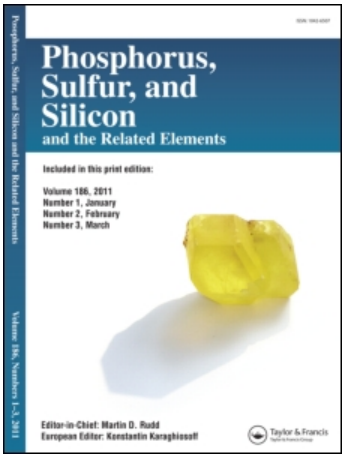

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Heterocyclic Sulfonesiv: A Novel Synthesis of Pyrrole and Fused Heterocyclic Sulfones

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HETEROCYCLIC SULFONES IV:[1-3] A NOVEL SYNTHESIS OF PYRROLE AND FUSED HETEROCYCLIC SULFONES

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The applicability and synthetic potency of the reagent diethyl 2-aryl-3-phenylsulfonylpropen-1,1-dicarboxylate **3** is reported. Compound **3** proved to be a key precursor in heterocyclic sulfones synthesis. Chemical and spectroscopic evidences for the structure of the newly synthesized compounds are described.

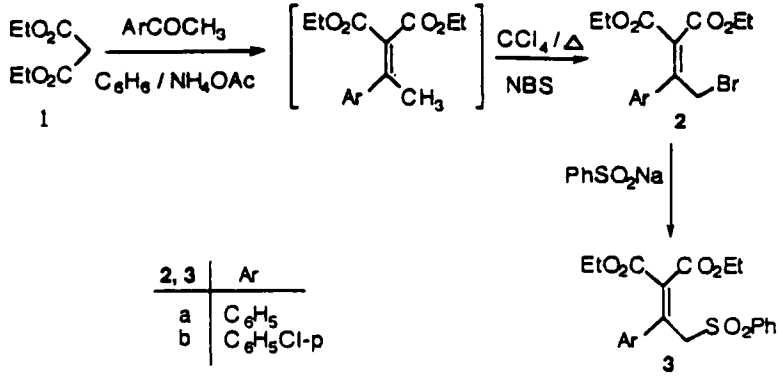
Keywords: Sulfones; pyrrole; benzoates; heterocycles

In view of the diverse biological and physiological activities of sulfones,[1-7] and in connection with our previous efforts directed towards the facile synthesis of heterocyclic ring systems,[8-12] we designed a simple program aimed at the development of convenient synthetic approches to heterocyclic sulfone systems of expected potential bioresponses utilizing the reagent **3** as a unique, key procursor. The newly synthesized sulfone derivatives appear to be promising for further chemical transformations as well as biological evaluations.

Diethyl 2-aryl-3-bromopropen-1,1,-dicarboxylate **2**, prepared in our laboratories from **1**[3] reacted with equimolar amounts of sodium benzenesulfinate in ethanolic solution to produce the corresponding reagent **3** (Scheme 1).

Compound **3** proved to be highly reactive towards various reagents forming a wide range of heterocyclic sulfone systems. Thus, compound **3**

* Corresponding Author.

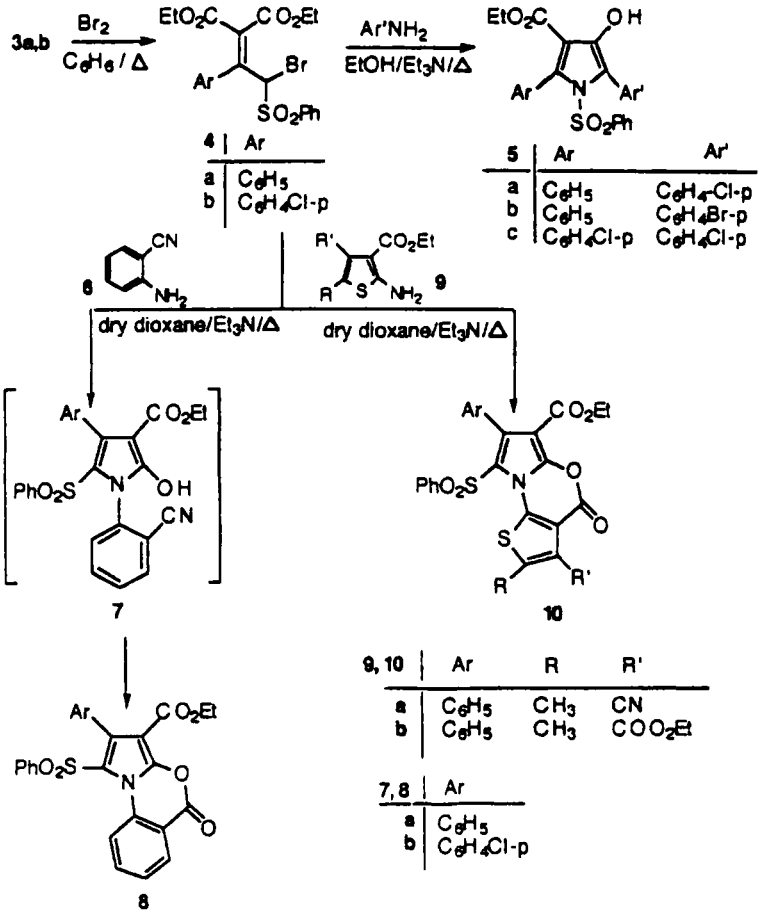


SCHEME 1

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-phenylsulfonylpropen-1,1-dicarboxylate **4**. Treatment of **4** with the appropriate primary aromatic amine in ethanolic/triethylamine solutions afforded the corresponding phenylsulfonylpyrrole derivatives **5**. The latter reaction yielded the corresponding ethyl 2-aryl-5-oxo-1-phenylsulfonylpyrrolo[2,1-*b*]-benzo-[*d*][1,3]oxazine-3-carboxylate **8** in a one-pot reaction if anthranilonitrile **6** was used. Similarly, the pyrrolo[2,1-*b*]thieno[2,3-*d*][1,3]oxazines **10** were obtained on treatment of **4a** with the appropriate ethyl 2-aminothiophene-3-carboxylate **9** (Scheme 2).

Compound **3a** reacted with arylidenemalononitrile **11** to yield the corresponding ethyl 4-aryl-3-cyano-2-hydroxy-6-phenyl-5-phenylsulfonyl-benzoates **13**. Compound **13** was assumed to be formed via addition of **3a** to the activated double bond in **11** to yield the Michael adducts **12** which intramolecularly cyclized and aromatized, via loss of HCN, to give the final isolable ethyl benzoate derivative **13**. Compound **13a** 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 **14** (Scheme 3).

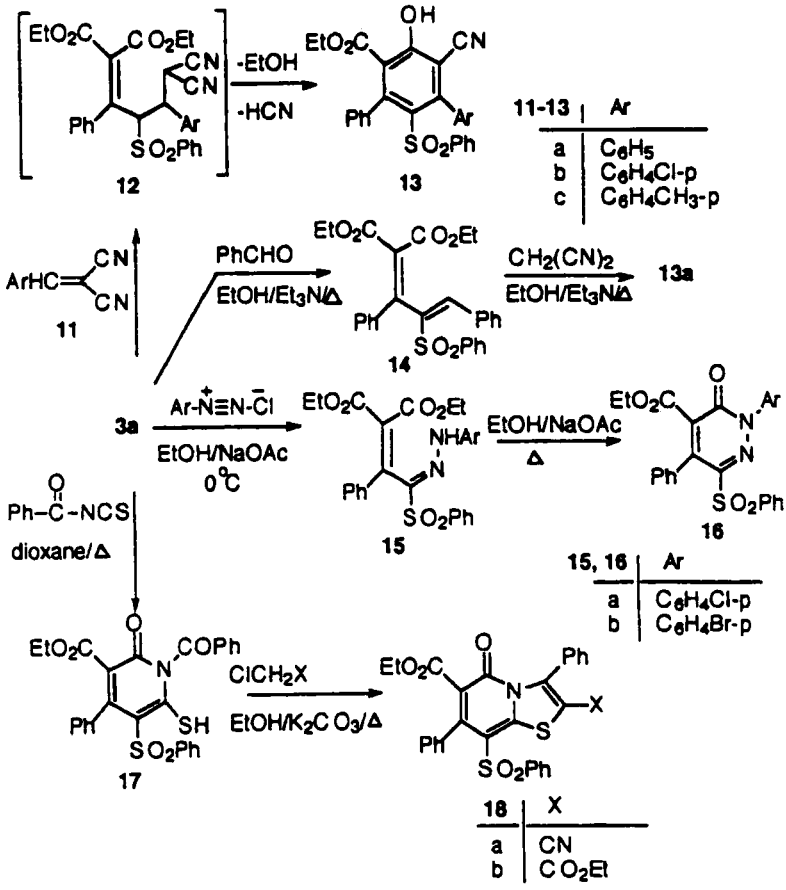
Compound **3a** readily coupled with equimolar amounts of aryldiazonium chloride to yield coupling products which may be formulated as hydrazone form **15** or its cyclic pyridazine form **18**. The hydrazone form **15** is preferred on the basis of its ^{1}H-NMR spectra which revealed the presence of multiplet signals corresponding for two ester groups. Further-



SCHEME 2

more, on boiling the hydrazone **15** in ethanolic sodium acetate solutions, the pyridazines **16** could be obtained.

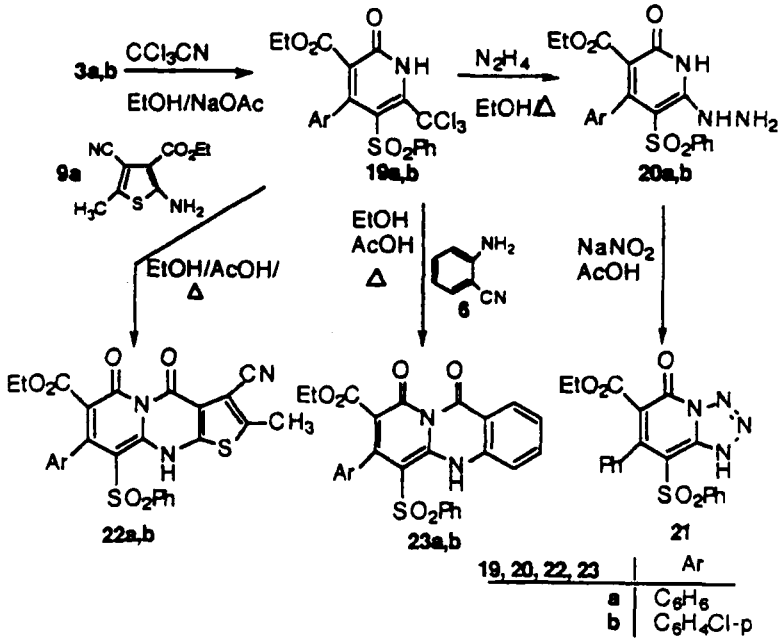
The phenysulfonylpyridine derivative **17** was obtained in a good yield from the reaction of **3a** with benzoyl isothiocyanate in boiling dry dioxane. Compound **17** reacted with each of chloroacetonitrile or ethyl chloroacetate in the presence of K_2CO_3 to yield the corresponding ethyl thiazolo[2,3-*a*]pyridine-6-carboxylate derivatives **18**.



SCHEME 3

Compound **3** reacted with equimolar amounts of trichloroacetonitrile in ethanolic/NaOAc solutions to produce exclusively the corresponding pyridine derivatives **19**. The trichloromethyl group in **19** proved to be highly reactive towards nucleophilic reagents. Thus, compound **19** reacted readily with equimolar amounts of hydrazine hydrate in ethanol under reflux to give the corresponding ethyl 6-hydrazinopyridine-3-carboxylate derivatives **20**. Compound **20a** could be successfully cyclized into the corresponding ethyl 5-oxo-7-phenyl-8-phenylsulfonyltetrazolo[1,5-*a*]pyridine-6-carboxylate (**21**) upon treatment with equimolar proportion of $NaNO_2$ in

glacial acetic acid (Scheme 4). Treatment of **19**with **9a**[13] in absolute ethanol solution containing glacial acetic acid, under reflux, furnished the coresponding ethyl 8-aryl-4,6-dioxo-9-phenylsulfonyl-10*H*-pyrido[1,2-*a*] -thieno[2,3-*d*]pyrimidine-7-carboxylates **22**. Similarly, ethyl pyrido[2,1-*b*] quinazoline-8-carboxylates **23** could be obtained upon treatment of **19** with anthranilonitrile **6**.



SCHEME 4

EXPERIMENTAL

All melting points were uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrometer. ^{1}H-NMR spectra were obtained on a Varian Gemini 200 MHz spectrometer using TMS as an internal reference. Chemical shifts are expresed as δ (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 **2a,b** have been prepared according to our previously reported methodology.[3]

Diethyl 2-Aryl-3-phenylsulfonylpropen-1,1-dicarboxylate (3a,b; General Procedure

To a solution of **2a,b** (0.02 mol) in ethanol (50 ml) was added sodium benzenesulfinate (0.02 mol). The reaction mixture was refluxed for 3 h, and the solvent was triturated with cold H_2O (20 ml), whereby the solid product formed was collected by filtration, washed thoroughly with H_2O, dried, and crystallized from the appropriate solvent.

Diethyl 2-Phenyl-3-phenylsulfonylpropen-1,1-dicarboxylate (3a)

Yield (5.2 g, 65%), m.p. 110 °C (ethanol); IR: 3000–2950 (CH_2), 1715, 1700 (2 C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.08–1.30 (m, 6H, 2 CH_3), 3.80–4.28 (m, 4H, 2 CH_2), 4.66 (s, 2H, CH_2), 6.90–7.85 (m, 10H, aromatic protons); MS m/z: 402 (M^+, 18%). Anal. calcd. for $C_{21}H_{22}O_6S$ (402.46): C 62.67, H 5.51, S 7.96. Found C 62.50, H 5.40, S 7.90.

Diethyl 2-(p-Chlorophenyl)-3-phenylsulfonylpropen-1,1-dicarboxylate (3b)

Yield (5.9 g, 68%), m.p. 117 °C (ethanol); IR: 3000–2960 (CH_2), 1712, 1700, (2C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.05–1.25 (m, 6H, 2 CH_3), 3.70–4.22 (m, 4H, 2 CH_2), 4.65 (s, 2H, CH_2), 6.95–7.74 (m, 9H, aromatic protons); Anal. Calcd. for $C_{21}H_{21}ClO_6S$ (436.90): C 57.73, H 4.84, Cl 8.11, S 7.33. Found C 57.80, H 4.70, Cl 8.00, S 7.50.

Diethyl 2-Aryl-3-bromo-3-phenylsulfonylpropen-1,1-dicarboxylate (4a,b; General Procedure)

To a solution of **3a,b** (0.02 mol) in dry benzene (50 ml), was added dropwise bromine (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 formed was collected by filtration, dried, and crystallized from the appropriate solvent.

Diethyl 3-Bromo-2-phenyl-3-phenylsulfonylpropen-1,1-dicarboxylate (4a)

Yield (5.6 g, 59%), m.p. 146 °C (ethanol); IR: 1718, 1705 (2 C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.05–1.33 (m, 6H, 2 CH_3), 3.85–4.45 (m, 4H,

2 CH_2), 5.61 (s, 1H, CH), 6.95–7.90 (m, 10H, aromatic protons); Anal. calcd. for $C_{21}H_{21}BrO_6S$ (481.36): C 52.39, H 4.40, Br 16.60, S 6.66. Found C 52.30, H 4.20, Br 16.50, S 6.40.

Diethyl 3-Bromo-2-(p-chlorophenyl)-3-phenylsulfonylpropen-1,1-dicarboxylate (4b)

Yield (6.2 g, 60%), m.p. 151 °C (ethanol); IR: 1715, 1705 (2 C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 0.95–1.30 (m, 6H, 2 CH_3), 3.90–4.32 (m, 4H, 2 CH_2), 5.59 (s, 1H, CH), 6.85–7.90 (m, 9H, aromatic protons); Anal. calcd. for $C_{21}H_{20}BrClO_6S$ (515.80): C 48.90, H 3.91, Br 15.49, Cl 6.87, S 6.22. Found C 48.80, H 3.90, Br 15.40, Cl 6.70, S 6.20.

Ethyl 1,4-Diaryl-2-hydroxy-5-phenylsulfonylpyrrole-3-carboxylates (5a-c, General Procedure)

To a warm solution of **4** (0.003 mol) in absolute ethanol (25 ml) containing anhydrous Et_3N (0.5 ml), was added the appropriate primary amine (0.003 mol). The reaction mixture was refluxed for 2 h, poured into cold water, then neutralized with dilute HCl. The solid product formed was collected by filtration, washed with water, dried and crystallized from the appropriate solvent.

Ethyl 1-(p-Chlorophenyl)-2-hydroxy-4-phenyl-5-phenylsulfonylpyrrole-3-carboxylate (5a)

Yield (0.79 g, 55%), m.p. 160 °C (ethanol); IR: 3500–3330 (OH), 1690 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.22 (t, 3H, J = 8.2 Hz, CH_3), 4.13 (q, 2H, J = 8.2 Hz, CH_2), 6.90–7.83 (m, 14H, aromatic protons), 13.15 (s, 1H, OH); MS m/z: 481 (M^+, 22%). Anal. calcd. for $C_{25}H_{20}ClNO_5S$ (481.95): C 62.30, H 4.18, Cl 7.35, N 2.91, S 6.5. Found C 62.30, H 4.00, Cl 7.30, N 2.70, S 6.50.

Ethyl 1-(p-Bromophenyl)-2-hydroxy-4-phenyl-5-phenylsulfonylpyrrole-3-carboxylate (5b)

Yield (0.82 g, 52%), m.p. 171 °C (ethanol); IR: 3495–3335 (OH), 1690 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.25 (t, 3H, J = 8.2 Hz, CH_3), 4.18

(q, 2H, J = 8.2 Hz, CH_2), 6.81–7.79 (m, 14H, aromatic protons), 13.19 (s, 1H, OH); Anal. calcd. for $C_{25}H_{20}BrNO_5S$ (526.40): C 57.04, H 3.83, Br 15.18, N 2.66, S 6.09. Found C 56.90, H 3.80, Br 15.10, N 2.40, S 6.00.

Ethyl 1,4-Di-(p-Chlorophenyl)-2-hydroxy--5-phenylsulfonylpyrrole-3-carboxylate (5c)

Yield (0.86 g, 56%), m.p. 176 °C (ethanol); IR: 3500–3325 (OH), 1690 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.28 (t, 3H, J = 8.2 Hz, CH_3), 4.51 (q, 2H, J = 8.2 Hz, CH_2), 6.95–7.80 (m, 13H, aromatic protons), 13.10 (s, 1H, OH); Anal. calcd. for $C_{25}H_{19}Cl_2NO_5S$ (516.39): C 58.14, H 3.71, Cl 13.73, N 2.71, S 6.21. Found C 58.10, H 3.60, Cl 13.70, N 2.60, S 6.00.

Ethyl 2-Aryl-5-oxo-1-phenylsulfonylpyrrolo[2,1-b]benzo[d][1,3]-oxazine-3-carboxylates (8a,b; General Procedure)

A mixture of **4** (0.003 mol) and anthranilonitrile (**6**) (0.003 mol) in dry dioxane (30 ml) containing anhydrous Et_3N (1.0 ml) was refluxed for 3h. The reaction mixture was left aside at room temperature overnight, poured into an ice/water mixture and neutralized with dilute HCl. The solid so-formed was filtered off, washed with water, dried and crystallized from the appropriate solvent.

Ethyl 5-Oxo-2-phenyl-1-phenylsulfonylpyrrolo[2,1-b]benzo[d][1,3]-oxazine-3-carboxylate (8a)

Yield (0.64 g, 45%), m.p. 182 °C (dioxane); IR: 1715, 1708 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.24 (t, 3H, J = 8.2 Hz, CH_3), 4.55 (q, 2H, J = 8.2 Hz, CH_2), 6.88–7.92 (m, 14H, aromatic protons); MS m/z: 312 (M^+, 16%); Anal. calcd. for $C_{26}H_{19}NO_6S$ (473.50): C 65.95, H 4.04, N 2.95, S 6.77. Found C 65.90, H 3.80, N 2.90, S 6.60.

Ethyl 2-(p-Chlorophenyl)-5-oxo-1-phenylsulfonylpyrrolo[2,1-b] benzo[d][1,3]oxazine-3-carboxylate (8b)

Yield (0.77 g, 51%), m.p. 189 °C (dioxane); IR: 1718, 1710 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.28 (t, 3H, J = 8.2 Hz, CH_3), 4.28 (q, 2H, J = 8.2 Hz, CH_2), 6.90–7.82 (m, 13H, aromatic protons); Anal. calcd. for

$C_{26}H_{18}ClNO_6S$ (507.94): C 61.48, H 3.57, Cl 6.98, N 2.75, S 6.31. Found C 61.40, H 3.40, Cl 6.90, N 2.50, S 6.20.

Ethyl 2-Aryl-5-oxo-1-phenylsulfonylpyrrolo[2,1-b]thieno[2,3-b][1,3]-oxazine-3-carboxylates (10a,b; General Procedure)

A mixture of **4a** (0.003 mol) and the appropriate ethyl 2-aminothiophene-3-carboxylate **9** (0.003 mol) in dry dioxane (30 ml) containing Et_3N (1.0 ml) was refluxed for 3 h. The reaction mixture was poured onto cold water and neutralized with dilute HCl. The resulting precipitate was collected by filtation, dried and crystallized from the appropriate solvent.

Ethyl 6-Cyano-7-methyl-5-oxo-2-phenyl-1-phenylsulfonylpyrrolo[2,1-b]-thieno[2,3-d]-[1,3]oxazine-3-carboxylate (10a)

Yield (0.65 g, 42%), m.p. 220 °C (dioxane); IR: 2218 (CN), 1720, 1712 (2 C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.15 (s, 3H, CH_3), 1.22 (t, 3H, J = 8.2 Hz, CH_3), 4.15 (q, 2H, J = 8.2 Hz, CH_2), 6.85–7.96 (m, 10H, aromatic protons); MS m/z: 518 (M^+, 14%); Anal. calcd. for $C_{26}H_{18}N_2O_6S_2$ (518.56): C 60.22, H 3.49, N 5.40, S 12.36. Found C 60.10, H 3.40, N 5.40, S 12.20.

Diethyl 7-Methyl-5-oxo-2-phenyl-1-phenylsulfonylpyrrolo[2,1-b] thieno-[2,3-b][1,3]-oxazine-3,6-dicarboxylate (10b)

Yield (0.66 g, 39%), m.p. 192 °C (dioxane); IR: 1722, 1718, 1710 (3 C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.15 (s, 3H, CH_3), 1.05–1.29 (m, 6H, 2 CH_3), 3.85–4.28 (m, 4H, 2 CH_2), 6.91–7.88 (m, 10H, aromatic protons); Anal. calcd. for $C_{28}H_{23}NO_8S_2$(565.61): C 59.45, H 4.09, N 2.47, S 11.33. Found C 59.40, H 3.80, N 2.40, S 11.20.

Ethyl 4-Aryl-3-cyano-2-hydroxy-6-phenyl-5-phenylsulfonylbenzoates (13a-c; General Procedure)

Method A

A mixture of 3a (0.002 mol) and the appropriate arylidenemalono-nitrile 11 (0.002 mol) in ethanol (25 ml) containing Et_3N (0.5 ml) was heated

under reflux for 3h. The reaction mixture was evaporated in vacuo, triturated with cold water and neutralized with dilute HCl. The solid product was collected by filtration, dried and crystallized from the appropriate solvent.

Ethyl 3-Cyano-4,6-diphenyl-2-hydroxy-5-phenylsulfonylbenzoate (13a)

Yield (0.66 g, 69%), m.p. 220 °C (ethanol); IR: 3615 (OH), 2216 (CN), 1710 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 0.96 (t, 3H, J = 8.3 Hz, CH_3), 4.10 (q, 2H, J = 8.3 Hz, CH_2), 5.96 (s, 1H, OH), 6.82–7.91 (m, 15H, aromatic protons); MS m/z: 483 (M^+, 15%); Anal. calcd. for $C_{28}H_{21}NO_5S$ (483.53): C 69.55, H 4.37, N 2.89, S 6.63. Found C 69.50, H 4.30, N 2.80, S 6.50.

Ethyl 4-(p-Chlorophenyl)-3-cyano-2-hydroxy-6-phenyl-5-phenylsulfonylbenzoate (13b)

Yield (0.68 g, 66%), m.p. 229 °C (dioxane); IR: 3620 (OH), 2218 (CN), 1710 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 0.92 (t, 3H, J = 8.3 Hz, CH_3), 4.23 (q, 2H, J = 8.3 Hz, CH_2), 5.94 (s, 1H, OH), 6.90–7.83 (m, 15H, aromatic protons); Anal. calcd. for $C_{28}H_{20}ClNO_5S$ (517.98): C 64.92, H 3.89, Cl 6.84, N 2.70, S 6.19. Found C 64.90, H 3.80, Cl 6.70, N 2.60, S 6.00.

Ethyl 3-Cyano-2-hydroxy-6-phenyl-5-phenylsulfonyl-4-(p-tolyl)benzoate (13c)

Yield (0.60 g, 60%), m.p. 206 °C (dioxane); IR: 3615 (OH), 3025 (CH_3), 2218 (CN), 1710 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 0.95 (t, 3H, J = 8.2 Hz, CH_3), 2.21 (s, 3H, CH_3), 4.28 (q, 2H, J = 8.2 Hz, CH_2), 5.96 (s, 1H, OH), 6.93–7.91 (m, 14H, aromatic protons); Anal. calcd. for $C_{29}H_{23}NO_5S$ (497.56): C 70.00, H 4.65, N 2.81, S 6.44. Found C 69.90, H 4.60, N 2.70, S 6.40.

Method B

A mixture of 14 (0.002 mol) and malononitrile (0.002 mol) in ethanol (25 ml) containing Et_3N (0.5 ml) was refluxed for 3 h. The reaction mixture

was poured into cold water and nuteralized with dilute HCl. The solid product formed was collected by filtration, dried, crystallized from ethanol, and found to be identical in all aspects (m.p., mixed m.p. and IR spectrum) with an authentic sample of **13a** prepared according to Method A.

Diethyl 2,4-Diphenyl-3-phenylsulfonylbut-1,3-diene-1,1-dicarboxylate (14)

A mixture of **3a** (0.003 mol) and benzaldehyde (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 at room temperature, poured into cold water and neutralized with dilute HCl. The solid product formed was filtered off, dried and crystallized from ethanol. Yield (1.0 g, 69%), m.p. 173°C (ethanol); IR: 1715, 1700 (2 C=O), 1650 (C=C) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 0.95–1.35 (m, 6H, 2 CH_3), 3.92–4.25 (m, 4H, 2 CH_2), 6.75–7.83 (m, 16H, aromatic protons and arylidene-CH); Anal. calcd. for $C_{28}H_{26}O_6S$ (490.57): C 68.55, H 5.34, S 6.53. Found C 68.50, H 5.20, S 6.40.

Diethyl 3-Arylhydrazono-2-phenyl-3-phenylsulfonylpropen-1,1-dicarboxylates (15a,b, General Procedure)

The appropriate aryldiazonium chloride (0.003 mol) [prepared by adding $NaNO_2$ (0.003 mol) to the appropriate primary aromatic amine (0.003 mol) in concentrated HCl (2 ml) at 0–5 °C and stirring] was added to a stirred solution of **3a** (0.003 mol) in ethanol (50 ml) containing NaOAc (2.0 g) dropwise while cooling at 0–5 °C and stirring. The reaction mixture was left aside at room temperature for 3 h, whereby the solid product formed was collected by filteration, dried and crystallized from the appropriate solvent.

Diethyl 3-(p-Chlorophenylhydrazono)-2-phenyl-3-phenylsulfonylpropen-1,1-dicarboxylate (15a)

Yield (1.0 g, 65%), m.p. 165 °C (ethanol); IR: 3350–3320 (NH), 1718, 1700 (2 C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 0.96–1.25 (m, 6H, 2 CH_3), 3.95–4.05 (m, 4H, 2 CH_2), 6.73–7.56 (m, 14H, aromatic protons), 11.28 (br s, 1H, NH); MS m/z: 541 (M^+, 18%); Anal. calcd. for $C_{27}H_{25}ClN_2O_6S$

(541.02): C 59.94, H 4.65, Cl 6.55, N 5.17, S 5.92. Found C 59.90, H 4.50, Cl 6.40, N 5.00, S 5.80.

Diethyl 3-(p-Bromophenylhydrazono)-2-phenyl-3-phenylsulfonylpropen-1,1-dicarboxylate (15b)

Yield (1.07 g, 61%), m.p. 171 °C (dioxane); IR: 3350–3318 (NH), 1715, 1705 (2 C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.02–1.28 (m, 6H, 2 CH_3), 3.95–4.12 (m, 4H, 2 CH_2), 6.81–7.63 (m, 14H, aromatic protons), 11.54 (br s, 1H, NH); Anal. calcd. for $C_{27}H_{25}BrN_2O_6S$ (585.47): C 55.39, H 4.30, Br 13.65, N 4.78, S 5.47. Found C 55.20, H 4.30, Br 13.50, N 4.60, S 5.40.

Ethyl 2-Aryl-2,3-dihydro-3-oxo-5-phenyl-6-phenylsulfonylpyridazine-4-carboxylates (16a,b, General Procedure)

A solution of **15** (0.002 mol) in ethanol (30 ml) containing NaOAc (1.0 g) was refluxed for 3 h. The reaction mixture was poured into cold water and neutralized with dilute HCl. The resulting precipitated solid was filtered off, dried and crystallized from the appropriate solvent.

Ethyl 2-(p-Chlorophenyl)-2,3-dihydro-3-oxo-5-phenyl-6-phenylsulfonyl-pyridazine-4-carboxylate (16a)

Yield (0.54 g, 55%), m.p. 195 °C (AcOH); IR: 1718, 1695 (2 C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.21 (t, 3H, J = 8.2 Hz, CH_3), 4.25 (q, 2H, J = 8.2 Hz, CH_2), 6.91–7.43 (m, 14H, aromatic protons); MS m/z 494 (M^+, 14%); Anal. calcd. for $C_{25}H_{19}ClN_2O_5S$ (494.94): C 60.66, H 3.86, Cl 7.16, N 5.66, S 6.47. Found C 60.50 H 3.80, Cl 7.00, N 5.50, S 6.40.

Ethyl 2-(p-Bromophenyl)-2,3-dihydro-3-oxo-5-phenyl-6-phenylsulfonyl-pyridazine-4-carboxylate (16b)

Yield (0.62 g, 58%), m.p. 206 °C (AcOH); IR: 1718, 1700 (2 C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.21 (t, 3H, J = 8.2 Hz, CH_3), 4.09 (q, 2H, J = 8.2 Hz, CH_2), 6.85–7.40 (m, 14H, aromatic protons); Anal. calcd. for $C_{25}H_{19}BrN_2O_5S$ (539.40): C 55.66, H 3.55, Br 14.81, N 5.19, S 5.94. Found C 55.60, H 3.40, Br 14.70, N 5.00, S 5.90.

Ethyl 1-Benzoyl-1,2-dihydro-2-oxo-6-mercapto-4-phenyl-5-phenylsulfonyl-pyridine-3-carboxylate (17)

To a suspension of NH_4SCN (0.005 mol) in dioxane (50 ml), was added benzoyl chloride (0.005 mol). The reaction mixture was refluxed for 2 min., then treated with **3a** (0.005 mol). The reaction mixture was refluxed for 2 h, poured into ice/water, whereby the solid product formed was filtered and crystallized from dioxane. Yield (1.90 g, 66%), m.p. 210 °C; IR: 2250 (SH), 1718, 1705, 1684 (3 C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.20 (t, 3H, J = 8.2 Hz, CH_3), 3.24 (s, 1H, SH), 4.25 (q, 2H, J = 8.2 Hz, CH_2), 6.90–7.68 (m, 15H, aromatic protons); MS m/z: 573 (M^+, 12%); Anal. calcd. for $C_{27}H_{21}NO_6S_2$ (519.58): C 62.41, H 4.07, N 2.69, S 12.13. Found C 62.40, H 4.00, N 2.80, S 12.40.

Ethyl 3,7-Dihydro-5-oxo-8-phenylsulfonylthiazolo[3,2-a]pyridine-6-carboxylate derivatives (18a,b, General Procedure)

To a suspension of **17** (0.002 mol) in ethanol (30 ml), was added aqueous solution K_2CO_3 (0.004 mol in 20 ml H_2O), and the appropriate α-chloro compound (0.002 mol). The reaction mixture was refluxed for 2 h, left to cool at room temperature and poured into cold water. The solid product formed was filtered off and crystallized from the appropriate solvent.

Ethyl 2-Cyano-3,7-diphenyl-5-oxo-8-phenylsulfonylthiazolo[3,2-a]-pyridine-6-carboxylate (18a)

Yield (0.67 g, 62%), m.p. > 250°C (dioxane); IR: 2218 (CN), 1715, 1700 (2 C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.15 (t, 3H, J = 8.2 Hz, CH_3), 4.12 (q, 2H, J = 8.2 Hz, CH_2), 6.93–7.55 (m, 15H, aromatic protons); MS m/z: 540 (M^+, 16%); Anal. calcd. for $C_{29}H_{20}N_2O_0S_2$(540.61): C 64.43, H 3.72, N 5.18, S 11.86. Found C 64.30, H 3.70, N 5.00, S 11.80.

Diethyl 3,7-Diphenyl-5-oxo-8-phenylsulfonylthiazolo[3,2-a]-pyridine-2,6-carboxylate (18b)

Yield (0.65 g, 56%), m.p. 212 °C (dioxane); IR: 1718, 1705, 1692 (3 C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 0.95–1.32 (m, 6H, 2 CH_3), 3.83–4.22 (m, 4H, 2 CH_2), 6.85–7.64 (m, 16H, aromatic protons). Anal. calcd. for

$C_{31}H_{25}NO_7S_2$ (587.66): C 63.35, H 4.28, N 2.38, S 10.91. Found C 63.20, H 4.20, N 2.20, S 10.90.

Ethyl 4-Aryl-1,2-dihydro-2-oxo-5-phenylsulfonyl-6-trichloromethyl-pyridine-3-carboxylates (19a,b, General Procedure)

To a suspension of **3a,b** (0.005 mol) in ethanol (30 ml) containing NaOAc (0.5 g), was added trichloroacetonitrile (0.005 mol). The reaction mixture was heated under reflux for 2 h and left aside at room temperature overnight. The mixture was poured into an ice/water mixture, neutralized with dilute HCl, filtered off, washed with water, dried and crystallized from the appropriate solvent.

Ethyl 1,2-Dihydro-2-oxo-4-phenyl-5-phenylsulfonyl-6-trichloromethyl-pyridine-3-carboxylate (19a)

Yield (1.53 g, 61%), m.p. 135 °C (ethanol); IR: 3370 (NH), 1715 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.12 (t, 3H, J = 8.2 Hz, CH_2), 6.70–7.82 (m, 10H, aromatic protons), 9.98 (br s, 1H, NH); MS m/z: 500 (M^+, 12%). Anal. calcd. for $C_{21}H_{16}Cl_3NO_5S$ (500.78): C 50.36, H 3.22, Cl 21.23, N 2.79, S 6.40. Found C 50.20, H 3.00, Cl 21.20, N 2.70, S 6.20.

Ethyl 4-(p-Chlorophenyl)-1,2-dihydro-2-oxo--phenylsulfonyl-6 -trichloro-methylpyridine-3-carboxylate (19b)

Yield (1.74 g, 65%), m.p. 142 °C (ethanol); IR: 3362 (NH), 1720, 1704 (2 C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.05 (t, 3H, J = 8.2 Hz, CH_3), 4.05 (q, 2H, J = 8.2 Hz, CH_2), 6.84–7.72 (m, 9H, aromatic protons), 10.52 (br s, 1H, NH); Anal. calcd. for $C_{21}H_{15}Cl_4NO_5S$ (535.22): C 47.12, H 2.82, Cl 26.49, N 2.61, S 5.99. Found C 47.00, H 2.80, Cl 26.30, N 2.60, S 5.80.

Ethyl 4-Aryl-1,2-dihydro-6-hydrazino-2-oxo-5-phenylsulfonylpyridine-3-carboxylates (20a,b, General Procedure)

A mixture of **19a,b** (0.003 mol) and hydrazine hydrate (0.003 mol) in ethanol (30 ml) was refluxed for 30 min. and then left at room temperature overnight. The mixture was poured into cold water, whereby the solid

product so-formed was filtered off and crystallized from the appropriate solvent.

Ethyl 4-(p-Chlorophenyl)-1,2-dihydro-6-hydrazino-2-oxo-5-phenyl-sulfonylpyridine-3-carboxylate (20a)

Yield (0.80 g, 65%), m.p. 146°C (ethanol); IR: 3420–3380 (NH_2, NH), 1712, 1700 (2 C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.10 (t, 3H, J = 8.2 Hz, CH_3), 3.25 (br s, 2H, NH2), 4.14 (q, 2H, J = 8.2 Hz, CH_2), 6.29 (br s, 1H, NH), 6.89–7.48 (m, 10H, aromatic protons), 8.35 (br s, 1H, NH); Anal. calcd. for $C_{20}H_{19}N_3O_5S$ (413.44): C 58.10, H 4.63, N 10.16, S 7.75. Found C 58.00, H 4.60, N 10.10, S 7.70.

Ethyl 1,2-Dihydro-6-hydrazino-2-oxo-4-phenyl-5-phenylsulfonyl-pyridine-3-carboxylate (20b)

Yield (0.83 g, 62%), m.p. 158 °C (ethanol); IR: 3428–3365 (NH_2, NH), 1715, 1708 (2 C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.12 (t, 3H, J = 8.2 Hz, CH_3), 3.61 (br s, 2H, NH_2), 4.23 (q, 2H, J = 8.2 Hz, CH_2), 6.35 (br s, 1H, NH), 6.92–7.51 (m, 9H, aromatic protons), 9.12 (br s, 1H, NH); Anal. calcd. for $C_{20}H_{18}ClN_3O_5S$ (447.89): C 53.63, H 4.05, Cl 7.91, N 9.38, S 7.15. Found C 53.50, H 4.00, Cl 7.80, N 9.20, S 7.10.

Ethyl 5-Oxo-7-phenyl-8-phenylsulfonyltetraazolo[1,5-a]pyridine-6-carboxylate (21)

A solution of **20a** (0.002 mol) in glacial acetic acid (25 ml) was treated with $NaNO_2$ (0.004 mol) portionwise while stirring at room temperature. The reaction mixture was stirred for additional 1 h, whereby the solid product separated was filtered off, washed with water and crystallized from acetic acid. Yield (0.52 g, 61%), m.p. > 270 °C (ethanol); IR: 3450–3415 (NH), 1715, 1705 (2 C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 0.95 (t, 3H, J = 8.2 Hz, CH_3), 4.00 (q, 2H, J = 8.2 Hz, CH_2), 6.85–7.55 (m, 10H, aromatic protons), 9.65 (br s, 1H, NH); Anal. calcd. for $C_{20}H_{16}N_4O_5S$ (424.43): C 56.59, H 3.79, N 13.19, S 7.55. Found C 56.50, H 3.70, N 13.00, S 7.40.

Ethyl 8-Aryl-4,6-dioxo-9-phenylsulfonyl-10H-pyrido[1,2-a]thieno [2,3-d]-pyrimidine-7-carboxylates (22a,b, General Procedure)

To a solution of **19a,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 (**9a**)[13] (0.002 mol). The reaction mixture was refluxed for 2 h., left aside to cool at room temperature and then poured into cold water. The solid product precipitated was filtered off, washed thoroughly with water and crystallized from the appropriate solvent.

Ethyl 3-Cyano-4,6-dioxo-8-phenyl-9-phenylsulfonyl-10H-pyrido [1,2-a]-thieno[2,3-d]-pyrimidine-7-carboxylate (22a)

Yield (0.70 g, 64%), m.p. 240 °C (DMF); IR: 3450–3420 (NH), 2220 (CN), 1718, 1710, 1705 (3 C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.12 (s, 3H, J = 8.2 Hz, CH_3), 2.15 (s, 3H, CH_3), 4.17 (q, 2H, J = 8.2 Hz, CH_2), 6.88–7.56 (m, 10H, aromatic protons), 9.61 (br s, 1H, NH); MS m/z: 545 (M^+, 18%); Anal. calcd. for $C_{27}H_{19}N_3O_6S_2$(545.58): C 59.44, H 3.51, N 7.70, S 11.75. Found C 59.40, H 3.40, N 7.70, S 11.60.

Ethyl 8-(p-Chlorophenyl)-3-cyano-4,6-dioxo-9-phenylsulfonyl-10H-pyrido-[1,2-a]-thieno[2,3-d]-pyrimidine-7-carboxylate (22b)

Yield (0.70 g, 61%), m.p. > 250 °C (DMF); IR: 3456–3435 (NH), 2216 (CN), 1720, 1712, 1695 (3 C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 0.96 (s, 3H, J = 8.2 Hz, CH_3), 2.12 (s, 3H, CH_3), 4.05 (q, 2H, J = 8.2 Hz, CH_2), 6.73–7.51 (m, 9H, aromatic protons), 9.42 (br s, 1H, NH); Anal. calcd. for $C_{27}H_{18}ClN_3O_6S_2$ (580.03): C 55.91, H 3.12, Cl 6.11, N 7.24, S 11.05. Found C 55.80, H 3.00, Cl 6.10, N 7.00, S 11.00.

Ethyl 7-Aryl-9,11-dioxo-6-phenylsulfonylpyrido[2,1-b]quinazoline-8-carboxylates (23a,b, General Procedure)

To a solution of **19a,b** (0.002 mol) in absolute ethanol (30 ml) containing glacial acetic acid (1.0 ml) was added anthranilonitrile (**6**) (0.002 mol). The reaction mixture was refluxed for 2 h., left aside at room temperature overnight and then poured into cold water. The solid product precipitated was filtered off, dried and crystallized from the appropriate solvent.

Ethyl 9,11-Dioxo-7-phenyl-6-phenylsulfonylpyrido[2,1-b] quinazoline-8-carboxylate (23a)

Yield (2.95 g, 59%), m.p. 180 °C (ethanol); IR: 3445–3400 (NH), 1720, 1712, 1705 (3 C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 0.98 (s, 3H, J = 8.2 Hz, CH_3), 4.12 (q, 2H, J = 8.2 Hz, CH_2), 6.95–7.81 (m, 14H, aromatic protons), 9.73 (br s, 1H, NH); Anal. calcd. for $C_{27}H_{20}N_2O_6S$ (500.52): C 64.79, H 4.03, N 5.59, S 6.40. Found C 64.60, H 4.00, N 5.60, S 6.50.

Ethyl 9,11-Dioxo-7-phenyl-6-phenylsulfonylpyrido[2,1-b] quinazoline-8-carboxylate (23a)

Yield (2.94 g, 55%), m.p. 192 °C (ethanol); IR: 3450–3415 (NH), 1718, 1710, 1700 (3 C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 0.95 (s, 3H, J = 8.2 Hz, CH_3), 4.00 (q, 2H, J = 8.2 Hz, CH_2), 6.80–7.75 (m, 13H, aromatic protons), 9.55 (br s, 1H, NH); Anal. calcd. for $C_{27}H_{19}ClN_2O_6S$ (534.97): C 60.62, H 3.57, Cl 6.62, N 5.23, S 6.00. Found C 60.620, H 3.40, Cl 6.60, N 5.10, S 6.00.

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