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Original article

L-Proline-catalysed facile green protocol for the synthesis and antimycobacterial evaluation of [1,4]-thiazines

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ABSTRACT

A series of ethyl 6-(4-chlorobenzoyl)-1,1-dioxo-3,5-diaryl-1,4-thiazinane-2-carboxylates was prepared in good yields (72–90%) from the reaction of ethyl 2-[(2-oxo-2-arylethyl)sulfonyl]acetate, substituted aromatic aldehydes and amines in presence of green catalyst, L-proline. These compounds were evaluated for *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv (MTB), multi-drug resistant *M. tuberculosis* (MDR-TB) and *Mycobacterium smegmatis* (MC^2) using agar dilution method. Ethyl 6-(4-chlorobenzoyl)-3,5-di(4-nitrophenyl)-1,1-dioxo-1,4-thiazinane-2-carboxylate was found to be the most promising compound (MIC: 0.68 μM) active against MTB and MDR-TB.

1. Introduction

Tuberculosis (TB) is a contagious and potentially fatal disease that can affect almost any part of the body but manifests mainly as an infection of the lungs. It is caused by a bacterial microorganism, the *tubercle bacillus* or *Mycobacterium tuberculosis* [1,2]. Tuberculosis (TB) has become an important public health problem worldwide since the mid-1980s due to two major factors, the acquired immuno deficiency syndrome (AIDS) epidemic and the advent of multi-drug resistant strains (MDR). In developing countries, TB is responsible for 20% of all deaths in adults, and each year there are about 8.9–9 millions of new cases of which 15% are children, and 1.7–2 millions of deaths of which 450,000 are children. Globally, the number of TB cases is currently rising at 2% per year with an estimate of 32% of the world population, about 2 billion people, being infected by latent TB. In the case of patients with AIDS, TB is the most common opportunistic infection which causes the death of 1 out of every 3 patients [3].

Single agent TB therapy rapidly leads to drug-resistant organisms [4], while multi-drug treatment needs to be prolonged as *M. tuberculosis* divides slowly and it is metabolically capable of becoming drug insensitive and/or bacilli may become sequestered [5,6]. Patient adherence is a major problem with such prolonged treatment regimens. Due to the increase of MDR-TB and AIDS cases worldwide and the lack of discovery of new drugs, there is an imperative need for discovery of short and effective TB drug regimens. Earlier, we have synthesized and reported tetrahydro-4*H*-pyrano[3,2-c]pyridines [7], spiro-pyrido-pyrrolizines, pyrrolidines [8a,b], piperidones [9a], thienoindoles [9b], and arylthieno-[2,3-*b*]thiophenes [9c] as pharmacophores for antimycobacterial activity. In continuation of our efforts in discovering new leads for antimycobacterial activities, we now report a facile L-proline-catalysed green synthesis of highly functionalized [1,4]-thiazines and the results of their evaluation for *in vitro* antimycobacterial activity against *M. tuberculosis* H37Rv (MTB), multi-drug resistant *M. tuberculosis* (MDR-TB) and *Mycobacterium smegmatis* (MC^2). The choice of L-proline as catalyst in this transformation is based on the fact that, besides being an abundant and inexpensive amino acid, it is known to catalyse diverse organic transformations, both enantio- and non-enantioselective ones such as aldol [10], Mannich [11],

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Michael [12], Diels Alder/Knoevenagel [13], unsymmetric Biginelli [14] and tandem [15,16] reactions. The efficiency of L-proline in diverse organic transformations is ascribable to multiple catalytic roles it can play, such as an acid or a base and both, as a nucleophile and its ability to form enamine/enaminium intermediates upon reaction with carbonyl/α,β-unsaturated carbonyl compounds.

2. Chemistry

The general procedure for the preparation of 6-(4-chlorobenzoyl)-1,1-dioxo-3,5-diaryl-1,4-thiazinane-2-carboxylates **3–29** is described in Scheme 1. A mixture of ethyl 2-[(2-oxo-2-arylethyl)sulfonyl]acetate **1**, aromatic aldehyde **2** and primary amine/ammonia in a 1:2:1 molar ratio in the presence of L-proline (30 mol%) in ethanol at room temperature for 2–4 h afforded the [1,4]-thiazine in good yields (72–90%) (Scheme 1). Two [1,4]-thiazines described in the present work, **16** and **18**, have been previously reported by Reddy et al. [17] in lower yields (72 and 69% respectively), from the reaction of ethyl 2-[(2-oxo-2-arylethyl)sulfonyl]acetate **1** with aromatic aldehyde **2** and ammonium acetate in ethanol, than that obtained in the present study employing L-proline (90 and 88% respectively). Chiral HPLC analysis of one representative [1,4]-thiazine, **16**, reveals a very low enantiomeric excess of 4.8%. The above results disclose that L-proline functions as an efficient but essentially as a non-enantioselective catalyst in this reaction.

The structure of [1,4]-thiazines was characterized by one- and two-dimensional NMR spectroscopic data. The ^{1}H NMR spectrum of thiazine **3** gives a doublet at 4.46 ppm ($J = 10.8$ Hz) assignable to H-2. This proton shows a H,H-COSY correlation with the doublet due to H-3 at 4.85 ppm (Fig. 1). The H-2 and H-3 chemical shifts and C,H-COSY correlations assign C-2 and C-3 respectively to 72.5 and 67.5 ppm. These assignments are also supported by the HMBCs (Fig. 2) of: (i) H-2 with the ester carbonyl at 161.6 ppm, C-3 at 67.5 ppm and *ipso* carbon of the aryl ring attached to C-3 at 137.4 ppm, (ii) H-3 with the signals at 137.4 and 129.3 ppm due to *ipso* and *ortho* carbons of the aryl ring attached to C-3 respectively. The J value (10.8 Hz) of H-2 and H-3 points to their axial orientations and, hence, the ester group at C-2 and aryl ring at C-3 are equatorially oriented. Another set of doublets at 5.03 and 5.29 ppm ($J = 10.8$ Hz) are assigned to H-5 and H-6 respectively, whose C,H-COSY correlations assign the signals at 66.8 and 71.6 ppm to C-5 and C-6 respectively. The 2H singlet at 3.58 ppm assignable to the benzylic protons show a C,H-COSY correlation with the carbon signal at 53.3 ppm. The assignment of benzylic protons is evident from their HMBCs with: (i) the C-3 at 67.5 ppm, (ii) the C-5 at 66.8 ppm, and (iii) the *ipso* and *ortho* carbons of the benzylic phenyl ring. The triplet at 0.95 ppm ($J = 7.1$ Hz) and the multiplet at 3.89–4.02 ppm are assigned to the ethyl of COOEt group. The aromatic protons give a multiplet at 7.09–7.62 ppm. The other [1,4]-thiazines (**4–29**) also show similar spectroscopic features.

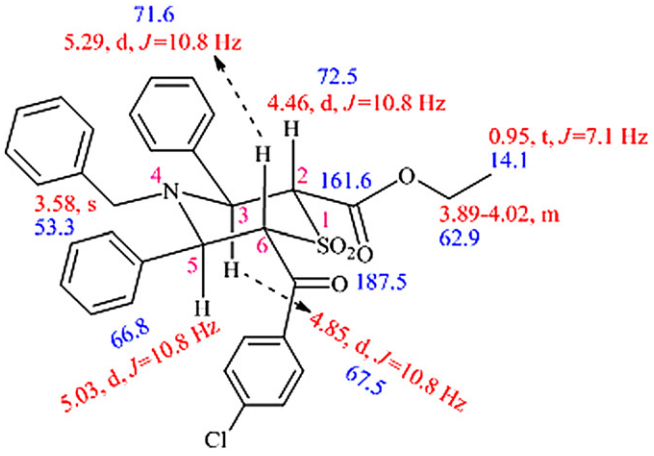


Fig. 1. ^{1}H and ^{13}C chemical shifts of **3**.

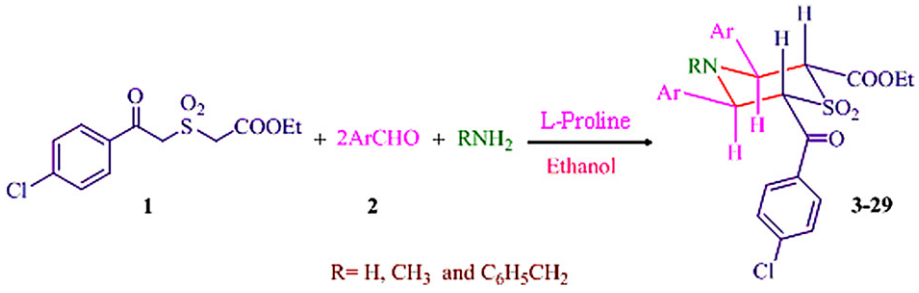
The probable mechanism for the formation of [1,4]-thiazines in presence of L-proline is depicted in Scheme 2. Presumably, the sulfone **1** reacts with L-proline affording the enamine **30**, which reacts with one mole of aldehyde to furnish the iminium intermediate **31**. This intermediate **31** forms the α,β-unsaturated iminium ion **32** (**a** and **b**), whose activity is enhanced by (i) the polarization of the positively charged conjugated eniminium functionality and (ii) the possible hydrogen bonding between carboxyl hydrogen and sulfonyl oxygen. Hence **32** could undergo facile Michael addition with amine to furnish **33**, which ultimately forms thiazines (**3–29**) in good yields via the intramolecular Mannich type reaction of the iminium intermediate **34**.

The essentially non-enantioselective catalysis by L-proline in this reaction is presumably explicable by the existence of the eniminium intermediate **32** in two conformations **32a** and **32b** each of which probably facilitates subsequent Michael addition of the amine on opposite faces of the eniminium functionality, from the side opposite to that of the carboxyl group of proline due to steric interaction with the incoming Michael donor, the amine.

3. Pharmacology

The [1,4]-thiazines (**3–29**) were screened *in vitro* for their antimycobacterial activity against MTB, MDR-TB and MC^2 and the MIC values were determined in duplicate by agar dilution method [18]. The MDR-TB clinical isolate was resistant to isoniazid. The MIC, defined as the minimum concentration of compound required to completely inhibit the bacterial growth, of the synthesized compounds and the standard drugs for comparison, are reported in Table 1.

When screened against MTB, all the compounds showed excellent *in vitro* activity with MIC ranging from 0.68 to 20.29 μM.



Scheme 1. Synthesis of [1,4]-thiazines.

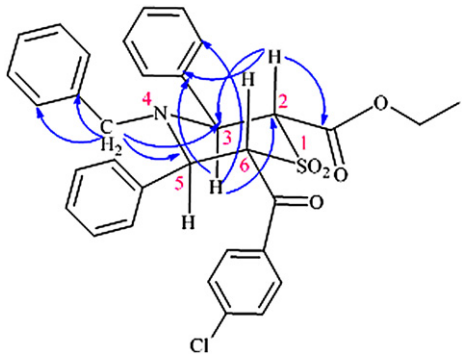
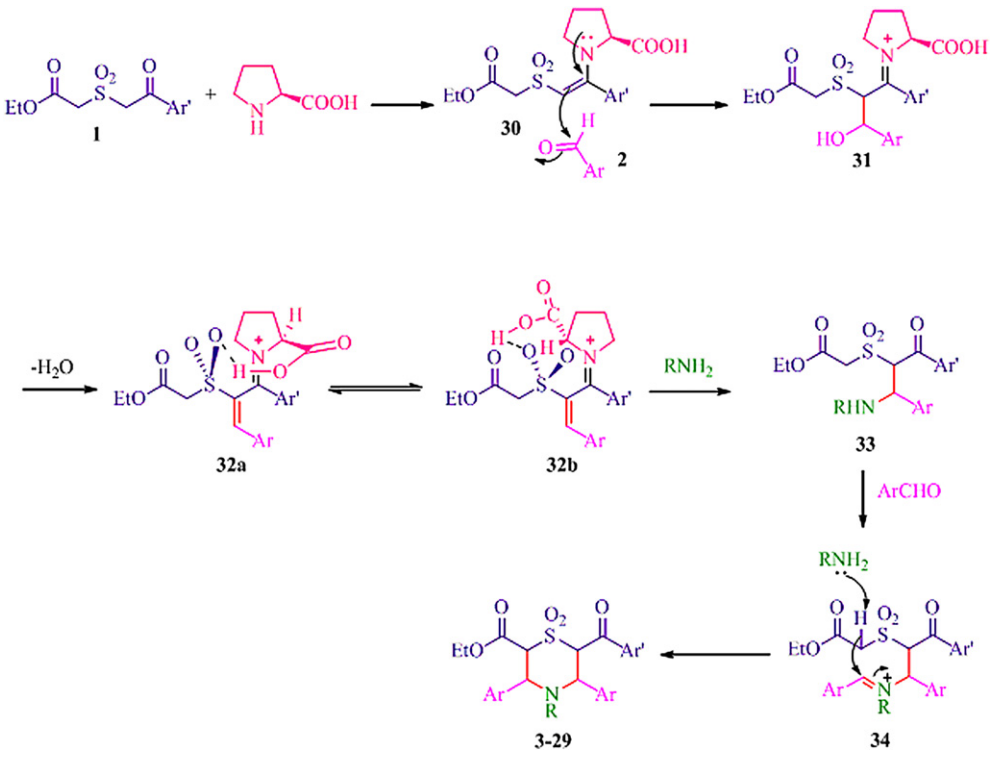


Fig. 2. HMBCs of **3**.

The influence of the groups attached to nitrogen of the thiazines, *viz.* HN-thiazines (**16–29**), MeN-thiazines (**9–15**) and $PhCH_2N$-thiazines (**3–8**) on the antimycobacterial activity against MTB deserves comment. Among MeN-thiazines, three compounds (**10**, **13** and **15**) displayed a MIC of 5.39, 6.36 and 5.80 respectively, while in the $PhCH_2N$-thiazines series, only one compound (**5**) (MIC = 5.02) showed an equal activity. Further, four HN-thiazines (**20**, **24**, **27** and **28**) showed MIC values ranging from 5.32 to 6.55 and six HN-thiazines (**17**–**19**, **22**, **26** and **29**) showed a higher activity with MIC values ranging from 0.68 to 3.03. From the above results, a general trend emerges, the order of activity being: HN-thiazines > MeN-thiazines > $PhCH_2N$-thiazines. This can probably be ascribed to enhancement of the activity of the thiazine pharmacophore by either the hydrogen donor property of the thiazines which is available only in NH thiazines or accessibility of lone pair of electrons on the nitrogen for hydrogen bonding interactions or both. The enhanced steric congestion at nitrogen in MeN- and $PhCH_2N$-thiazines could also diminish the accessibility of lone pair of electrons on the nitrogen lowering their activity relative to the HN-thiazines.

The HN-thiazines (**19**) and (**22**) with *para*-methoxy (MIC = 0.72) and *para*-nitro phenyl group (MIC = 0.68) respectively showed the highest activity against MTB. When the nitro group is either at the *ortho*- (**26**) or *meta*- (**20**) position of the phenyl ring of HN-thiazines, the activity is diminished with MIC values of 3.03 and 5.32 respectively relative to the *para*-nitro analog (**22**) with the MIC of 0.68 disclosing that the activity is sensitive to the position of the substituent in the aryl ring. The HN-thiazine with *para*-NMe_2 (**25**) group showed much less activity (MIC = 10.70) than that with either *para*-NO_2 (**22**) or *para*-MeO group (**19**), suggesting that besides electronic effects other factors also influence the activity. Among the halogenated HN-thiazines, it is found that the order of activity is: 2,4-dichloro > 4-chloro > 3-fluoro with their MIC values respectively being 1.23, 2.75 and 5.86. Among the heteroaryl compounds, the [1,4]-thiazine with 2-furyl group (**28**: MIC = 6.55) is found to be twice as active as the 2-thienyl group (**21**: MIC = 12.25). When the aryl ring in HN-thiazine is phenyl, 1-naphthyl or *para*-dimethyaminophenyl, the activity is diminished, the MIC value of these compounds being 12.55, 10.45 and10.70 respectively. The most active thiazine (**22**) against MTB with MIC of 0.68 is 11 and 75 times more active than ethambutol and pyrazinamide respectively, while its activity is 2 and 6 times less than that of isoniazid and rifampicin respectively.

Only four HN-thiazines (**17**, **18**, **19** and **22**) with enhanced activity with respect to MTB were tested against MDR-TB as representative examples. It is gratifying to note that all these compounds (**17**, **18**, **19** and **22**) showed greater activity against MDR-TB than all the four standard first line drugs, except **17** which showed one-sixth activity of rifampicin. The thiazine (**22**) with *para*-nitro group showed the highest activity against MDR-TB, being 67, 6, 90, 597 times higher than that of isoniazid, rifampicin, ethambutol and pyrazinamide respectively. The activity of the compounds against MDR-TB is significantly influenced by the substituent in the aryl ring of the thiazines, the order of activity being: **22** (4-$O_2NC_6H_4$) > **19** (4-$H_3COC_6H_4$) > **18** (4-$H_3CC_6H_4$) > **17**



Scheme 2. Mechanism for the formation of [1,4]-thiazines.

Table 1
Yield, physical constant, and antimycobacterial activity of [1,4]-thiazines.

Thiazine	R	Ar	Yield (%)	m.p. (°C)	MIC (μM)		
					MTB	MDR-TB	MC^2
3	$C_6H_5CH_2$	C_6H_5	76	163	42.51	NT	42.51
4	$C_6H_5CH_2$	4-ClC_6H_4	78	161	9.51	NT	38.05
5	$C_6H_5CH_2$	4-FC_6H_4	72	139	5.02	NT	40.06
6	$C_6H_5CH_2$	3-FC_6H_4	78	162	10.01	NT	40.06
7	$C_6H_5CH_2$	4-$H_3CC_6H_4$	76	168	20.29	NT	40.57
8	$C_6H_5CH_2$	4-$H_3COC_6H_4$	79	102	9.64	NT	NT
9	CH_3	C_6H_5	87	176	24.41	NT	48.83
10	CH_3	4-ClC_6H_4	85	172	5.39	NT	43.04
11	CH_3	2-$H_3CC_6H_4$	83	167	11.57	NT	23.15
12	CH_3	2-BrC_6H_4	88	173	9.33	NT	18.66
13	CH_3	2-furyl	90	154	6.36	NT	50.82
14	CH_3	3-$O_2NC_6H_4$	82	190	20.76	NT	41.53
15	CH_3	4-$H_3CC_6H_4$	83	149	5.80	NT	NT
16	H	C_6H_5	90 (72)[a]	140	12.55	NT	50.20
17	H	4-ClC_6H_4	89	134	2.75	5.52	11.03
18	H	4-$H_3CC_6H_4$	88 (69)[a]	153	1.48	1.48	2.97
19	H	4-$H_3COC_6H_4$	90	128	0.72	1.40	1.40
20	H	3-$O_2NC_6H_4$	87	151	5.32	NT	10.63
21	H	2-thienyl	84	195	12.25	NT	12.25
22	H	4-$O_2NC_6H_4$	90	173	0.68	0.68	10.63
23	H	1-naphthyl	82	180	10.45	NT	20.90
24	H	2-$H_3COC_6H_4$	81	166	5.61	NT	11.20
25	H	4-$(Me)_2NC_6H_4$	87	158	10.70	NT	NT
26	H	2-$O_2NC_6H_4$	85	178	3.03	NT	NT
27	H	3-FC_6H_4	88	165	5.86	NT	NT
28	H	2-furyl	86	163	6.55	NT	NT
29	H	2,4-$Cl_2C_6H_3$	82	202	1.23	NT	NT
Isoniazid					0.36	45.57	45.57
Rifampicin					0.12	3.80	NT
Ethambutol					7.64	61.18	NT
Pyrazinamide					50.77	406.13	NT

[a] Yields in parentheses from Ref. [17]. MTB: *M. tuberculosis*; MDR-TB: multi-drug resistant *M. tuberculosis*; NT: not tested.

(4-ClC_6H_4). Most of the thiazines evaluated against MC^2 have MIC values ranging from 1.40 to 50.82 μM.

4. Conclusion

The present work describes a four-component reaction of ethyl 2-[(2-oxo-2-arylethyl)sulfonyl]acetate, substituted aromatic aldehydes and amines in presence of green catalyst, L-proline providing a rapid access to the biologically important [1,4]-thiazines. The antimycobacterial potency of these compounds renders them valid leads for synthesizing new compounds endowed with enhanced activity.

5. Experimental protocols

Melting points reported in this work are uncorrected. The ^1H NMR, ^{13}C NMR, H,H-COSY, C,H-COSY and HMBC spectra were recorded on a Bruker (Avance) 300 MHz instrument using $CDCl_3$ and DMSO-d_6 as solvent. 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 method). Elemental analyses were performed on a Perkin–Elmer 2400 Series II Elemental CHN Analyser. HPLC analysis was carried out on a SHIMADZU SCL-10A vp model with CHIRALCEL OD-H column using *n*-hexane/isopropyl alcohol [90:10 (v/v)] eluent at a flow rate of 0.5 mL/min.

5.1. General procedure for the preparation of ethyl 6-(4-chlorobenzoyl)-1,1-dioxo-3,5-diaryl-1,4-thiazinane-2-carboxylates

To a solution of ammonia/primary amine (1.6 mmol) and L-proline (30 mol%) in ethanol (10 mL), aromatic aldehyde (3.2 mmol) and ethyl 2-[(2-oxo-2-arylethyl)sulfonyl]acetate (1.6 mmol) were added and the reaction mixture was kept at room temperature for 2–4 h. The solid obtained was recrystallised from ethanol–ethyl acetate mixture (7:3 v/v).

*5.1.1. (±)-Ethyl 4-benzyl-6-(4-chlorobenzoyl)-1,1-dioxo-3,5-diphenyl-1,4-thiazinane-2-carboxylate (**3**)*

Isolated as colorless solid (441 mg, 76%) m.p = 163 °C; IR (KBr) 1730, 1680, 1315, 1142 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.95 (3H, t, *J* = 7.1 Hz, $COOCH_2CH_3$), 3.58 (2H, s, NCH_2Ph), 3.89–4.02 (2H, m, $COOCH_2CH_3$), 4.46 (1H, d, *J* = 10.8 Hz, H-2), 4.85 (1H, d, *J* = 10.8 Hz, H-3), 5.03 (1H, d, *J* = 10.8 Hz, H-5), 5.29 (1H, d, *J* = 10.8 Hz, H-6), 7.09–7.62 (19H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.1, 53.3, 63.0, 66.8, 67.5, 71.6, 72.5, 127.3, 127.4, 128.3, 128.7, 128.9, 129.1, 129.2, 129.3, 129.5, 130.2, 136.1, 137.1, 137.4, 137.6, 140.9, 161.6, 187.5. Anal. Calcd. For $C_{33}H_{30}ClNO_5S$: C, 67.39; H, 5.14; N, 2.38; Obsd. C, 67.34; H, 5.18; N, 2.42.

*5.1.2. (±)-Ethyl 4-benzyl-6-(4-chlorobenzoyl)-3,5-di(4-chlorophenyl)-1,1-dioxo-1,4-thiazinane 2-carboxylate (**4**)*

Isolated as colorless solid (505 mg, 78%) m.p = 161 °C; IR (KBr) 1724, 1678, 1320, 1138 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.01 (3H, t, *J* = 7.2 Hz, $COOCH_2CH_3$), 3.52 (2H, s, NCH_2Ph), 4.01 (2H, q, *J* = 7.2 Hz, $COOCH_2CH_3$), 4.43 (1H, d, *J* = 10.8 Hz, H-2), 4.82 (1H, d, *J* = 10.8 Hz, H-3), 5.03 (1H, d, *J* = 10.8 Hz, H-5), 5.26 (1H, d, *J* = 10.8 Hz, H-6), 7.08–7.68 (17H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.7, 53.4, 62.9, 66.1, 66.6, 70.8, 71.7, 128.1, 128.4, 128.9, 129.1, 129.3, 129.4, 129.6, 129.9, 130.4, 134.5, 134.6, 134.8, 135.4, 135.6, 136.6, 140.9, 160.9, 186.5. Anal. Calcd. For $C_{33}H_{28}Cl_3NO_5S$: C, 60.33; H, 4.30; N, 2.13; Obsd. C, 60.30; H, 4.25; N, 2.20.

*5.1.3. (±)-Ethyl 4-benzyl-6-(4-chlorobenzoyl)-3,5-di(4-fluorophenyl)-1,1-dioxo-1,4-thiazinane 2-carboxylate (**5**)*

Isolated as colorless solid (444 mg, 72%) m.p = 139 °C; IR (KBr) 1734, 1684, 1318, 1140 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.98 (3H, t, *J* = 7.1 Hz, $COOCH_2CH_3$), 3.53 (2H, s, NCH_2Ph), 3.98–4.01 (2H, m, $COOCH_2CH_3$), 4.51 (1H, d, *J* = 11 Hz, H-2), 4.83 (1H, d, *J* = 11 Hz, H-3), 5.02 (1H, d, *J* = 10.5 Hz, H-5), 5.33(1H, d, *J* = 10.5 Hz, H-6), 6.79–7.67 (17H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.7, 53.2, 62.7, 66.1, 66.8, 70.6, 71.7, 115.4, 115.7, 116.1, 126.8, 127.9, 128.1, 128.2, 128.5, 128.9, 129.4, 129.6, 129.9, 130.9, 132.7, 135.3, 136.9, 140.8, 161.2, 162.0, 163.8, 164.3, 186.9; Anal. Calcd. For $C_{33}H_{28}ClF_2NO_5S$: C, 63.51; H, 4.52; N, 2.24; Obsd. C, 63.57; H, 4.50; N, 2.32.

*5.1.4. (±)-Ethyl 4-benzyl-6-(4-chlorobenzoyl)-3,5-di(3-fluorophenyl)-1,1-dioxo-1,4-thiazinane 2-carboxylate (**6**)*

Isolated as colorless solid (480 mg, 78%) m.p = 162 °C; IR (KBr) 1734, 1678, 1317, 1139 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.98 (3H, t, *J* = 6.9 Hz, $COOCH_2CH_3$), 3.59 (2H, s, NCH_2Ph), 3.97–4.08 (2H, m, $COOCH_2CH_3$), 4.47 (1H, d, *J* = 11 Hz, H-2), 4.86 (1H, d, *J* = 11 Hz, H-3), 5.06 (1H, d, *J* = 10.8 Hz, H-5), 5.30 (1H, d, *J* = 10.8 Hz, H-6), 6.98–7.68 (17H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.7, 53.3, 62.8, 65.9, 66.6, 70.6, 71.6, 115.7, 116.0, 116.3, 125.0, 127.2, 128.1, 128.6, 129.0, 129.9, 130.3, 130.4, 135.3, 136.1, 139.4, 139.5, 139.6, 139.7, 140.9, 160.9, 161.4, 162.1, 167.9, 186.6; Anal. Calcd. For $C_{33}H_{28}ClF_2NO_5S$: C, 63.51; H, 4.52; N, 2.24; Obsd. C, 63.57; H, 4.50; N, 2.32.

*5.1.5. (±)-Ethyl 4-benzyl-6-(4-chlorobenzoyl)-3,5-di(4-methylphenyl)-1,1-dioxo-1,4-thiazinane 2-carboxylate (**7**)*

Isolated as colorless solid (462 mg, 76%) m.p = 168 °C; IR (KBr) 1724, 1683, 1317, 1146 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.01 (3H, t, *J* = 6.9 Hz, $COOCH_2CH_3$), 2.16 (3H, s, CH_3), 2.30 (3H, s, CH_3), 3.55 (2H, s, NCH_2Ph), 3.93–4.04 (2H, m, $COOCH_2CH_3$), 4.42 (1H, d, *J* = 10.8 Hz, H-2), 4.77 (1H, d, *J* = 10.8 Hz, H-3), 4.96 (1H, d, *J* = 10.7 Hz, H-5), 5.26 (1H, d, *J* = 10.7 Hz, H-6), 6.75–7.64 (17H, m,

Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.1, 21.4, 21.5, 53.2, 62.9, 66.6, 67.2, 71.6, 72.6, 127.0, 128.2, 129.2, 129.4, 129.7, 130.3, 134.4, 134.6, 136.2, 137.5, 138.8, 139.1, 140.8, 161.6, 187.5; Anal. Calcd. For $C_{35}H_{34}ClNO_5S$: C, 68.22; H, 5.56; N, 2.27; Obsd. C, 68.28; H, 5.61; N, 2.23.

*5.1.6. (±)-Ethyl 4-benzyl-6-(4-chlorobenzoyl)-3,5-di(4-methoxyphenyl)-1,1-dioxo-1,4-thiazinane 2-carboxylate (**8**)*

Isolated as colorless solid (506 mg, 79%) m.p = 102 °C; IR (KBr) 1740, 1675, 1300, 1150 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.01 (3H, t, J = 6.9 Hz, $COOCH_2CH_3$), 3.56 (2H, s, NCH_2Ph), 3.66 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.99–4.03 (2H, m, $COOCH_2CH_3$), 4.51 (1H, d, J = 10.8 Hz, H-2), 4.78 (1H, d, J = 10.8 Hz, H-3), 4.96 (1H, d, J = 10.5 Hz, H-5), 5.34 (1H, d, J = 10.5 Hz, H-6), 6.63–7.66 (17H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.7, 52.8, 55.1, 55.2, 62.5, 65.9, 66.6, 71.0, 72.1, 113.9, 126.5, 127.7, 128.5, 128.8, 128.9, 129.1, 129.9, 130.3, 135.6, 137.3, 140.4, 159.3, 159.7, 161.3, 187.1; Anal. Calcd. For $C_{35}H_{34}ClNO_7S$: C, 64.86; H, 5.29; N, 2.16; Obsd. C, 64.91; H, 5.32; N, 2.21.

*5.1.7. (±)-Ethyl 6-(4-chlorobenzoyl)-4-methyl-1,1-dioxo-3,5-diphenyl-1,4-thiazinane-2-carboxylate (**9**)*

Isolated as colorless solid (439 mg, 87%) m.p = 176 °C; IR (KBr) 1730, 1684, 1315, 1147 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.97 (3H, t, J = 6.9 Hz, $COOCH_2CH_3$), 1.78 (3H, s, NCH_3), 3.97–4.05 (2H, m, $COOCH_2CH_3$), 4.36 (1H, d, J = 11 Hz, H-2), 4.49 (1H, d, J = 11 Hz, H-3), 4.54 (1H, d, J = 10.8 Hz, H-5), 5.33(1H, d, J = 10.8 Hz, H-6), 7.10–7.65 (14H, m, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 12.6, 36.3, 61.0, 66.6, 67.8, 68.4, 68.9, 126.1, 126.7, 127.2, 127.5, 127.6, 128.6, 128.9, 129.4, 134.4, 137.4, 137.5, 139.2, 160.7, 186.7; Anal. Calcd. For $C_{27}H_{26}ClNO_5S$: C, 63.34; H, 5.12; N, 2.74; Obsd. C, 63.30; H, 5.17; N, 2.68.

*5.1.8. (±)-Ethyl 6-(4-chlorobenzoyl)-3,5-di(4-chlorophenyl)-4-methyl-1,1-dioxo-1,4-thiazinane-2-carboxylate (**10**)*

Isolated as colorless solid (487 mg, 85%) m.p = 172 °C; IR (KBr) 1735, 1676, 1315, 1145 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.03 (3H, t, J = 6.9 Hz, $COOCH_2CH_3$), 1.76 (3H, s, NCH_3), 3.99–4.06 (2H, m, $COOCH_2CH_3$), 4.34 (1H, d, J = 11 Hz, H-2), 4.45 (1H, d, J = 11 Hz, H-3), 4.54 (1H, d, J = 10.7 Hz, H-5), 5.28 (1H, d, J = 10.7 Hz, H-6), 7.17–7.69 (12H, m, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 12.9, 36.5, 61.5, 66.8, 67.8, 68.3, 68.9, 127.9, 128.0, 128.3, 129.0, 129.7, 130.1, 132.9, 133.3, 134.4, 136.3, 136.5, 139.8, 160.7, 186.8; Anal. Calcd. For $C_{27}H_{24}Cl_3NO_5S$: C, 55.82; H, 4.16; N, 2.41; Obsd. C, 55.77; H, 4.24; N, 2.46.

*5.1.9. (±)-Ethyl 6-(4-chlorobenzoyl)-4-methyl-3,5-di(2-methylphenyl)-1,1-dioxo-1,4-thiazinane- 2-carboxylate (**11**)*

Isolated as colorless solid (442 mg, 83%) m.p = 167 °C; IR (KBr) 1738, 1700, 1318, 1148 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.93 (3H, t, J = 6.9 Hz, $COOCH_2CH_3$), 1.75 (3H, s, NCH_3), 2.16 (3H, s, CH_3), 2.49 (3H, s, CH_3), 3.92–4.04 (2H, m, $COOCH_2CH_3$), 4.59 (1H, d, J = 11 Hz, H-2), 4.79 (1H, d, J = 11 Hz, H-3), 4.92 (1H, d, J = 10.5 Hz, H-5), 5.44 (1H, d, J = 10.5 Hz, H-6), 6.98–7.70 (12H, m, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 12.7, 19.0, 19.1, 35.5, 61.2, 62.7, 63.3, 67.6, 68.6, 125.6, 126.3, 126.6, 126.9, 127.2, 127.8, 129.6, 131.0, 134.6, 135.6, 135.7, 136.0, 139.4, 160.9, 186.7; Anal. Calcd. For $C_{29}H_{30}ClNO_5S$: C, 64.49; H, 5.60; N, 2.59; Obsd. C, 64.52; H, 5.67; N, 2.55.

*5.1.10. (±)-Ethyl 3,5-di(2-bromophenyl)-6-(4-chlorobenzoyl)-4-methyl-1,1-dioxo-1,4-thiazinane-2-carboxylate (**12**)*

Isolated as colorless solid (582 mg, 88%) m.p = 173 °C; IR (KBr) 1735, 1689, 1316, 1148 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H 0.91 (3H, t, J = 7.1 Hz, $COOCH_2CH_3$), 1.72 (3H, s, NCH_3), 3.87–3.94 (2H, m, $COOCH_2CH_3$), 4.95 (1H, d, J = 11 Hz, H-2), 5.08 (1H, d, J = 10.7 Hz, H-5), 5.28 (1H, d, J = 11 Hz, H-3), 6.15 (1H, d, J = 10.7 Hz, H-6), 6.90–7.84 (12H, m, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 13.5, 36.4, 62.2, 66.1, 66.5, 67.5, 68.5, 125.0, 125.3, 128.3, 128.5, 129.2, 129.4, 130.0, 130.2, 130.6, 130.7, 133.0, 135.1, 137.0, 137.3, 140.1, 161.2, 186.8. Anal. Calcd. For $C_{27}H_{24}Br_2ClNO_5S$: C, 48.42; H, 3.61; N, 2.09; Obsd. C, 48.39; H, 3.64; N, 2.05.

*5.1.11. (±)-Ethyl 6-(4-chlorobenzoyl)-3,5-di(2-furyl)-4-methyl-1,1-dioxo-1,4-thiazinane-2-carboxylate (**13**)*

Isolated as colorless solid (437 mg, 90%) m.p = 154 °C; IR (KBr) 1740, 1683, 1314, 1142 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H 1.00 (3H, t, J = 7.1 Hz, $COOCH_2CH_3$), 1.81 (3H, s, NCH_3), 4.01 (2H, q, J = 7.1 Hz, $COOCH_2CH_3$), 4.50 (1H, d, J = 11 Hz, H-2), 4.66 (1H, d, J = 10.8 Hz, H-5), 5.06 (1H, d, J = 11 Hz, H-3), 5.34 (1H, d, J = 10.8 Hz, H-6), 6.08–7.98 (10H, m, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 11.8, 32.9, 59.0, 60.0, 60.2, 62.3, 63.2, 108.1, 108.8, 127.2, 129.2, 133.0, 138.1, 141.0, 144.4, 148.0, 148.3, 159.6, 185.4. Anal. Calcd. For $C_{23}H_{22}ClNO_7S$: C, 56.15; H, 4.51; N, 2.85; Obsd. C, 56.18; H, 4.47; N, 2.82.

*5.1.12. (±)-Ethyl 6-(4-chlorobenzoyl)-4-methyl-3,5-di(3-nitrophenyl)-1,1-dioxo-1,4-thiazinane-2-carboxylate (**14**)*

Isolated as yellow solid (487 mg, 82%) m.p = 190 °C; IR (KBr) 1730, 1684, 1316, 1143 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H 1.01 (3H, t, J = 7.1 Hz, $COOCH_2CH_3$), 1.81 (3H, s, NCH_3), 4.01 (2H, q, J = 7.1 Hz, $COOCH_2CH_3$), 4.48 (1H, d, J = 11.1 Hz, H-2), 4.66 (1H, d, J = 10.7 Hz, H-5), 5.56 (1H, d, J = 11.1 Hz, H-3), 6.58 (1H, d, J = 10.7 Hz, H-6), 7.38–8.25 (12H, m, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 12.3, 38.9, 61.0, 66.6, 67.0, 67.4, 67.7, 121.7, 122.0, 122.4, 127.5, 128.6, 129.3, 133.6, 134.0, 139.4, 139.5, 139.6, 146.8, 147.0, 160.1, 185.9. Anal. Calcd. For $C_{27}H_{24}ClN_3O_9S$: C, 53.87; H, 4.02; N, 6.98; Obsd. C, 53.82; H, 3.97; N, 7.03.

*5.1.13. (±)-Ethyl 6-(4-chlorobenzoyl)-4-methyl-3,5-di(4-methylphenyl)-1,1-dioxo-1,4-thiazinane- 2-carboxylate (**15**)*

Isolated as colorless solid (442 mg, 83%) m.p = 149 °C; IR (KBr) 1724, 1682, 1318, 1146 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.99 (3H, t, J = 7.2 Hz, $COOCH_2CH_3$), 1.76 (3H, s, NCH_3), 2.33 (3H, s, CH_3), 2.37 (3H, s, CH_3), 3.96–4.06 (2H, m, $COOCH_2CH_3$), 4.30 (1H, d, J = 10.8 Hz, H-2), 4.47 (1H, d, J = 10.8 Hz, H-3), 4.49 (1H, d, J = 11 Hz, H-5), 5.38 (1H, d, J = 11 Hz, H-6), 6.97–7.99 (12H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.7, 21.0, 21.2, 40.0, 62.5, 68.9, 69.6, 70.8, 71.8, 128.2, 128.6, 128.9, 129.5, 130.0, 134.9, 135.1, 135.7, 138.3, 138.6, 140.5, 161.1, 186.8. Anal. Calcd. For $C_{29}H_{30}ClNO_5S$: C, 64.49; H, 5.60; N, 2.59; Obsd. C, 64.52; H, 5.67; N, 2.55.

*5.1.14. (±)-Ethyl 6-(4-chlorobenzoyl)-1,1-dioxo-3,5-diphenyl-1,4-thiazinane-2-carboxylate (**16**)*

Isolated as colorless solid (442 mg, 90%) m.p = 140 °C; IR (KBr) 3400, 1730, 1685, 1315, 1142 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.06 (3H, t, J = 7.1 Hz, $COOCH_2CH_3$), 2.01 (NH, br s), 4.05–4.12 (2H, m, $COOCH_2CH_3$), 4.37 (1H, d, J = 10.7 Hz, H-2), 4.80 (1H, d, J = 10.7 Hz, H-3), 5.01 (1H, d, J = 10.2 Hz, H-5), 5.23 (1H, d, J = 10.2 Hz, H-6), 7.18–7.81 (14H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.2, 62.3, 62.8, 63.1, 73.0, 73.6, 128.3, 128.4, 129.3, 129.4, 129.6, 130.7, 136.0, 138.2, 138.3, 141.2, 161.5, 187.0. E.e = 4.8% determined by HPLC: CHIRALCEL OD-H column; *n*-hexane/isopropyl alcohol [90:10 (v/v)]; flow rate: 0.5 mL/min; λ = 254 nm; t_R (major) = 38.18 min; t_R (minor) = 65.09 min. Anal. Calcd. For $C_{26}H_{24}ClNO_5S$: C, 62.71; H, 4.86; N, 2.81; Obsd. C, 62.77; H, 4.91; N, 2.79.

*5.1.15. (±)-Ethyl 6-(4-chlorobenzoyl)-3,5-di(4-chlorophenyl)-1,1-dioxo-1,4-thiazinane-2-carboxylate (**17**)*

Isolated as colorless solid (498 mg, 89%) m.p = 134 °C; IR (KBr) 3295, 1726, 1680, 1320, 1145 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H

1.11 (3H, t, $J = 7.2$ Hz, $COOCH_2CH_3$), 2.03 (NH, br s), 4.05–4.17 (2H, m, $COOCH_2CH_3$), 4.28 (1H, d, $J = 10.5$ Hz, H-2), 4.77 (1H, d, $J = 10.5$ Hz, H-3), 4.99 (1H, d, $J = 10.4$ Hz, H-5), 5.14 (1H, d, $J = 10.4$ Hz, H-6), 7.20–7.89 (12H, m, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 13.7, 61.1, 61.4, 62.1, 69.1, 70.1, 128.5, 128.6, 129.3, 130.0, 130.8, 132.8, 133.1, 135.4, 137.6, 138.9, 140.3, 161.8, 188.0. Anal. Calcd. For $C_{26}H_{22}Cl_3NO_5S$: C, 55.09; H, 3.91; N, 2.47; Obsd. C, 55.05; H, 3.93; N, 2.51.

*5.1.16. (±)-Ethyl 6-(4-chlorobenzoyl)-3,5-di(4-methoxyphenyl)-1,1-dioxo-1,4-thiazinane-2-carboxylate (**19**)*

Isolated as colorless solid (496 mg, 90%) m.p = 128 °C; IR (KBr) 3495, 1728, 1685, 1320, 1146 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.09 (3H, t, $J = 7.1$ Hz, $COOCH_2CH_3$), 2.01 (NH, br s), 3.70 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 4.07–4.14 (2H, m, $COOCH_2CH_3$), 4.29 (1H, d, $J = 10.5$ Hz, H-2), 4.72 (1H, d, $J = 10.5$ Hz, H-3), 4.93 (1H, d, $J = 10.2$ Hz, H-5), 5.15 (1H, d, $J = 10.2$ Hz, H-6), 6.73 (2H, d, $J = 8.7$ Hz, Ar-H), 6.86 (2H, d, $J = 8.7$ Hz, Ar-H), 7.26–7.41 (6H, m, Ar-H), 7.80 (2H, d, $J = 8.7$ Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.8, 55.1, 55.3, 61.2, 61.7, 62.6, 72.6, 73.2, 114.1, 114.2, 127.4, 128.9, 129.1, 129.8, 129.9, 130.1, 130.3, 159.7, 160.0, 161.2, 186.7. Anal. Calcd. For $C_{28}H_{28}ClNO_7S$: C, 60.26; H, 5.06; N, 2.51; Obsd. C, 60.31; H, 5.03; N, 2.48.

*5.1.17. (±)-Ethyl 6-(4-chlorobenzoyl)-3,5-di(3-nitrophenyl)-1,1-dioxo-1,4-thiazinane-2-carboxylate (**20**)*

Isolated as yellow solid (503 mg, 87%) m.p = 151 °C; IR (KBr) 3285, 1732, 1678, 1317, 1138 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H 1.03 (3H, t, $J = 7.1$ Hz, $COOCH_2CH_3$), 3.17 (NH, br s), 4.02–4.06 (2H, m, $COOCH_2CH_3$), 4.89 (1H, d, $J = 10.8$ Hz, H-2), 5.06 (1H, d, $J = 10.2$ Hz, H-5), 5.15 (1H, d, $J = 10.8$ Hz, H-3), 6.32 (1H, d, $J = 10.2$ Hz, H-6), 7.32–8.51 (12H, m, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 12.3, 59.6, 60.0, 60.8, 67.7, 68.4, 121.2, 121.4, 121.8, 122.1, 127.5, 128.3, 128.4, 129.3, 133.6, 133.7, 133.8, 139.1, 139.2, 139.3, 146.4, 146.6, 160.1, 186.1. Anal. Calcd. For $C_{26}H_{22}ClN_3O_9S$: C, 53.11; H, 3.77; N, 7.15; Obsd. C, 53.16; H, 3.82; N, 7.21.

*5.1.18. (±)-Ethyl 6-(4-chlorobenzoyl)-1,1-dioxo-3,5-di(2-thienyl)-1,4-thiazinane-2-carboxylate (**21**)*

Isolated as colorless solid (423 mg, 84%) m.p = 195 °C; IR (KBr) 3328, 1730, 1685, 1315, 1140 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.14 (3H, t, $J = 7.1$ Hz, $COOCH_2CH_3$), 2.52 (NH, br s), 4.16 (2H, q, $J = 7.1$ Hz, $COOCH_2CH_3$), 4.29 (1H, d, $J = 10.5$ Hz, H-2), 5.15 (1H, d, $J = 10.5$ Hz, H-3), 5.16 (1H, d, $J = 10.1$ Hz, H-5), 5.35 (1H, d, $J = 10.1$ Hz, H-6), 6.81–7.85 (10H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.8, 57.2, 57.8, 62.8, 72.8, 73.5, 125.9, 126.2, 126.7, 127.0, 127.4, 129.1, 130.4, 135.4, 140.1, 140.2, 141.0, 160.9, 186.4. Anal. Calcd. For $C_{22}H_{20}ClNO_5S_3$: C, 51.81; H, 3.95; N, 2.75; Obsd. C, 51.84 H, 4.01; N, 2.72.

*5.1.19. (±)-Ethyl 6-(4-chlorobenzoyl)-3,5-di(4-nitrophenyl)-1,1-dioxo-1,4-thiazinane-2-carboxylate (**22**)*

Isolated as yellow solid (522 mg, 90%) m.p = 173 °C; IR (KBr) 3402, 1734, 1675, 1318, 1140 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H 1.09 (3H, t, $J = 7.2$ Hz, $COOCH_2CH_3$), 2.79 (NH, br s), 4.02–4.16 (2H, m, $COOCH_2CH_3$), 4.90 (1H, d, $J = 10.5$ Hz, H-2), 5.01 (1H, d, $J = 10.5$ Hz, H-3), 5.10 (1H, d, $J = 10.4$ Hz, H-5), 6.01 (1H, d, $J = 10.4$ Hz, H-6), 7.42–8.29 (12H, m, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 12.8, 60.3, 60.7, 61.6, 68.7, 69.3, 122.6, 126.8, 128.1, 128.2, 128,5, 129.6, 129.8, 134.2, 140.0, 144.5, 146.6, 146.8, 160.5, 186.3. Anal. Calcd. For $C_{26}H_{22}ClN_3O_9S$: C, 53.11; H, 3.77; N, 7.15; Obsd. C, 53.16; H, 3.82; N, 7.21.

*5.1.20. (±)-Ethyl 6-(4-chlorobenzoyl)-3,5-di(1-naphthyl)-1,1-dioxo-1,4-thiazinane-2-carboxylate (**23**)*

Isolated as colorless solid (484 mg, 82%) m.p = 180 °C; IR (KBr) 3230, 1728, 1687, 1318, 1142 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H 1.09 (3H, t, $J = 7.2$ Hz, $COOCH_2CH_3$), 2.45 (NH, br s), 4.07–4.14 (2H, m, $COOCH_2CH_3$), 4.49 (1H, d, $J = 10.5$ Hz, H-2), 4.81 (1H, d, $J = 10.5$ Hz, H-3), 4.98 (1H, d, $J = 10.2$ Hz, H-5), 5.35 (1H, d, $J = 10.2$ Hz, H-6), 7.25–7.81 (18H, m, Ar-H), ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 13.5, 54.1, 56.3, 62.0, 69.3, 72.6, 122.4, 123.4, 124.9, 125.9, 126.2, 126.6, 127.3, 128.5, 129.0, 129.8, 130.7, 130.9, 131.5, 132.6, 133.4, 135.3, 136.2, 136.3, 137.3, 140.3, 162.2, 188.0. Anal. Calcd. For $C_{34}H_{28}ClNO_5S$: C, 68.28; H, 4.72; N, 2.34; Obsd. C, 68.23; H, 4.69; N, 2.38.

*5.1.21. (±)-Ethyl 6-(4-chlorobenzoyl)-3,5-di(2-methoxyphenyl)-1,1-dioxo-1,4-thiazinane-2-carboxylate (**24**)*

Isolated as colorless solid (446 mg, 81%) m.p = 166 °C; IR (KBr) 3430, 1735, 1678, 1310, 1145 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.01 (3H, t, $J = 7.1$ Hz, $COOCH_2CH_3$), 1.98 (NH, br s), 3.82 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.03 (2H, q, $J = 7.1$ Hz, $COOCH_2CH_3$), 4.92 (1H, d, $J = 11.1$ Hz, H-2), 4.96 (1H, d, $J = 11.1$ Hz, H-3), 5.70 (1H, d, $J = 10.2$ Hz, H-5), 6.43 (1H, d, $J = 10.2$ Hz, H-6), 6.67–7.76 (12H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.8, 55.2, 55.4, 61.9, 62.3, 62.8, 68.6, 69.5, 110.9, 111.2, 121.2, 121.5, 124.7, 128.9, 129.8, 130.0, 131.4, 131.9, 136.0, 140.4, 156.7, 157.2, 162.1, 188.0. Anal. Calcd. For $C_{28}H_{28}ClNO_7S$: C, 60.26; H, 5.06; N, 2.51; Obsd. C, 60.31; H, 5.03; N, 2.48.

*5.1.22. (±)-Ethyl 6-(4-chlorobenzoyl)-3,5-di[4-(dimethylamino)phenyl]-1,1-dioxo-1,4-thiazinane-2-carboxylate (**25**)*

Isolated as yellow solid (502 mg, 87%) m.p = 158 °C; IR (KBr) 3199, 1728, 1684, 1317, 1143 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.10 (3H, t, $J = 7.2$ Hz, $COOCH_2CH_3$), 1.97 (NH, br s), 2.81 (3H, s, Ar-N(CH_3)$_2$), 2.84 (3H, s, Ar-N(CH_3)$_2$), 2.93 (3H, s, Ar-N(CH_3)$_2$), 2.95 (3H, s, Ar-N(CH_3)$_2$), 4.05–4.15 (2H, m, $COOCH_2CH_3$), 4.29 (1H, d, $J = 10.7$ Hz, H-2), 4.65 (1H, d, $J = 10.7$ Hz, H-3), 4.86 (1H, d, $J = 10.2$ Hz, H-5), 5.16 (1H, d, $J = 10.2$ Hz, H-6), 6.42–7.84 (12H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.9, 40.2, 40.3, 40.4, 40.5, 61.2, 61.7, 62.4, 72.6, 73.3, 112.1, 112.2, 125.5, 128.4, 128.5, 128.7, 128.9, 129.8, 130.4, 135.8, 150.4, 150.7, 161.4, 186.9. Anal. Calcd. For $C_{30}H_{34}ClN_3O_5S$: C, 61.69; H, 5.87; N, 7.19; Obsd. C, 61.71; H, 5.84; N, 7.22.

*5.1.23. (±)-Ethyl 6-(4-chlorobenzoyl)-3,5-di(2-nitrophenyl)-1,1-dioxo-1,4-thiazinane-2-carboxylate (**26**)*

Isolated as yellow solid (493 mg, 85%) m.p = 178 °C; IR (KBr) 3319, 1735, 1687, 1318, 1139 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.99 (3H, t, $J = 7.2$ Hz, $COOCH_2CH_3$), 2.56 (NH, br s), 4.05–4.12 (2H, m, $COOCH_2CH_3$), 5.22 (1H, d, $J = 11.1$ Hz, H-2), 5.28 (1H, d, $J = 11.1$ Hz, H-3), 5.48 (1H, d, $J = 11.1$ Hz, H-5), 6.37 (1H, d, $J = 11.1$ Hz, H-6), 7.36–7.91 (12H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.7, 56.5, 62.6, 63.3, 66.6, 67.8, 124.9, 125.6, 127.9, 129.1, 130.7, 130.9, 132.6, 133.1, 133.8, 134.9, 141.3, 141.5, 147.9, 149.9, 150.2, 150.4, 164.8, 186.7. Anal. Calcd. For $C_{26}H_{22}ClN_3O_9S$: C, 53.11; H, 3.77; N, 7.15; Obsd. C, 53.16; H, 3.82; N, 7.21.

*5.1.24. (±)-Ethyl 6-(4-chlorobenzoyl)-3,5-di(3-fluorophenyl)-1,1-dioxo-1,4-thiazinane-2-carboxylate (**27**)*

Isolated as colorless solid (464 mg, 88%) m.p = 165 °C; IR (KBr) 3450, 1729, 1682, 1320, 1138 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.09 (3H, t, $J = 7.2$ Hz, $COOCH_2CH_3$), 2.12 (NH, br s), 4.08–4.15 (2H, m, $COOCH_2CH_3$), 4.35 (1H, d, $J = 10.7$ Hz, H-2), 4.81 (1H, d, $J = 10.7$ Hz, H-3), 5.02 (1H, d, $J = 10.2$ Hz, H-5), 5.20 (1H, d, $J = 10.2$ Hz, H-6), 6.90–7.83 (12H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.8, 61.2, 61.7, 62.9, 72.3, 72.9, 114.6, 114.7, 114.9, 115.0, 115.9, 116.2, 116.5, 123.9, 128.6, 129.1, 130.4, 130.6, 135.2, 139.9, 140.0, 140.1, 141.2, 160.8, 186.2. Anal. Calcd. For $C_{26}H_{22}ClF_2NO_5S$: C, 58.48; H, 4.15; N, 2.62; Obsd. C, 58.52; H, 4.21; N, 2.66.

*5.1.25. (±)-Ethyl 6-(4-chlorobenzoyl)-3,5-di(2-furyl)-1,1-dioxo-1,4-thiazinane-2-carboxylate (**28**)*

Isolated as colorless solid (406 mg, 86%) m.p = 163 °C; IR (KBr) 3430, 1734, 1682, 1318, 1135 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.17 (3H, t, J = 7.2 Hz, $COOCH_2CH_3$), 2.21 (NH, br s), 4.15–4.25 (2H, m, $COOCH_2CH_3$), 4.40 (1H, d, J = 10.8 Hz, H-2), 4.96 (1H, d, J = 10.8 Hz, H-3), 5.15 (1H, d, J = 10.4 Hz, H-5), 5.31 (1H, d, J = 10.4 Hz, H-6), 6.19–6.38 (4H, m, Ar-H), 7.18–7.45 (4H, m, Ar-H), 7.90 (2H, d, J = 8.7 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.9, 54.9, 55.5, 62.9, 69.5, 70.3, 108.8, 109.1, 110.5, 129.1, 130.4, 135.1, 141.1, 142.7, 143.0, 149.8, 149.9, 161.0, 186.3. Anal. Calcd. For $C_{22}H_{20}ClNO_7S$: C, 55.29; H, 4.22; N, 2.93; Obsd. C, 55.31; H, 4.27; N, 2.98.

*5.1.26. (±)-Ethyl 6-(4-chlorobenzoyl)-3,5-di(2,4-dichlorophenyl)-1,1-dioxo-1,4-thiazinane-2-carboxylate (**29**)*

Isolated as colorless solid (514 mg, 82%) m.p = 202 °C; IR (KBr) 3290, 1734, 1679, 1320, 1143 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ_H 0.99 (3H, t, J = 7.2 Hz, $COOCH_2CH_3$), 2.30 (NH, br s), 3.97–4.05 (2H, m, $COOCH_2CH_3$), 5.02–5.28 (3H, m, H-2, H-3 and H-5), 6.13 (1H, d, J = 10.1 Hz, H-6), 6.98–8.03 (10H, m, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 12.2, 55.5, 56.0, 60.9, 67.8, 79.6, 125.9, 126.5, 127.6, 127.7, 127.9, 128.8, 129.1, 129.4, 131.1, 132.6, 132.9, 133.5, 133.6, 136.5, 139.1, 139.2, 160.0, 186.9. Anal. Calcd. For $C_{26}H_{20}Cl_5NO_5S$: C, 49.12; H, 3.17; N, 2.20; Obsd. C, 49.18; H, 3.21; N, 2.25.

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Appendix. Supplementary information

Supplementary information associated with this can article be found, in the online version, at doi: 10.1016/j.ejmech.2009.09.001.

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