87; S, 6.22%); $\nu_{max}$ 1715, 1705 (2 CO); $\delta_H$ (DMSO-$d_6$) 0.95–1.30 (6H, m, 2 × $CH_3$), 3.90–4.32 (4H, m, 2 × $CH_2$), 5.59 (1H, s, CH), 6.85–7.90 (9H, m, ArH).

### Synthesis of ethyl 1,4-diaryl-2-hydroxy-5-(phenylsulfonyl)-pyrrole-3-carboxylates 8a–c (general procedure)

To a warm solution of bromide **7** (0.003 mol) in absolute ethanol (25 ml) containing anhydrous $Et_3N$ (0.5 ml) was added the appropriate primary aromatic amine (0.003 mol). The reaction mixture was refluxed for 2 h, poured onto cold water, then neutralised with dil. HCl. The solid product was collected by filtration, washed with water, dried and crystallised from an appropriate solvent.

**Ethyl 1-(*p*-chlorophenyl)-2-hydroxy-4-phenyl-5-(phenylsulfonyl)pyrrole-3-carboxylate 8a.** Yield 0.79 g (55%), mp 160–161 °C (from ethanol) (Found: C, 62.3; H, 4.0; Cl, 7.3; N, 2.7; S, 6.5. $C_{25}H_{20}ClNO_5S$ requires C, 62.30; H, 4.18; Cl, 7.35; N, 2.91; S, 6.65%); $\nu_{max}$ 3500–3330 (OH), 1690 (CO); $\delta_H$ (DMSO-$d_6$) 1.22 (3H, t, *J* 8.2 Hz, $CH_3$), 4.13 (2H, q, *J* 8.2 Hz, $CH_2$), 6.90–7.83 (14H, m, ArH), 13.15 (1H, s, OH, exchangeable); *m*/*z* 324 (100%), 481 ($M^+$, 22%).

**Ethyl 1-(*p*-bromophenyl)-2-hydroxy-4-phenyl-5-(phenylsulfonyl)pyrrole-3-carboxylate 8b.** Yield 0.82 g (52%), mp 171–172 °C (from ethanol) (Found: C, 56.9; H, 3.8; Br, 15.1; N, 2.4; S, 6.0. $C_{25}H_{20}BrNO_5S$ requires C, 57.04; H, 3.83, Br, 15.18; N, 2.66; S, 6.09%); $\nu_{max}$ 3495–3335 (OH), 1690 (CO); $\delta_H$ (DMSO-$d_6$) 1.25 (3H, t, *J* 8.2 Hz, $CH_3$), 4.18 (2H, q, *J* 8.2 Hz, $CH_2$), 6.81–7.79 (14H, m, ArH), 13.19 (1H, s, OH, exchangeable).

**Ethyl 1,4-bis(*p*-chlorophenyl)-2-hydroxy-5-(phenylsulfonyl)-pyrrole-3-carboxylate 8c.** Yield 0.86 g (56%), mp 176–177 °C (from ethanol) (Found: C, 58.1; H, 3.6; Cl, 13.7; N, 2.6; S, 6.0. $C_{25}H_{19}Cl_2NO_5S$ requires C, 58.14; H, 3.71; Cl, 13.73; N, 2.71; S, 6.21%); $\nu_{max}$ 3500–3325 (OH), 1690 (CO); $\delta_H$ (DMSO-$d_6$) 1.28

(3H, t, *J* 8.2 Hz, $CH_3$), 4.51 (2H, q, *J* 8.2 Hz, $CH_2$), 6.95–7.80 (13H, m, ArH), 13.10 (1H, s, OH, exchangeable).

### Synthesis of ethyl 2-aryl-5-oxo-1-(phenylsulfonyl)benzo[*d*]-pyrrolo[2,1-*b*][1,3]oxazine-3-carboxylates 11a,b (general procedure)

A mixture of bromide **7** (0.003 mol) and anthranilonitrile **9** (0.35 g, 0.003 mol) in dry 1,4-dioxane (30 ml) containing anhydrous $Et_3N$ (1.0 ml) was refluxed for 3 h. The reaction mixture was left aside at room temperature overnight, poured onto an ice–water mixture, and neutralised with dil. HCl. The solid product was filtered off, washed with water, dried, and crystallised from an appropriate solvent.

**Ethyl 5-oxo-2-phenyl-1-(phenylsulfonyl)-5*H*-benzo[*d*]pyrrolo-[2,1-*b*][1,3]oxazine-3-carboxylate 11a.** Yield 0.64 g (45%), mp 182–183 °C (from 1,4-dioxane) (Found: C, 65.9; H, 3.8; N, 2.9; S, 6.6. $C_{26}H_{19}NO_6S$ requires C, 65.95; H, 4.04; N, 2.95; S, 6.77%); $\nu_{max}$ 1715, 1708 (2 CO); $\delta_H$ (DMSO-$d_6$) 1.24 (3H, t, *J* 8.2 Hz, $CH_3$), 4.55 (2H, q, *J* 8.2 Hz, $CH_2$), 6.88–7.92 (14H, m, ArH); *m*/*z* 312 ($M^+$, 16%).

**Ethyl 2-(*p*-chlorophenyl)-5-oxo-1-(phenylsulfonyl)-5*H*-benzo-[*d*]pyrrolo[2,1-*b*][1,3]oxazine-3-carboxylate 11b.** Yield 0.77 g (51%), mp 189–190 °C (from 1,4-dioxane) (Found: C, 61.4; H, 3.4; Cl, 6.9; N, 2.5; S, 6.2. $C_{26}H_{18}ClNO_6S$ requires C, 61.48; H, 3.57; Cl, 6.98; N, 2.75; S, 6.31%); $\nu_{max}$ 1718, 1710 (2 CO); $\delta_H$ (DMSO-$d_6$) 1.28 (3H, t, *J* 8.2 Hz, $CH_3$), 4.28 (2H, q, *J* 8.3 Hz, $CH_2$), 6.90–7.82 (13H, m, ArH).

### Synthesis of ethyl 7-aryl-4-oxo-8-(phenylsulfonyl)-4*H*-pyrrolo-[2,1-*b*]thieno[2,3-*d*][1,3]oxazine-6-carboxylates 13a,b (general procedure)

A mixture of **7a** (1.44 g, 0.003 mol) and the appropriate ethyl 2-aminothiophene-3-carboxylate **12**[14] (0.003 mol) in dry 1,4-dioxane (30 ml) containing $Et_3N$ (1.0 ml) was refluxed for 3 h. The reaction mixture was poured onto cold water and neutralised with dil. HCl. The resulting precipitate was collected by filtration, dried and crystallised from an appropriate solvent.

**Ethyl 3-cyano-2-methyl-4-oxo-7-phenyl-8-(phenylsulfonyl)-4*H*-pyrrolo[2,1-*b*]thieno[2,3-*d*][1,3]oxazine-6-carboxylate 13a.** Yield 0.65 g (42%), mp 220–222 °C (from 1,4-dioxane) (Found: C, 60.1; H, 3.4; N, 5.4; S, 12.2. $C_{26}H_{18}N_2O_6S_2$ requires C, 60.22; H, 3.49; N, 5.40; S, 12.36%); $\nu_{max}$ 2218 (CN), 1720, 1712 (2 CO); $\delta_H$ (DMSO-$d_6$) 1.15 (3H, s, $CH_3$), 1.22 (3H, t, *J* 8.2 Hz, $CH_3$), 4.15 (2H, q, *J* 8.2 Hz, $CH_2$), 6.85–7.96 (10H, m, ArH); *m*/*z* 473 (100%), 518 ($M^+$, 14%).

**Diethyl 2-methyl-4-oxo-7-phenyl-8-(phenylsulfonyl)-4*H*-pyrrolo[2,1-*b*]thieno[2,3-*d*][1,3]oxazine-3,6-dicarboxylate 13b.** Yield 0.66 g (39%), mp 192–193 °C (from 1,4-dioxane) (Found: C, 59.4; H, 3.8; N, 2.4; S, 11.2. $C_{28}H_{23}NO_8S_2$ requires C, 59.45; H, 4.09; N, 2.47; S, 11.33%); $\nu_{max}$ 1722, 1718, 1710 (3 CO); $\delta_H$ (DMSO-$d_6$) 1.15 (3H, s, $CH_3$), 1.05–1.29 (6H, m, 2 × $CH_3$), 3.85–4.28 (4H, m, 2 × $CH_2$), 6.91–7.88 (10 H, m, ArH).

### Synthesis of ethyl 4-aryl-3-cyano-2-hydroxy-6-phenyl-5-(phenylsulfonyl)benzoates 16a–c (general procedure)

**Method A.** A mixture of **3a** (0.80 g, 0.002 mol) and the appropriate arylidenemalononitrile **14** (0.002 mol) in ethanol (25 ml) containing $Et_3N$ (0.5 ml) was heated under reflux for 3 h. The reaction mixture was evaporated *in vacuo*, and the residue was triturated with cold water and neutralised with dil. HCl. The solid product was collected by filtration, dried and crystallised from an appropriate solvent.

**Ethyl 3-cyano-2-hydroxy-4,6-diphenyl-5-(phenylsulfonyl)-benzoate 16a.** Yield 0.66 g (69%), mp 220–222 °C (from ethanol) (Found: C, 69.5; H, 4.3; N, 2.8; S, 6.5. $C_{28}H_{21}NO_5S$ requires C, 69.55; H, 4.37; N, 2.89; S, 6.63%); $\nu_{max}$ 3615 (OH), 2216 (CN), 1710 (CO); $\delta_H$ (DMSO-$d_6$) 0.96 (3H, t, *J* 8.3 Hz, $CH_3$), 4.10 (2H, q, *J* 8.3, $CH_2$), 5.96 (1H, s, OH, exchangeable), 6.82–7.91 (15H, m, ArH); *m*/*z* 296 (100%), 483 ($M^+$, 15%).

**Ethyl 4-(*p*-chlorophenyl)-3-cyano-2-hydroxy-6-phenyl-5-(phenylsulfonyl)benzoate 16b.** Yield 0.68 g (66%), mp 229–230 °C (from 1,4-dioxane) (Found: C, 64.9; H, 3.8; Cl, 6.7; N, 2.6; S, 6.0. $C_{28}H_{20}ClNO_5S$ requires C, 64.92; H, 3.89; Cl, 6.84; N, 2.70; S, 6.19%); $\nu_{max}$ 3620 (OH), 2218 (CN), 1710 (CO); $\delta_H$ (DMSO-$d_6$) 0.92 (3H, t, *J* 8.2 Hz, $CH_3$), 4.23 (2H, q, *J* 8.2 Hz, $CH_2$), 5.94 (1H, s, OH, exchangeable), 6.90–7.83 (14H, m, Ar–H).

**Ethyl 3-cyano-2-hydroxy-6-phenyl-5-(phenylsulfonyl)-4-(*p*-tolyl)benzoate 16c.** Yield 0.60 g (60%), mp 206–207 °C (from 1,4-dioxane) (Found: C, 69.9; H, 4.6; N, 2.7; S, 6.4. $C_{29}H_{23}NO_5S$ requires C, 70.00; H, 4.65; N, 2.81; S, 6.44%); $\nu_{max}$ 3615 (OH), 3025 ($CH_3$), 2218 (CN), 1710 (CO); $\delta_H$ (DMSO-$d_6$) 0.95 (3H, t, *J* 8.0 Hz, $CH_3$), 2.21 (3H, s, $CH_3$), 4.28 (2H, q, *J* 8.2 Hz, $CH_2$), 5.96 (1H, s, OH exchangeable), 6.93–7.91 (14H, m, Ar–H).

**Method B.** A mixture of compound **17** (see below) (0.98 g, 0.002 mol) and malononitrile (0.13 g, 0.002 mol) in ethanol (25 ml) containing $Et_3N$ (0.5 ml) was refluxed for 3 h. The reaction mixture was poured onto cold water and neutralised with dil. HCl. The solid product was collected by filtration, dried, crystallised from ethanol, and found to be identical in all aspects (mp, mixed-mp, and IR spectrum) with an authentic sample of **16a** prepared according to method A.

### Synthesis of diethyl 2,4-diphenyl-3-(phenylsulfonyl)buta-1,3-diene-1,1-dicarboxylate 17

A mixture of **3a** (1.20 g, 0.003 mol) and benzaldehyde (0.32 g, 0.003 mol) in absolute ethanol (30 ml) containing $Et_3N$ (0.5 ml) was refluxed for 3 h. The reaction mixture was left to cool to room temperature, poured onto cold water, and neutralised with dil. HCl. The solid product was filtered off, dried, and crystallised from ethanol (1.0 g, 69%), mp 173–175 °C (from ethanol) (Found: C, 68.5; H, 5.2; S, 6.4. $C_{28}H_{26}O_6S$ requires C, 68.55; H, 5.34; S, 6.53%); $\nu_{max}$ 1715, 1700 (2 CO), 1650 (C=C); $\delta_H$ (DMSO-$d_6$) 0.95–1.35 (6H, m, 2 × $CH_3$), 3.92–4.25 (4H, m, 2 × $CH_2$), 6.75–7.83 (16H, m, Ar–H + olefinic CH).

### Synthesis of diethyl 3-arylhydrazono-2-phenyl-3-(phenylsulfonyl)-propene-1,1-dicarboxylates 18a,b (general procedure)

To a stirred solution of **3a** (1.20 g, 0.003 mol) in ethanol (50 ml) containing NaOAc (2.0 g) was added the appropriate arene-diazonium chloride (0.003 mol) [prepared by adding $NaNO_2$ (0.20 g, 0.003 mol) to the appropriate primary aromatic amine (0.003 mol) in stirred conc. HCl (2 ml) at 0–5 °C] while the mixture was cooled to 0–5 °C and stirred. The reaction mixture was left aside at room temperature for 3 h, whereby the solid product was collected by filtration, dried, and crystallised from an appropriate solvent.

**Diethyl 3-(*p*-chlorophenylhydrazono)-2-phenyl-3-(phenylsulfonyl)propene-1,1-dicarboxylate 18a.** Yield 1.0 g (65%), mp 165–166 °C (from ethanol) (Found: C, 59.9; H, 4.5; Cl, 6.4; N, 5.0; S, 5.8. $C_{27}H_{25}ClN_2O_6S$ requires C, 59.94; H, 4.65; Cl, 6.55; N, 5.17; S, 5.92%); $\nu_{max}$ 3350–3320 (NH), 1718, 1700 (2 CO); $\delta_H$ (DMSO-$d_6$) 0.96–1.25 (6H, m, 2 × $CH_3$), 3.95–4.05 (4H, m, 2 × $CH_2$), 6.73–7.56 (14H, m, Ar–H), 11.28 (1H, br s, NH, exchangeable); *m*/*z* 494 (100%), 541 ($M^+$, 18%).

**Diethyl 3-(*p*-bromophenylhydrazono)-2-phenyl-3-(phenylsulfonyl)propene-1,1-dicarboxylate 18b.** Yield 1.07 g (61%), mp 171–172 °C (from 1,4-dioxane) (Found: C, 55.2; H, 4.3; Br, 13.5; N, 4.6; S, 5.4. $C_{27}H_{25}BrN_2O_6S$ requires C, 55.39; H, 4.30; Br, 13.65; N, 4.78; S, 5.47%); $\nu_{max}$ 3350–3318 (NH), 1715, 1705 (2 CO); $\delta_H$ (DMSO-$d_6$) 1.02–1.28 (6H, m, 2 × $CH_3$), 3.95–4.12 (4H, m, 2 × $CH_2$), 6.81–7.63 (14H, m, Ar–H), 11.54 (1H, br s, NH, exchangeable).

### Synthesis of ethyl 2-aryl-2,3-dihydro-3-oxo-5-phenyl-6-(phenylsulfonyl)pyridazine-4-carboxylates 19a,b (general procedure)

A solution of a hydrazone **18** (0.002 mol) in ethanol (30 ml) containing NaOAc (1.0 g) was refluxed for 3 h. The reaction mixture was poured onto cold water and neutralised with dil. HCl. The formed precipitate was filtered off, dried, and crystallised from an appropriate solvent.

**Ethyl 2-(*p*-chlorophenyl)-2,3-dihydro-3-oxo-5-phenyl-6-(phenylsulfonyl)pyridazine-4-carboxylate 19a.** Yield 0.54 g (55%), mp 195–196 °C (from AcOH) (Found: C, 60.5; H, 3.8; Cl, 7.0; N, 5.5; S, 6.4. $C_{25}H_{19}ClN_2O_5S$ requires C, 60.66; H, 3.86; Cl, 7.16; N, 5.66; S, 6.47%); $\nu_{max}$ 1718, 1695 (2 CO); $\delta_H$ (DMSO-$d_6$) 1.21 (3H, t, *J* 8.2 Hz, $CH_3$), 4.25 (2H, q, *J* 8.2 Hz, $CH_2$), 6.91–7.43 (14H, m, ArH); *m*/*z* 494 ($M^+$, 14%).

**Ethyl 2-(*p*-bromophenyl)-2,3-dihydro-3-oxo-5-phenyl-6-(phenylsulfonyl)pyridazine-4-carboxylate 19b.** Yield 0.62 g (58%), mp 206–208 °C (from AcOH) (Found: C, 55.6; H, 3.4; Br, 14.7; N, 5.0; S, 5.9. $C_{25}H_{19}BrN_2O_5S$ requires C, 55.66; H, 3.55; Br, 14.81; N, 5.19; S, 5.94%); $\nu_{max}$ 1715, 1700 (2 CO); $\delta_H$ (DMSO-$d_6$) 1.05 (3H, t, *J* 8.2 Hz, $CH_3$), 4.09 (2H, q, *J* 8.2 Hz, $CH_2$), 6.85–7.40 (14H, m, ArH).

### Synthesis of ethyl 1-benzoyl-1,2-dihydro-6-mercapto-2-oxo-4-phenyl-5-(phenylsulfonyl)pyridine-3-carboxylate 20

To a suspension of $NH_4SCN$ (0.38 g, 0.005 mol) in 1,4-dioxane (50 ml) was added benzoyl chloride (0.70 g, 0.005 mol). The reaction mixture was refluxed for 2 min, then treated with **3a** (2.0 g, 0.005 mol). The reaction mixture was refluxed for 2 h and poured onto ice–water, whereby the solid product was filtered off, and crystallised from 1,4-dioxane (1.90 g, 66%), mp 210–212 °C (Found: C, 56.4; H, 3.6; N, 13.8; S, 11.0. $C_{27}H_{21}NO_6S_2$ requires C, 56.54; H, 3.69; N, 13.93; S, 11.18%); $\nu_{max}$ 2250 (SH), 1718, 1705, 1684 (3 × CO); $\delta_H$ (DMSO-$d_6$) 1.20 (3H, t, *J* 8.2 Hz, $CH_3$), 3.24 (1H, s, SH, exchangeable), 4.25 (2H, q, *J* 8.2 Hz, $CH_2$), 6.90–7.68 (15H, m, ArH); *m*/*z* 422 (100%), 573 ($M^+$, 12%).

### Synthesis of ethyl 5-oxo-8-(phenylsulfonyl)-5*H*-thiazolo[3,2-*a*]-pyridine-6-carboxylates 21a,b (general procedure)

To a suspension of thiol **20** (1.15 g, 0.002 mol) in ethanol (30 ml) were added aq. $K_2CO_3$ (0.55 g, 0.004 mol in 20 ml of water) and the appropriate α-chloro compound (0.002 mol). The reaction mixture was refluxed for 2 h, left to cool to room temperature, and poured onto cold water. The solid product was filtered off, and crystallised from an appropriate solvent.

**Ethyl 2-cyano-5-oxo-3,7-diphenyl-8-(phenylsulfonyl)-5*H*-thiazolo[3,2-*a*]pyridine-6-carboxylate 21a.** Yield 0.67 g (62%), mp > 250 °C (from 1,4-dioxane) (Found: C, 64.3; H, 3.7; N, 5.0; S, 11.8. $C_{29}H_{20}N_2O_5S_2$ requires C, 64.43; H, 3.72; N, 5.18; S, 11.86%); $\nu_{max}$ 2218 (CN), 1715, 1700 (2 CO); $\delta_H$ (DMSO-$d_6$) 1.15 (3H, t, *J* 8.2 Hz, $CH_3$), 4.12 (2H, q, *J* 8.2 Hz, $CH_2$), 6.93–7.55 (15H, m, ArH); *m*/*z* 495 (100%), 540 ($M^+$, 16%).

**Diethyl 5-oxo-3,7-diphenyl-8-(phenylsulfonyl)thiazolo[3,2-*a*]-pyridine-2,6-dicarboxylate 21b.** Yield 0.65 g (56%), mp 212–213 °C (from 1,4-dioxane) (Found: C, 63.2; H, 4.2; N, 2.2; S, 10.9. $C_{31}H_{25}NO_7S_2$ requires C, 63.35; H, 4.28; N, 2.38; S, 10.91%); $\nu_{max}$ 1718, 1705, 1692 (3 × CO); $\delta_H$ (DMSO-$d_6$) 0.95–1.32 (6H, m, 2 × $CH_3$), 3.83–4.22 (4H, m, 2 × $CH_2$), 6.85–7.64 (15H, m, ArH).

### Synthesis of ethyl 4-aryl-1,2-dihydro-2-oxo-5-(phenylsulfonyl)-6-(trichloromethyl)pyridine-3-carboxylates 22a,b (general procedure)

To a solution of **3a**,**b** (0.005 mol) in ethanol (30 ml) containing NaOAc (0.5 g) was added trichloroacetonitrile (0.72 g, 0.005 mol). The reaction mixture was heated under reflux for 2 h and left aside at room temperature overnight. The mixture was poured onto an ice–water mixture, neutralised with dil. HCl, and the precipitate was filtered off, washed with water, dried, and crystallised from an appropriate solvent.

**Ethyl 1,2-dihydro-2-oxo-4-phenyl-5-(phenylsulfonyl)-6-(trichloromethyl)pyridine-3-carboxylate 22a.** Yield 1.53 g (61%), mp 135–136 °C (from ethanol) (Found: C, 50.2; H, 3.0; Cl, 21.2; N, 2.7; S, 6.2. $C_{21}H_{16}Cl_3NO_5S$ requires C, 50.36; H, 3.22; Cl, 21.23; N, 2.79; S, 6.40%); $\nu_{max}$ 3370 (NH), 1715, 1700 (2 CO); $\delta_H$ (DMSO-$d_6$) 1.12 (3H, t, *J* 8.2 Hz, $CH_3$), 4.25 (2H, q, *J* 8.2 Hz, $CH_2$), 6.70–7.82 (10H, m, ArH), 9.98 (1H, br s, NH, exchangeable); *m*/*z* 336 (100%), 500 ($M^+$, 12%).

**Ethyl 4-(*p*-chlorophenyl)-1,2-dihydro-2-oxo-5-(phenylsulfonyl)-6-(trichloromethyl)pyridine-3-carboxylate 22b.** Yield 1.74 g (65%), mp 142–143 °C (from ethanol) (Found: C, 47.0; H, 2.8; Cl, 26.3; N, 2.6; S, 5.8. $C_{21}H_{15}Cl_4NO_5S$ requires C, 47.12; H, 2.82; Cl, 26.49; N, 2.61; S, 5.99%); $\nu_{max}$ 3362 (NH), 1720, 1704 (2 CO); $\delta_H$ (DMSO-$d_6$) 1.05 (3H, t, *J* 8.2 Hz, $CH_3$), 4.05 (2H, q, *J* 8.2 Hz, $CH_2$), 6.84–7.72 (9H, m, Ar–H), 10.52 (1H, br s, NH, exchangeable).

### Synthesis of ethyl 4-aryl-6-hydrazino-1,2-dihydro-2-oxo-5-(phenylsulfonyl)pyridine-3-carboxylates 23a,b (general procedure)

A mixture of **22a**,**b** (0.003 mol) and hydrazine hydrate (0.10 g, 0.003 mol) in ethanol (30 ml) was refluxed for 30 min, and then left at room temperature overnight. The mixture was poured onto cold water, whereupon the solid product was filtered off, and crystallised from an appropriate solvent.

**Ethyl 6-hydrazino-1,2-dihydro-2-oxo-4-phenyl-5-(phenylsulfonyl)pyridine-3-carboxylate 23a.** Yield 0.80 g (65%), mp 146–147 °C (from ethanol) (Found: C, 58.0; H, 4.6; N, 10.1; S, 7.7. $C_{20}H_{19}N_3O_5S$ requires C, 58.10; H, 4.63; N, 10.16; S, 7.75%); $\nu_{max}$ 3420–3380 ($NH_2$, NH), 1712, 1700 (2 CO); $\delta_H$ (DMSO-$d_6$) 1.10 (3H, t, *J* 8.2 Hz, $CH_3$), 3.25 (2H, br s, $NH_2$, exchangeable), 4.14 (2H, q, *J* 8.2 Hz, $CH_2$), 6.29 (1H, br s, NH, exchangeable), 6.89–7.48 (10H, m, ArH), 8.35 (1H, br s, NH, exchangeable).

**Ethyl 4-(*p*-chlorophenyl)-6-hydrazino-1,2-dihydro-2-oxo-5-(phenylsulfonyl)pyridine-3-carboxylate 23b.** Yield 0.83 g (62%), mp 158–159 °C (from ethanol) (Found: C, 53.5; H, 4.0; Cl, 7.8; N, 9.2; S, 7.1. $C_{20}H_{18}ClN_3O_5S$ requires C, 53.63; H, 4.05; Cl, 7.91; N, 9.38; S, 7.15%); $\nu_{max}$ 3428–3365 ($NH_2$, NH), 1715, 1708 (2 CO); $\delta_H$ (DMSO-$d_6$) 1.12 (3H, t, *J* 8.2 Hz, $CH_3$), 3.61 (2H, br s, $NH_2$ exchangeable), 4.23 (2H, q, *J* 8.2 Hz, $CH_2$). 6.35 (1H, br s, NH exchangeable), 6.92–7.71 (9H, m, ArH), 9.12 (1H, br s, NH, exchangeable).

### Synthesis of ethyl 1,5-dihydro-5-oxo-7-phenyl-8-(phenylsulfonyl)-tetrazolo[1,5-*a*]pyridine-6-carboxylate 24

A stirred solution of **23a** (0.83 g, 0.002 mol) in glacial acetic acid (25 ml) was treated with $NaNO_2$ (0.28 g, 0.004 mol) portionwise at room temperature. The reaction mixture was stirred for an additional 1 h, whereupon the *solid product* that separated was filtered off, washed with water, and crystallised

from acetic acid (0.52 g, 61%), mp > 270 °C (Found: C, 56.5; H, 3.7; N, 13.0; S, 7.4. $C_{20}H_{16}N_4O_5S$ requires C, 56.59; H, 3.79; N, 13.19; S, 7.55%); $\nu_{max}$ 3450–3415 (NH), 1715, 1705 (2 CO); $\delta_H$ (DMSO-$d_6$) 0.95 (3H, t, *J* 8.2 Hz, $CH_3$), 4.00 (2H, q, *J* 8.2 Hz, $CH_2$), 6.85–7.55 (10H, m, ArH), 9.65 (1H, br s, NH, exchangeable).

**Synthesis of ethyl 8-aryl-3-cyano-6,10-dihydro-2-methyl-4,6-dioxo-9-(phenylsulfonyl)-4*H*-pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidine-7-carboxylates 25a,b (general procedure)**

To a solution of **22a**,**b** (0.002 mol) in absolute ethanol (30 ml) containing glacial acetic acid (1 ml) was added ethyl 2-amino-4-cyano-5-methylthiophene-3-carboxylate[14] **12a** (0.42 g, 0.002 mol). The reaction mixture was refluxed for 2 h, left aside to cool to room temperature, and was then poured onto cold water. The solid product precipitate was filtered off, washed thoroughly with water, and crystallised from an appropriate solvent.

**Ethyl 3-cyano-6,10-dihydro-2-methyl-4,6-dioxo-8-phenyl-9-(phenylsulfonyl)-4*H*-pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidine-7-carboxylate 25a.** Yield 0.70 g (64%), mp 240–241 °C (from DMF) (Found: C, 59.4; H, 3.4; N, 7.7; S, 11.6. $C_{27}H_{19}N_3O_6S_2$ requires C, 59.44; H, 3.51; N, 7.70; S, 11.75%); $\nu_{max}$ 3450–3420 (NH), 2220 (CN), 1718, 1710, 1700 (3 CO); $\delta_H$ (DMSO-$d_6$) 1.12 (3H, s, *J* 8.2 Hz, $CH_3$), 2.15 (3H, s, $CH_3$), 4.17 (2H, q, *J* 8.2 Hz, $CH_2$), 6.88–7.56 (10H, m, Ar–H), 9.61 (1H, br s, NH, exchangeable); *m*/*z* 500 (100%), 545 ($M^+$, 18%).

**Ethyl 8-(*p*-chlorophenyl)-3-cyano-6,10-dihydro-2-methyl-4,6-dioxo-9-(phenylsulfonyl)-4*H*-pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidine-7-carboxylate 25b.** Yield 0.70 g (61%), mp > 250 °C (from DMF) (Found: C, 55.8; H, 3.0; Cl, 6.1; N, 7.0; S, 11.0. $C_{27}H_{18}ClN_3O_6S_2$ requires C, 55.91; H, 3.12; Cl, 6.11; N, 7.24; S, 11.05%); $\nu_{max}$ 3456–3435 (NH), 2216 (CN), 1720, 1712, 1695 (3 CO); $\delta_H$ (DMSO-$d_6$) 0.96 (3H, s, *J* 8.2 Hz, $CH_3$), 2.12 (3H, s, $CH_3$), 4.05 (2H, q, *J* 8.2 Hz, $CH_2$), 6.73–7.51 (9H, m, Ar–H), 9.42 (1H, br s, NH, exchangeable).

**Synthesis of ethyl 7-aryl-5,11-dihydro-9,11-dioxo-6-(phenylsulfonyl)-9*H*-pyrido[2,1-*b*]quinazoline-8-carboxylates 26a,b (general procedure)**

To a solution of **22a**,**b** (0.002 mol) in absolute ethanol (30 ml) containing glacial acetic acid (1.0 ml) was added anthranilonitrile **9** (0.24 g, 0.002 mol). The reaction mixture was refluxed for 2 h, left aside at room temperature overnight, and then poured onto cold water. The solid product precipitate was filtered off, dried, and crystallised from an appropriate solvent.

**Ethyl 5,11-dihydro-9,11-dioxo-7-phenyl-6-(phenylsulfonyl)-9*H*-pyrido[2,1-*b*]quinazoline-8-carboxylate 26a.** Yield 2.95 g (59%), mp 180–181 °C (from ethanol) (Found: C, 64.6; H, 4.0; N, 5.6; S, 6.5. $C_{27}H_{20}N_2O_6S$ requires C, 64.79; H, 4.03; N, 5.59; S, 6.40%); $\nu_{max}$ 3445–3400 (NH), 1720, 1712, 1705 (3 CO); $\delta_H$ (DMSO-$d_6$) 0.98 (3H, t, *J* 8.2 Hz, $CH_3$), 4.12 (2H, q, *J* 8.2 Hz, $CH_2$), 6.95–7.81 (14H, m, ArH), 9.73 (1H, br s, NH, exchangeable).

**Ethyl 7-(*p*-chlorophenyl)-5,11-dihydro-9,11-dioxo-6-(phenylsulfonyl)-9*H*-pyrido[2,1-*b*]quinazoline-8-carboxylate 26b.** Yield 2.94 g (55%), mp 192–193 °C (from ethanol) (Found: C, 60.6; H, 3.4; Cl, 6.6; N, 5.1; S, 6.0. $C_{27}H_{19}ClN_2O_6S$ requires C, 60.62; H, 3.57; Cl, 6.62; N, 5.23; S, 6.00%); $\nu_{max}$ 3450–3415 (NH), 1718, 1710, 1700 (3 CO); $\delta_H$ (DMSO-$d_6$) 0.95 (3H, t, *J* 8.2 Hz, $CH_3$), 4.00 (2H, q, *J* 8.2 Hz, $CH_2$), 6.80–7.75 (13H, m, ArH), 9.55 (1H, br s, NH, exchangeable).

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