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### Original article

### Anti-tubercular agents. Part 6: Synthesis and antimycobacterial activity of novel arylsulfonamido conjugated oxazolidinones

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#### 1. Introduction

Tuberculosis (TB), one of the earliest recorded human diseases, remains the leading single-agent killer in the world [1]. The World Health Organization (WHO) estimates that approximately onethird of the global community is infected with Mycobacterium tuberculosis and more than 9 million incident cases and approximately 2 million deaths have occurred world wide due to TB [2-4]. The frightening TB is due to use and misuse of existing antibiotics and poor compliance with the long duration of current chemotherapy that involves four different drugs for two months and two drugs for four months that have created an epidemic of drug resistant TB. The prevalence of multi-drug resistant and extensively drug resistant tuberculosis (MDR- and XDR-TB) strains is reported to be high in the countries where adequate supplies of the drugs are not available [5,6]. Further, after synergism with HIV co-infection, the current trends suggest that TB will be among the 10 leading causes of global disease burden in the year 2020 [7]. Hence, there is an urgent need to identify new regimens involving novel mechanism of action to address resistance crisis as well as the global health emergency.

### ABSTRACT

As a part of investigation of new anti-tubercular agents in this laboratory, herein we describe the synthesis of a new class of arylsulfonamido conjugated oxazolidinones. The *in vitro* activity of these conjugated (**6a**–**f**, **7a–d**, **9a–c** and **11a–c**) molecules against *Mycobacterium tuberculosis*  $H_{37}Rv$  by using rifampicin and linezolide as positive controls is discussed, compounds 7c and 9a-c are found to be the most active members in this series. Further, cytotoxicity of the potent conjugates of the series (7c, and 9a-c) was evaluated on human foreskin fibroblast (HFF) cells by using MTT assay. Finally, these studies suggest that compounds 7c and 9a may serve as promising lead scaffolds for further generation of new as anti-TB agents. © 2011 Elsevier Masson SAS. All rights reserved.

> The search for novel chemotherapeutic agents for the treatment of TB is an active research field stimulated by the discovery of new biological targets, eventually to develop new drugs without serious side effects. Linezolid (1, Fig. 1) is the first and only oxazolidinone that belongs to the bacterial RNA inhibitor class of synthetic antibacterial drug which is available for the treatment of Gram-positive bacteria including first-line drug resistance infections in humans [8,9]. Recently, this drug has also been suggested as an alternative treatment for patients infected with *M. tuberculosis* isolates [10]. However, the in vitro activity of linezolid against M. tuberculosis remains limited [11]. On the other hand, the benzothiadiazine 1,1-dioxides (BTDs) belong to a class of cyclic sulfonamides that have been extensively studied as potassium channel openers [12] and has also shown broad spectrum of activity against several bacterial pathogens including M. tuberculosis [13,14]. From this laboratory several series of compounds based on benzothiadiazine 1,1-dioxide scaffold have been reported with good in vitro antimycobacterial activity. Amongst all the compounds tested, compounds 2 and 3 (Fig. 1) have displayed potential inhibitory activity against M. tuberculosis with an MIC of 0.75 and 1 ug/mL respectively [15–18]. These results have encouraged us for the synthesis of new arylsulfonamido conjugates of oxazolidinones and evaluated for their antitubercular activity. Hence herein, we anticipated that the present work would reveal novel agents in chemotherapy of tuberculosis.

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Fig. 1. Linezolid and promising benzothiadiazines.

### 2. Chemistry

The key intermediates (*S*)-*N*-[[3-(3-fluoro-4-(morpholinyl/thiomorpholinyl/piperzinyl)phenyl)-2-oxo-5-oxazolidinyl]methyl] amine (**4a–c**) and 3-chloro-4-(alkyl/aryl)-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (**5a–c**) were synthesized from previously described literature procedures [15,19,20]. The C5-side arm modified oxazolidinone–BTD series (**6a–f**) was prepared by the coupling reaction between (*S*)-*N*-[[3-(3-fluoro-4-(morpholinyl/thiomorpholinyl)phenyl)-2-oxo-5-oxazolidinyl]methyl]amine (**4a–b**) and 3-chloro-4-(alkyl/aryl)-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (**5a–c**) employing triethylamine as a base in good yields. The other series, C5-side armed modified oxazolidinones (**7a–d**) were prepared by the formation of the sulfonamide bond between arylsulfonyl chlorides and (*S*)-*N*-[[3-(3-fluoro-4-morpholinyl)phenyl)-2oxo-5-oxazolidinyl]methyl]amine (**4a**) employing NaH in dry THF as illustrated in Scheme 1.

The C-ring modified oxazolidinone–BTD series of compounds **9a–c** was prepared as outlined in Scheme 2. *N*-acylation of compound **4c** with acetic anhydride in pyridine affords *N*-acylated-piperzinyl-oxazolidinone intermediate, this upon cbz deprotection by Pd/C in MeOH gave compound **8**. The coupling reaction between 3-chloro-4-(alkyl/aryl)-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (**5a–c**) and compound **8** by employing triethylamine as a base obtained conjugates **9a–c** in good yields.

The conjugates **11a**–**c** were obtained from the coupling reaction of **4c** with **5a**–**c** affords compounds **10a**–**c**. Compounds **10a**–**c** undergoes cbz deprotection with Pd/C in methanol followed by amide coupling with 4-(5-(4-chlorophenyl)-furan-2-yl)-2-acrylic acid, employing EDCI and HoBt, to provide a new series of C-ring and C5-side arm modified oxazolidinone–arylsulfonamido conjugates (**11a**–**c**) in good yields as outlined in Scheme 3. *M. tuberculosis*  $H_{37}$ Rv using the microplate alamar blue assay (MABA) at 1–6.25 µg/mL concentrations. The drugs in clinical use, rifampicin and linezolid were included in these assays as reference compounds [21,22]. The *in vitro* test results for these conjugates are outlined in Table 1 as minimum inhibitory concentration (MIC) and the activity ranges from 1 to >6.25 µg/mL.

In the structure activity relationship (SAR) studies, some interesting trends have been observed in these conjugates. The derivatization with various arylsulfonyl chlorides instead of acyl group at C5-side arm of oxazolidinones, one of the conjugate 7c  $(R = 4F-C_6H_4; MIC = 1 \mu g/mL)$  has shown good activity against M. tuberculosis. Whereas the introduction of a bulky group like benzothiadiazine (6a-f) with various substituents in its ring at C5-side arm has led to loss of anti-tubercular activity, indicating that modification with arylsulfonyl chlorides is preferable at C5-side arm. Among the C-ring modified compounds (9a-c), these conjugated with BTD (9a, 9b) have shown promising antimycobacterial activity with an MIC = 1  $\mu$ g/mL, thus suggesting that modification at this position is also preferable. But, the modifications on both C5side arm and C-ring of the oxazolidinones (**11a–c**) have exhibited significant reduction in activity. Further, the in vivo antimycobacterial activity evaluation of these new potent agents is underway to assess their clinical potential. The physicochemical parameters are listed in Table 1, C log P refers to calculated hydrophobicity of the compounds, respectively,  $C \log P$  have been calculated from ChemDraw version 9.0. The thumb rule for C log P values, to a drug like molecule must be lower than "5" to by-pass the cell barrier. The MIC values of the active conjugates seem to correlate to some extent with the lipophilicity ( $C \log P$ ), **7c** (R = 4fluorophenyl, C log P: 2.75; MIC: 1), **9a** (R = methyl, C log P: 0.70; MIC: 1), **9b** (R = ethyl, C log P: 1.23; MIC: 1), and **9c** (R = phenyl, C log P: 2.20; MIC: 6.25).

### 3. Results and discussion

#### 3.1. Antimycobacterial activity

The antimycobacterial activities of the novel oxazolidinone conjugates (6a-f, 7a-d, 9a-c, and 11a-c) were evaluated against

As described in experimental procedure, the maximum tolerated test (MTT) was performed to evaluate the *in vitro* cytotoxicity of the promising compounds (**7c** and **9a**–**c**) against human foreskin fibroblast (HFF) cells. These compounds were not cytotoxic as



3.2. Cytotoxicity assay

Scheme 1. Synthetic route for the preparation of C-5 side arm modified oxazolidinone-benzothiadiazine/arylsulfonamido conjugates (**6a**-**f** and **7a**-**d**): Reagents and conditions; (i) TEA, THF, 0 °C-rt, 6 h; (ii) aryl sulfonylchlorides, NaH, dry THF, 0 °C, 6 h.



Scheme 2. Synthetic route for the preparation of C-ring modified oxazolidinone-benzothiadiazine conjugates (9a-c): Reagents and conditions; (i) Ac<sub>2</sub>O, pyridine, rt, 1 h; (ii) Pd/C, H<sub>2</sub>, MeOH, rt, 12 h; (iii) 5a-c, TEA, THF, rt, 6 h.

indicated by their IC<sub>50</sub> values. The MIC and IC<sub>50</sub> values of the tested compounds (**7c** and **9a**–**c**) suggest that compounds **7c** and **9a** exhibit *in vitro* antimycobacterial activity at non-cytotoxic concentrations. The IC<sub>50</sub> and selective index (SI) values of these are shown in Table 2 [23]. The good selectivity index values (SI = IC<sub>50</sub>/MIC) for these conjugates indicate its potential usefulness in the drug development for tuberculosis.

#### 4. Conclusion

In conclusion, our work demonstrates the synthesis and biological evaluation of novel benzothiadiazine/arylsufonamido conjugated oxazolidinones as potential antimycobacterial agents. Amongst the oxazolidanone derivatives, **7c**, **9a** and **9b** have shown good *in vitro* activity against *M. tuberculosis* H<sub>37</sub>Rv. Impressively, active compounds **7c** and **9a** were nontoxic toward HFF cells (IC<sub>50</sub> > 100  $\mu$ M). In addition these new agents, merit further studies to explore them as potential chemotherapeutics for tuberculosis and for lead optimization to design novel antitubercular agents.

### 5. Experimental section

#### 5.1. Pharmacology

All the new synthesized conjugates and reference compounds rifampicin, linezolid were initially screened against *M. tuberculosis* and the active compounds were tested for their cytotoxicity data by using MTT assay.

### 5.1.1. Antimycobacterial assay

The antimycobacterial activities of oxazolidinone-arylsulfonamido conjugates (**6a–f**, **7a–d**, **9a–c**, and **11a–c**) were evaluated against *M. tuberculosis*  $H_{37}$ Rv. All the compounds were initially screened against *M. tuberculosis*  $H_{37}$ Rv at the single concentration of 100 (µg/mL) by Tube Method with minor modifications. The active compounds from this screening were further tested for Minimum Inhibitory Concentration (MIC) determination using the broth micro-dilution assay [24,25]. The tubes and micro titer plates were incubated for 3–4 weeks at 37 °C in CO<sub>2</sub> incubator and read visually for the absence of growth turbidity.

#### 5.1.2. Cytotoxicity assay

The potent conjugates **7c** and **9a**–**c** were evaluated for cytotoxic effect on human foreskin fibroblast (HFF cells) cell lines using MTT assay, in a 96 well plate format. Cells were incubated in Dulbecco's Modified Eagle's Medium (DMEM) containing 10% fetal calf serum (FCS) with the test material (2–100  $\mu$ g/ml) for 24 h at 37 °C in CO<sub>2</sub> incubator. After the completion of incubation 3-(4,5-dimethylth-iazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was added and cells were further incubated for 3 h at 37 °C in CO<sub>2</sub> incubator. Formation of formazan salt by mitochondrial dehydrogenases and was determined by Elisa reader at 565 nm (Multiskan Spectrum; Thermo Electron Corporation, USA). The percentage cytotoxicity was calculated with respect to the untreated cells.

#### 5.2. Characterization

Reactions were monitored by TLC, performed on silica gel glass plates containing 60 F-254 and visualization on TLC was achieved by UV light or iodine indicator. Column chromatography was



Scheme 3. Synthetic route for the preparation of C-ring and C-5 side arm modified oxazolidinone–benzothiadiazine conjugates (11a–c): Reagents and conditions: (i) TEA, THF, 0 °C–rt, 12 h; (ii) Pd/C, H<sub>2</sub>, MeOH, rt, 12 h; (iii) 4-(5-(4-chlorophenyl)-furan-2-yl)-2-acrylic acid, EDCI, HoBt, rt, over night.

#### Table 1

Antimycobacterial activity of arylsulfonamido conjugated oxazolidinones (6a–f, 7a–d, 9a–c and 11a–c) in  $\mu g/mL$ 

Compounds	C log P <sup>b</sup>	R	Х	MIC (µg/mL)
6a	2.25	Me	0	>6.25
6b	2.78	Et	0	>6.25
6c	3.29	Ph	0	>6.25
6d	3.24	Me	S	>6.25
6e	3.77	Et	S	>6.25
6f	4.28	Ph	S	>6.25
7a	2.31	Н	0	>6.25
7b	3.32	Cl	0	>6.25
7c	2.75	F	0	1
7d	2.80	OMe	0	>6.25
9a	0.70	Me	_	1
9b	1.23	Et	_	1
9c	2.20	Ph	_	6.25
11a	5.23	Me	_	>6.25
11b	5.85	Et	_	>6.25
11c	6.36	Ph	_	>6.25
RMP <sup>a</sup>				0.12
Linezolid				2

<sup>a</sup> Rifampicin.

<sup>b</sup>  $C \log P$  (hydrophobicity) was calculated using the ChemDraw Ultra, version 9.0.

performed with Merck (Navi Mumbai, India) 60-120 mesh silica gel. Spectral patterns were designated as s. singlet: d. doublet: dd. double doublet; t, triplet; bs, broad singlet; m, multiplet. <sup>1</sup>H NMR spectra were recorded on Gemini (200 MHz) (Varian Inc, Palo Alto, CA, USA) or [Avance (300 MHz); Bruker, Fallanden, Switzerland] instruments. Chemical shifts ( $\delta$ ) were reported in ppm, downfield from internal TMS standard. The LC-MS was recorded on instrument LC-MSD-Trap-SL. ESI spectra were recorded on Micro mass, Quattro LC using ESI+ software with capillary voltage of 3.98 kV and ESI mode positive ion trap detector. High-resolution mass spectra (HRMS) were recorded on QSTAR XL Hybrid MS/MS mass spectrometer. Elemental analyses were performed on an elemental analyzer (Model: VARIO EL, Elementar, Hanau, Germany). Starting materials and reagents were purchased from Lancaster (Alfa Aesar, Johnson Matthey Co, Ward Hill, MA, USA), Sigma–Aldrich (St Louis, MO, USA) and Spectrochem Pvt Ltd (Mumbai, India).

## 5.2.1. (*R*)-[{*N*-3-[3-fluoro-4-(4-morphonyl)phenyl]-2-oxo-5-oxazolidinyl}amine]4-methyl-1,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide (**6a**)

To a solution of (*S*)-*N*-[[3-(3-fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl]methyl]amine (**4a**) (295 mg, 1.0 mmol) and triethylamine (0.4 mL, 3 mmol) in dry dichloromethane (25 mL), 3-chloro-4methyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (**5a**) (230 mg, 1.0 mmol) was added and the reaction mixture was stirred at room temperature for 6 h. After completion of reaction as indicated by TLC, the solvent was removed under reduced pressure and the product was purified by column chromatography by using ethyl acetate, hexane (7:3) system gives the product **6a** (yield 415 mg, 85%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7. 95 (dd, 1H, *J* = 7.7, 1.3 Hz, BTD-*H*), 7.58 (t, 1H, *J* = 7.3 Hz, BTD-*H*), 7.45 (dd, 1H, *J* = 14.5, 2.4 Hz, oxa–Ar–*H*), 7.36 (t, 1H, J = 7.55 Hz, BTD-*H*) 7.14 (t, 1H, *J* = 7.5 Hz, BTD-*H*), 7.02 (d, 1H, *J* = 8.4 Hz, oxa–Ar–*H*), 6.89 (t, 1H, 9.0 Hz, oxa–Ar–*H*), 6.52 (bs, 1H,

able 2	
$C_{50}$ (µM) and selectivity index (SI) values of active compounds ( <b>7c</b> and <b>9a–c</b> ).	

Entry	Compounds	MIC (µg/mL)	IC <sub>50</sub> (μM)	SI
1	7c	1	>100	>100
2	9a	1	>100	>100
3	9b	1	>50	>50
4	9c	6.25	>50	>8

-NH), 4.93–4.98 (m, 1H, oxa–CH–), 4.05–4.11 (m, 2H, oxa–CH<sub>2</sub>–), 3.79–3.83 (m, 4H, *J* = 4.1 Hz, oxa–morpholine–OCH<sub>2</sub>–), 3.66–3.75 (m, 2H, oxa–CH<sub>2</sub>–), 3.63 (s, 3H, BTD–CH<sub>3</sub>), 2.97–3.01 (m, 4H, oxa–morpholine–NCH<sub>2</sub>–); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  156.8, 154.7, 153.5, 152.5, 137.3, 136.4, 132.8, 125.3, 124.5, 123.9, 118.7, 115.4, 114.0, 107.4, 71.4, 66.7, 50.8, 47.9, 41.4, 39.1; ESIMS: *m/z* 490 (M + H)<sup>+</sup>, 512 (M + Na)<sup>+</sup>; HRMS: (ESI *m/z*) for C<sub>22</sub>H<sub>24</sub>FN<sub>5</sub>O<sub>5</sub>S calcd. 490.1582, found 490.1558 (M + H)<sup>+</sup>; Anal. calcd. for C<sub>22</sub>H<sub>24</sub>FN<sub>5</sub>O<sub>5</sub>S: C, 53.98; H, 4.94; N, 14.31. Found: C, 53.92; H, 4.93, N, 14.28.

## 5.2.2. (*R*)-[{*N*-3-[3-fluoro-4-(4-morphonyl)phenyl]-2-oxo-5-oxazolidinyl}amine]4-ethylyl-1,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide (**6b**)

The compound **6b** was prepared according to the above-described method using 4a (295 mg, 1.0 mmol) and 5b (244 mg, 1.0 mmol) (yield 327 mg, 65%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.87 (dd, 1H, J = 7.7, 1.3 Hz, BTD-H), 7.57 (t, 1H, J = 8.49 Hz, BTD-H), 7.42 (dd, 1H, J = 14.5, 2.4 Hz, oxa-Ar-H) 7.38 (t, 1H, J = 7.4 Hz, BTD-H), 7.17 (d, 1H, J = 8.4 Hz, BTD-H), 7.02 (d, 1H, J = 7.5 Hz, oxa-Ar-H), 6.82 (t, 1H, 9.0 Hz, oxa-Ar-H), 6.54 (bs, 1H, -NH), 4.98-5.06 (m, 1H, oxa-CH-), 4.10 (q, 2H, BTD-CH<sub>2</sub>CH<sub>3</sub>), 4.02-4.12 (m, 2H, oxa-CH<sub>2</sub>-), 3.79-3.82 (m, 4H, J=4.3 Hz, oxa-morpholine-NCH<sub>2</sub>-), 3.64-3.76 (m, 2H,  $oxa-CH_2-$ ), 2.97-3.03 (t, 4H, I = 4.9 Hz,  $oxa-morpholine-NCH_2-$ ), 1.39 (t, 3H, I = 6.7 Hz, BTD-CH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ 156.8, 154.7, 153.5, 152.5, 137.3, 136.4, 132.8, 125.3, 124.5, 123.9, 118.7, 115.4, 114.0, 107.4, 71.4, 66.7, 50.8, 47.9, 45.3, 41.4, 12.8; ESIMS: m/z 504  $(M + H)^+$ , 572  $(M + Na)^+$ ; HRMS: (ESI m/z) for C<sub>23</sub>H<sub>26</sub>FN<sub>5</sub>O<sub>5</sub>S calcd. 504.5464, found 504.5458  $(M + H)^+$ ; Anal. calcd. for C<sub>23</sub>H<sub>26</sub>FN<sub>5</sub>O<sub>5</sub>S: C. 54.86: H. 5.20: N. 13.91. Found: C. 54.80: H. 5.20. N. 13.90.

# 5.2.3. (*R*)-[{*N*-3-[3-fluoro-4-(4-morphonyl)phenyl]-2-oxo-5-oxazolidinyl}amine]4-phenyl-1,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide (**6c**)

The compound 6c was prepared according to the abovedescribed method using 4a (295 mg, 1.0 mmol) and 5c (293 mg, 1.0 mmol) (yield 358 mg, 65%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.90 (dd, 1H, J = 9.4 Hz, BTD-H), 7.62 (d, 1H, J = 8.1 Hz, BTD-H), 7.53–7.52 (m, 2H, BTD–Ar–H), 7.44–7.42 (m, 3H, J=9.05, BTD-Ar-H, oxa-Ar-H), 7.38 (t, 1H, J = 7.5 Hz, BTD-H), 7.21-7.17 (m, 2H, J=8.4 Hz, BTD-H, BTD-Ar-H), 6.96 (t, 1H, J=8.6, oxa-Ar-H), 6.84 (t, 1H, J = 9.0 Hz, oxa-Ar-H), 5.43 (bs, 1H, -NH), 4.83-5.03 (m, 1H, oxa-CH-), 4.03-3.89 (m, 2H, oxa-CH<sub>2</sub>-), 3.78-3.80 (t, 4H, oxa-morpholine-OCH2-), 3.64-3.77 (t, 2H, oxa-CH<sub>2</sub>-) 2.96-3.00 (t, 4H, oxa-morpholine-NCH<sub>2</sub>-); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): § 156.8, 153.8, 153.5, 150.9, 138.0, 136.2, 134.4, 132.5, 132.2, 131.7, 131.0, 129.3, 124.8, 123.9, 118.7, 116.5, 113.7, 107.3, 70.9, 66.7, 50.8, 47.4, 44.8; ESIMS: m/z 552  $(M + H)^+$ , 575  $(M + Na)^+$ ; HRMS: (ESI m/z) for C<sub>27</sub>H<sub>26</sub>FN<sub>5</sub>O<sub>5</sub>S calcd. 552.1769, found 552.1753 (M + H)<sup>+</sup>; Anal. calcd. for C<sub>27</sub>H<sub>26</sub>FN<sub>5</sub>O<sub>5</sub>S: C. 58.79: H, 4.75; N, 12.70. Found: C, 58.80; H, 4.70, N, 12.74.

## 5.2.4. (R)-[{N-3-[3-fluoro-4-(4-thiomorphonyl)phenyl]-2-oxo-5-oxazolidinyl}amine]4-methyl-1,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide (**6d**)

The compound **6d** was prepared according to the above-described method using **4b** (311 mg, 1.0 mmol) and **5a** (230 mg, 1.0 mmol) (yield 343 mg, 68%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.86 (dd, 1H, J = 8.05, BTD–H), 7.59 (t, 1H, J = 8.7 Hz, BTD–H), 7.42 (dd, 1H, J = 13.7, 2.1 Hz, oxa–Ar–H), 7.38 (dd, 1H, J = 7.54 Hz, BTD–H), 7.26 (d, 1H, BTD–H), 7.10 (d, 1H, J = 8.05 Hz, oxa–Ar–H), 6.97 (d, 1H, J = 9.5 Hz, oxa–Ar–H), 6.50 (bs, 1H, –NH), 4.91–5.03 (m, 1H, oxa–CH–), 4.08–4.15 (m, 2H, oxa–CH<sub>2</sub>–), 3.64–3.88 (m, 2H, oxa–CH<sub>2</sub>–), 3.52 (s, 3H, BTD– $CH_3$ ), 3.22–3.27 (m, 4H, oxa–thiomorpholine–SCH<sub>2</sub>–), 2.75–2.77 (m, 4H, oxa–thiomorpholine–NCH<sub>2</sub>–); <sup>13</sup>C NMR (CDCl<sub>3</sub>).

75 MHz):  $\delta$  157.0, 154.7, 153.7, 152.5, 137.3, 136.4, 132.6, 125.4, 124.6, 124.0, 120.2, 115.4, 114.0, 107.4, 71.4, 53.2, 47.9, 41.4, 39.2, 27.8; ESIMS: *m*/*z* 506 (M + H)<sup>+</sup>, 529 (M + Na)<sup>+</sup>; HRMS: (ESI *m*/*z*) for C<sub>22</sub>H<sub>24</sub>FN<sub>5</sub>O4S<sub>2</sub> calcd. 506.1254, found 506.1246 (M + H)<sup>+</sup>; Anal. calcd. for C<sub>22</sub>H<sub>24</sub>FN<sub>5</sub>O<sub>4</sub>S<sub>2</sub>: C, 52.26; H, 4.78; N, 13.84. Found: C, 52.20; H, 4.76, N, 13.84.

# 5.2.5. (R)-[{N-3-[3-fluoro-4-(4-thiomorphonyl)phenyl]-2-oxo-5-oxazolidinyl}amine]4- ethyl-1,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide (**6e**)

The compound **6e** was prepared according to the abovedescribed method using 4b (311 g, 1.0 mmol) and 5b (244 mg, 1.0 mmol) (yield 352 mg, 68%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.87 (dd, 1H, J = 8.0 Hz, BTD-H), 7.59 (t, 1H, J = 8.7 Hz, BTD-H), 7.42 (dd, 1H, J = 13.9, 2.1 Hz, oxa-Ar-H), 7.38 (t, 1H, J = 7.5 Hz, BTD-H), 7.30 (t, 1H, I = 7.3 Hz, BTD-H), 7.14 (d, 1H, I = 8.7 Hz, oxa-Ar-H), 6.99(dd, 1H, J = 8.7, 2.1 Hz, BTD-H), 6.63 (bs, 1H, -NH), 5.05-4.98 (m, 1H, oxa-CH-), 3.65-4.01 (m, 6H, 2× oxa-CH<sub>2</sub>-, BTD-CH<sub>2</sub>CH<sub>3</sub>), 3.22–3.26 (m, 4H, J = 5.1 Hz, oxa–thiomorpholine–SCH<sub>2</sub>–), 2.73-2.78 (m, 4H, oxa-thiomorpholine-NCH2-), 1.40 (t, 3H, J = 7.2 Hz, BTD-CH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  157.0, 154.7, 153.7, 152.5, 137.3, 136.4, 132.6, 125.4, 124.6, 124.0, 120.2, 115.4, 114.0, 107.4, 71.4, 53.2, 47.9, 45.3, 41.4, 27.8, 12.8; ESIMS: m/z 520  $(M + H)^+$ , 543  $(M + Na)^+$ ; HRMS: (ESI m/z) for C<sub>23</sub>H<sub>26</sub>FN<sub>5</sub>O<sub>4</sub>S<sub>2</sub> calcd. 520.1442, found 520.1434  $(M + H)^+$ ; Anal. calcd. for C<sub>23</sub>H<sub>26</sub>FN<sub>5</sub>O<sub>4</sub>S<sub>2</sub>: C, 53.16; H, 5.04; N, 13.48. Found: C, 53.14; H, 5.00, N, 13.40.

### 5.2.6. (*R*)-[{*N*-3-[3-fluoro-4-(4-thiomorphonyl)phenyl]-2-oxo-5-oxazolidinyl}amine]4-phenyl-1,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide (**6f**)

The compound **6f** was prepared according to the above-described method using **4b** (311 mg, 1.0 mmol) and **5c** (293 mg, 1.0 mmol) (yield 368 mg, 65%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  7.91 (dd, 1H, J = 8.7 Hz, BTD-H), 7.66-7.52 (m, 3H, J = 8.0 Hz, BTD-H, BTD-Ar-*H*), 7.45–7.41 (m, 3H, *J* = 14.2 Hz, BTD–Ar–H, oxa–Ar–H) 7.39 (dd, 1H, J = 7.4 Hz, BTD-H), 7.29 (t, 1H, J = 7.4 Hz, BTD-Ar-H), 6.82-7.11 (m, 2H, I = 8.7 Hz, BTD-H, oxa-Ar-H), 6.72 (d, 1H, I =8.7 Hz, oxa-Ar-H), 5.37 (bs, 1H, -NH), 4.94-5.03 (m, 1H, oxa-CH-), 4.03-3.94 (m, 2H, oxa-CH<sub>2</sub>-), 3.73-3.97 (m, 2H, oxa-CH<sub>2</sub>-) 3.26-3.21 (t, 4H, oxa-thiomorpholine-SCH2-) 2.73-2.76 (t, 4H, oxa-thiomorpholine-NCH<sub>2</sub>-); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  157.1, 154.8, 153.5, 151.9, 137.0, 136.2, 134.4, 132.5, 132.2, 131.7, 131.0, 129.3, 124.8, 123.9, 118.7, 116.5, 113.7, 107.3, 71.4, 53.3, 47.4, 41.4, 27.7; ESIMS: m/z 568 (M+H)<sup>+</sup>, 591 (M+Na)<sup>+</sup>; HRMS: (ESI m/z) for  $C_{27}H_{26}FN_5O_4S_2$  calcd. 568.1430, found 568.1454 (M + H)<sup>+</sup>; Anal. calcd. for C<sub>27</sub>H<sub>26</sub>FN<sub>5</sub>O<sub>4</sub>S<sub>2</sub>: C, 57.13; H, 4.62; N, 12.34. Found: C, 57.10; H, 4.55, N, 12.32.

### 5.2.7. (R)-[{N-3-[3-fluoro-4-(4-morphonyl)phenyl]-2-oxo-5-oxazolidinyl}methyl] benzensulfonamide (**7a**)

The target compound **7a** was obtained by reacting **4a** (295 mg, 1.0 mmol) with benzenesulphonyl chloride (211 mg, 1.2 mmol), and NaH (50 mg, 2.0 mmol) in dry THF (50 mL). After stirring the reaction mixture for 6 h, the reaction mixture was poured on to crushed ice (5 g) and the reaction mixture extracted and purified by column chromatography affords final product as white solid. (Yield 304 mg, 70%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  7.75–7.68 (m, 2H, Ar–H), 7.62–7.55 (m, 2H, Ar–H), 7.44 (dd, 1H, *J* = 14.4, 2.7 Hz, oxa–Ar–H), 6.98 (t, 1H, *J* = 9.3 Hz, oxa–Ar–H), 6.0 (bs, 1H, –NH), 4.99–5.04 (m, 1H, oxa–CH–), 4.32–3.99 (m, 2H, oxa–CH<sub>2</sub>–), 3.78–3.82 (m, 4H, *J* = 4.5 Hz, morpholin–OCH<sub>2</sub>–), 3.40 (m, 2H, oxa–CH<sub>2</sub>–), 2.98–3.02 (m, 4H, *J* = 4.5 Hz, morpholine–NCH<sub>2</sub>–); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  155.3, 154.4, 142.3, 136.4, 135.2, 132.8, 129.3, 127.3, 118.7, 113.9, 107.4, 71.9, 66.8, 50.8, 47.5, 41.8; ESIMS:

*m*/*z* 436 (M <sup>+</sup> + H); Anal. calcd. for C<sub>20</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>5</sub>S: C, 55.16; H, 5.09; N, 9.65. Found: C, 55.14; H, 5.307 N, 9.64.

### 5.2.8. (R)-[{N-3-[3-fluoro-4-(4-morphonyl)phenyl]-2-oxo-5-oxazolidinyl}methyl]4-chlorobenzensulfonamide (**7b**)

The compound **7b** was prepared according to the abovedescribed method using **4a** (295 mg, 1 mmol). (Yield 328 mg, 70%) <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  7.81–7.76 (m, 2H, Ar–*H*), 7.74–7.70 (m, 2H, Ar–*H*), 7.44 (dd, 1H, *J* = 15.0, 2.4 Hz, oxa–Ar–*H*), 7.05 (dd, 1H, *J* = 8.7 Hz, oxa–Ar–*H*), 6.95 (t, 1H, *J* = 9.3 Hz, oxa–Ar–*H*), 6.05 (bs, 1H, –N*H*), 4.95–5.10 (m, 1H, oxa–*CH*–), 4.32–4.01 (m, 2H, oxa–*CH*<sub>2</sub>–), 3.65–3.77 (m, 4H, morpholin–O–*CH*<sub>2</sub>–), 3.38–4.26 (m, 2H, oxa–*CH*<sub>2</sub>–), 2.61–3.04 (m, 4H, *J* = 4.5 Hz, morpholin–N–*CH*<sub>2</sub>–); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  155.3, 154.4, 140.1, 138.7, 136.4, 132.8, 129.1, 128.4, 118.7, 113.9, 107.4, 71.9, 66.8, 50.8, 47.5, 41.8; ESIMS: *m/z* 470 (M <sup>+</sup> + H); Anal. calcd. for C<sub>20</sub>H<sub>21</sub>ClFN<sub>3</sub>O<sub>5</sub>S: C, 51.12; H, 4.50; N, 8.94. Found: C, 51.14; H, 4.48, N, 8.92.

### 5.2.9. (*R*)-[{*N*-3-[3-fluoro-4-(4-morphonyl)phenyl]-2-oxo-5-oxazolidinyl}methyl]4-fluorobenzensulfonamide (**7***c*)

The compound **7c** was prepared according to the abovedescribed method using **4a** (295 mg, 1 mmol). (Yield 317 mg, 70%) <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  7.85–7.80 (m, 2H, Ar–H), 7.72–7.71 (m, 2H, Ar–H), 7.42 (dd, 1H, *J* = 15.0, 2.4 Hz, oxa–Ar–H), 7.07 (dd, 1H, *J* = 8.7 Hz, oxa–Ar–H), 6.86 (t, 1H, *J* = 9.3 Hz, oxa–Ar–H), 6.02 (bs, 1H, –NH), 4.97–5.11 (m, 1H, oxa–CH–), 4.34–3.97 (m, 2H, oxa–CH<sub>2</sub>–), 3.68–3.75 (m, 4H, *J* = 4.5 Hz, morpholin–OCH<sub>2</sub>–), 3.44–3.35 (m, 2H, oxa–CH<sub>2</sub>–), 2.67–3.06 (m, 4H, *J* = 4.5 Hz, morpholin–CH<sub>2</sub>–); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  168.5, 155.3, 154.4, 136.9, 136.4, 132.8, 130.8, 118.7, 118.5, 113.9, 107.4, 71.9, 66.8, 50.8, 47.5, 41.8; ESIMS: *m*/*z* 454 (M<sup>+</sup> + H); Anal. calcd. for C<sub>20</sub>H<sub>21</sub>F<sub>2</sub>N<sub>30</sub>S<sub>5</sub>S: C, 52.97; H, 4.67; N, 9.27. Found: C, 52.95; H, 4.64, N, 9.25.

### 5.2.10. (R)-[{N-3-[3-fluoro-4-(4-morphonyl)phenyl]-2-oxo-5-oxazolidinyl}methyl]4-methylbenzensulfonamide (**7d**)

The compound **7d** was prepared according to the abovedescribed method using **4a** (295 mg, 1 mmol). (Yield 314 mg, 70%) <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  7.42–7.29 (m, 5H, Ar–*H*) 7.45 (dd, 1H, *J* = 15.0, 2.4 Hz, oxa–Ar–*H*), 7.06 (dd, 1H, *J* = 8.7 Hz, oxa–Ar–*H*), 6.94 (t, 1H, *J* = 9.3 Hz, oxa–Ar–*H*), 6.02 (bs, 1H, –N*H*), 5.11 (m, 1H, oxa–CH–), 4.34–3.97 (m, 2H, *J* = 9.3 Hz, oxa–CH<sub>2</sub>–), 3.75–3.87 (m, 4H, *J* = 4.5 Hz, morpholine–O–CH<sub>2</sub>–), 3.36–3.44 (m, 2H, oxa–CH<sub>2</sub>–), 2.63–3.06 (m, 4H, *J* = 4.5 Hz, morpholine–N–CH<sub>2</sub>–), 2.34 (s, 3H, Ar–CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  155.3, 154.4, 142.2, 137.8, 136.4, 132.8, 1301.2, 126.4, 118.7, 113.9, 107.4, 71.9, 66.8, 50.8, 47.5, 41.8, 20.8 ESIMS: *m/z* 450 (M<sup>+</sup> + H); Anal. calcd. for C<sub>21</sub>H<sub>24</sub>FN<sub>3</sub>O<sub>5</sub>S: C, 56.11; H, 5.38; N, 9.35. Found: C, 56.10; H, 5.36, N, 9.33.

### 5.2.11. (S)–N-((3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxo-5-oxazolidin-yl)methyl)acetamide (**8**)

The compound **4c** (428 mg, 1 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (40 mL), treated with pyridine (0.10 mL, 2.0 mmol) followed by Ac<sub>2</sub>O (0.094 mL, 1.0 mmol), and allowed to stir at 25 °C for 1 h. Then the reaction solution was washed with H<sub>2</sub>O followed by brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography (1.5–3.5% MeOH/CHCl<sub>3</sub>) gave *N*-acylated-piperzinyl-oxazolidinone intermediate as an off-white solid (68 mg, 61%). The obtained intermediate (470 mg, 1 mmol) was dissolved in MeOH (15 mL) was degassed, then 10 wt % Pd/C (450 mg, 3.00 mmol) was added. The mixture was filtered through a bed of Celite, washed with methanol, the filtrate was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and filtered, and concentrated to afford compound **8** as a light yellow glass (303 mg, 90%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.42 (dd, 1H, *J* = 14.4, 2.6 Hz, oxa–Ar–*H*), 7.06 (dd, 1H, *J* = 8.8, 1.8 Hz, oxa–Ar–*H*), 6.98–6.86 (m, 1H, oxa–Ar–*H*), 6.33–6.23 (m, 1H, –N*H*), 4.83–4.69 (m, 1H, oxa–CH–), 4.02 (t, 1H, *J* = 9.0 Hz, oxa–CH<sub>2</sub>–), 3.75 (dd, 1H, *J* = 8.8, 6.7 Hz, oxa–CH<sub>2</sub>–), 3.70 (ddd, 1H, *J* = 14.7, 5.9, 2.9 Hz, oxa–CH<sub>2</sub>–), 3.61 (dt, 1H, *J* = 14.6, 6.1 Hz, oxa–CH<sub>2</sub>–), 3.09–3.05 (m, 4H, piperazine–CH<sub>2</sub>–), 3.04–3.01 (m, 4H, piperazine–CH<sub>2</sub>–), 2.12 (s, 3H, –CO–CH<sub>3</sub>); HRMS (ESI) [M+H]<sup>+</sup> calcd. for C<sub>16</sub>H<sub>21</sub>FN<sub>4</sub>O<sub>3</sub> 337.1676, found 337.1670.

## 5.2.12. (R)-[{N-3-[3-fluoro-4-(4-(4-methyl-1,1-dioxo-1,4-dihydro-1,2,4-benzothiadiazine-3-yl)piperzino)phenyl]-2-oxo-5-oxazolidinyl}methyl]acetamide (**9a**)

To a solution of 3-chloro-4-methyl-4H-1,2,4-benzothiadiazine 1,1dioxanes (5a, 230 mg, 1.0 mmol) and triethylamine (0.4 mL, 3.0 mmol) in dry dichloromethane (25 mL), (R)-N-[[3-[3-fluoro-4-(N-1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide (8) (336 mg, 1.0 mmol) was added and the reaction mixture was stirred at room temperature for 6 h. After completion of reaction as indicated by TLC, the solvent was removed under reduced pressure and the product was purified by column chromatography by using chloroform, methanol (10:1) system gives the product (**9a**) (yield 371 mg, 70%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  7.88 (dd, 1H, J = 8.0 Hz, BTD-H), 7.55 (t, 1H, J = 8.0 Hz, BTD-H), 7.44 (dd, 1H, J = 2.9, 13.9 Hz, oxa-Ar-H), 7.36-7.30 (m, 2H, BTD-H), 7.02 (d, 1H, J = 8.0 Hz, oxa-Ar-H), 6.86 (t, 1H, J = 8.7 Hz, oxa-Ar-H), 6.38 (bs, 1H, -NH), 4.76-4.80 (m, 1H, oxa-CH-), 3.89-4.07 (m, 2H, oxa-CH<sub>2</sub>-), 3.75 (s, 3H. BTD-CH<sub>3</sub>), 3.62-3.71 (m, 6H, piperazine-CH<sub>2</sub>-, oxa-CH<sub>2</sub>-), 2.68–3.10 (m, 4H, piperazine–CH<sub>2</sub>–), 2.15 (s, 3H, –CO–CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ 171.3, 156.5, 154.9, 154.6, 153.5, 152.4, 137.3, 136.4, 132.9, 132.8, 125.4, 124.6, 123.8, 119.3, 119.2, 115.4, 114.1, 114.0, 107.8, 107.6, 72.1, 52.0, 47.9, 45.9, 42.2, 37.5, 23.3; ESIMS: m/z 531  $(M + H)^+$ , 554  $(M + Na)^+$ , HRMS: (ESI m/z) for C<sub>24</sub>H<sub>27</sub>FN<sub>6</sub>O<sub>5</sub>S calcd. 531.1818, found 531.1805 (M + H)<sup>+</sup>; Anal. calcd. for C<sub>24</sub>H<sub>27</sub>FN<sub>6</sub>O<sub>5</sub>S: C, 54.33; H, 5.13; N, 15.84. Found: C, 54.29; H, 5.09; N, 15.82.

## 5.2.13. (R)-[{N-3-[3-fluoro-4-(4-(4-ethyl-1,1-dioxo-1,4-dihydro-1,2,4-benzothiadiazine-3-yl)piperzino)phenyl]-2-oxo-5-oxazolidinyl}methyl]acetamide (**9b**)

The compound 9b was prepared according to the above-described method using **5b** (244 mg, 1.0 mmol) (Yield 353 mg, 65%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  7.92 (dd, 1H, J = 8.0 Hz, BTD-H), 7.57-7.60 (m, 1H, J = 8.0 Hz, BTD-H), 7.44 (dd, 1H, J = 13.9, 2.9 Hz, oxa-Ar-H), 7.37–7.28 (m, 2H, BTD–H), 7.02 (d, 1H, J = 8.0 Hz, oxa–Ar–H), 6.85–6.91 (m, 1H, J=8.7 Hz, oxa–Ar–H), 6.38 (bs, 1H, –NH), 4.74-4.80 (m, 1H, oxa-CH-), 4.08 (t, 2H oxa-CH2-), 4.07 (q, 2H, BTD-CH<sub>2</sub>CH<sub>3</sub>), 3.81-3.75 (m, 2H, oxa-CH<sub>2</sub>-), 3.62-3.70 (m, 4H, piperazine-CH<sub>2</sub>-), 3.09-3.15 (m, 4H, piperazine-CH<sub>2</sub>-), 2.16 (s, 3H, -CO-CH<sub>3</sub>), 1.24 (t, 3H, BTD-CH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ 171.3, 156.5, 154.9, 154.6, 153.5, 152.4, 137.3, 136.4, 132.9, 132.8, 125.4, 124.6, 123.8, 119.3, 119.2, 115.4, 114.1, 114.0, 107.8, 107.6, 72.1, 52.0, 47.9, 45.9, 45.3, 42.2, 23.3, 12.4; ESIMS: m/z 545 (M + H)<sup>+</sup>, 568 (M + Na)<sup>+</sup>; HRMS: (ESI *m*/*z*) for C<sub>25</sub>H<sub>29</sub>FN<sub>6</sub>O<sub>5</sub>S calcd. 545.1838, found 545.1826  $(M + H)^+$ ; Anal. calcd. for C<sub>25</sub>H<sub>29</sub>FN<sub>6</sub>O<sub>5</sub>S: C, 55.14; H, 5.37; N, 15.43. Found: C, 55.12; H, 5.34, N, 15.40.

## 5.2.14. (R)-[{N-3-[3-fluoro-4-(4-(4-phenyl-1,1-dioxo-1,4-dihydro-1,2,4-benzothiadiazine-3-yl)piperzino)phenyl]-2-oxo-5-oxazolidinyl}methyl]acetamide (**9c**)

The compound **9c** was prepared according to the abovedescribed method using **5c** (292 mg, 1.0 mmol). (Yield 391 mg, 66%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  7.94 (dd, 1H, *J* = 7.4 Hz, BTD-*H*), 7.54–7.59 (m, 1H, *J* = 6.8 Hz, BTD-*H*), 7.54–7.52 (m, 4H, *J* = 3.77 Hz, BTD-Ar-*H*), 7.48–7.41 (m, 3H, J = 14.4, 2.7, BTD-*H*, oxa–Ar-*H*), 7.35–7.30 (m, 2H, *J* = 9.05 Hz, BTD-*H*), 7.04 (d, 1H, *J* = 9.0 Hz, oxa–Ar–*H*), 6.84 (t, 1H, *J* = 9.0 Hz, oxa–Ar–*H*), 6.31 (bs, 1H, –*NH*), 4.71–4.80 (m, 1H, oxo–*CH*–), 4.10–4.00 (m, 2H, *J* = 9.0 Hz, oxa–*CH*<sub>2</sub>), 3.84–3.92 (m, 6H, oxa–*CH*<sub>2</sub>, piperazine–*CH*<sub>2</sub>–), 3.14–3.06 (m, 4H, piperazine–*CH*<sub>2</sub>–), 2.15 (s, 3H, –*CO*–*CH*<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  171.5, 156.8, 153.8, 153.5, 150.9, 138.0, 137.2, 134.4, 132.9, 132.6, 131.7, 131.0, 129.3, 124.8, 123.9, 119.4, 116.5, 114.1, 113.9, 107.6, 107.3, 71.9, 52.2, 47.9, 45.6, 42.4, 23.3; ESIMS: *m*/*z* 593 (M + H)<sup>+</sup>, 616 (M + Na)<sup>+</sup>; HRMS: (ESI *m*/*z*) for C<sub>29</sub>H<sub>29</sub>FN<sub>6</sub>O<sub>5</sub>S calcd. 593.1834, found 593.1827 (M + H)<sup>+</sup>; Anal. calcd. for C<sub>29</sub>H<sub>29</sub>FN<sub>6</sub>O<sub>5</sub>S: C, 58.77, H, 4.93, N, 14.83. Found: C, 58.75; H, 4.91, N, 14.79.

### 5.2.15. (R)-[{N-3-[3-fluoro-4-(4-(4-carbobenzoxy)piperzino) phenyl]-2-oxo-5-oxazolidinyl}methyl]amino-4-methyl-1,4-dihydro-1,2,4-benzothiadiazine 1,1-dione (**10a**)

To a solution of 3-chloro-4-methyl-4H-1,2,4-benzothiadiazine 1,1-dioxanes (5a, 276 mg, 1.2 mmol) and triethylamine (3.0 mmol) in dry dichloromethane (25 mL), compound 4c (428 mg, 1.0 mmol) was added and the reaction mixture was stirred at room temperature for 12 h. After completion of reaction as indicated by TLC, the solvent was removed under reduced pressure and the product was purified by column chromatography by using chloroform, methanol (10:1) system gives the product (**10a**). (Yield 460 mg, 74%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.83 (dd, 1H, J = 8.0 Hz, BTD-H), 7.58 (t, 1H, J = 6.8 Hz, BTD-H), 7.45 (dd, 1H, J = 14.0, 2.5 Hz, oxa-Ar-H), 7.32 (d, 1H, J = 6.5 Hz, BTD-H), 7.29–7.27 (m, 4H, BTD-H,  $3 \times$  cbz-Ar-H), 7.09 (d, 1H, I = 8.0 Hz, oxa-Ar-H), 6.92 (dd, 1H, I = 9.0 Hz, oxa-Ar-H), 6.76 (m, 2H, cbz-Ar-H), 5.55 (bs, 1H, -NH), 5.06 (s, 2H, cbz-CH<sub>2</sub>-), 4.82-4.90 (m, 1H, oxa-CH-), 3.93-3.84 (m, 2H, oxa-CH<sub>2</sub>-), 3.75-3.71 (m, 2H, oxa-CH<sub>2</sub>-), 3.67 (s, 3H, BTD-CH<sub>3</sub>), 3.56-3.65 (m, 4H, piperazine– $CH_2$ –), 2.87 (m, 4H, piperazine– $CH_2$ –); ESIMS: m/z623  $(M + H)^+$ .

### 5.2.16. (R)-[{N-3-[3-fluoro-4-(4-(4-carbobenzoxy)piperzino) phenyl]-2-oxo-5-oxazolidinyl}methyl]amino-4-ethyl-1,4-dihydro-1,2,4-benzothiadiazine 1,1-dione (**10b**)

The compound **10b** was prepared according to the abovedescribed method using **5b** (292 mg, 1.2 mmol). (Yield 445 mg, 70%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  7.83 (d, 1H, *J* = 8.0 Hz, BTD-*H*), 7.59 (t, 1H, *J* = 6.8 Hz, BTD-*H*), 7.45 (m, 1H, *J* = 14.2, 2.5 Hz, oxa-Ar-*H*), 7.32 (d, 1H, *J* = 6.5 Hz, BTD-*H*), 7.27–7.23 (m, 4H, BTD-*H*, cbz-Ar-*H*), 7.10 (d, 1H, *J* = 8.0 Hz, oxa-Ar-*H*), 6.94–6.98 (m, 1H, *J* = 9.0 Hz, oxa-Ar-*H*), 6.76 (m, 2H, cbz-Ar-*H*), 5.58 (bs, 1H, -N*H*), 5.06 (s, 2H, cbz-*CH*<sub>2</sub>-), 4.85–4.93 (m, 1H, oxa-*CH*-), 4.06 (q, 2H, BTD-*CH*<sub>2</sub>CH<sub>3</sub>), 3.93–3.85 (m, 2H, oxa-*CH*<sub>2</sub>-), 3.56–3.75 (m, 6H, oxa-*CH*<sub>2</sub>-, piperazine-*CH*<sub>2</sub>-), 2.87 (m, 4H, piperazine-*CH*<sub>2</sub>-), 1.30 (t, 3H, BTD-*C*H<sub>2</sub>CH<sub>3</sub>); ESIMS: *m*/*z* 637 (M + H)<sup>+</sup>.

### 5.2.17. (R)-[{N-3-[3-fluoro-4-(4-(4-carbobenzoxy)piperzino) phenyl]-2-oxo-5-oxazolidinyl}methyl]amino-4-phenyl-1,4-dihydro-1,2,4-benzothiadiazine 1,1-dione (**10c**)

The compound **10c** was prepared according to the abovedescribed method using **5c** (350 mg, 1.2 mmol). (Yield 478 mg, 70%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  7.92 (d, 1H, *J* = 7.3 Hz, BTD-*H*), 7.54–7.62 (m, 3H, *J* = 7.3 Hz, BTD–*H*, BTD–Ar–*H*), 7.45–7.42 (m, 2H, *J* = 9.0 Hz, BTD–*H*), 7.39 (d, 1H, *J* = 13.6 Hz, oxa–*H*), 7.35–7.33 (m, 2H, BTD–Ar–*H*), 7.26 (m, 5H, cbz–Ar–H, BTD–*H*), 6.96 (d, 1H, *J* = 8.0 Hz, oxa–Ar–*H*), 6.83 (t, 1H, *J* = 9.5 Hz, oxa–Ar–*H*), 6.29 (d, 1H, *J* = 8.0 Hz), 5.58 (bs, 1H, –NH), 5.10 (s, 2H, cbz–CH<sub>2</sub>–), 4.83–4.90 (m, 1H, oxa–CH–), 4.78–4.05 (m, 2H, oxa–CH<sub>2</sub>–), 3.72–3.87 (m, 2H, oxa–CH<sub>2</sub>–), 3.62–3.67 (m, 4H, piperazine–CH<sub>2</sub>–), 2.95–3.01 (m, 4H, piperazine–CH<sub>2</sub>–); ESIMS: *m*/*z* 685 (M + H)<sup>+</sup>. 5.2.18. (R)-[{N-3-[3-fluoro-4-(4-(4-(E)-3-[5-(4-chlorophenyl)-2-furyl]-2-propenyoyl)piperzino)phenyl]-2-oxo-5-oxazolidinyl} methyl]amino-4-methyl-1,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide (**11a**)

The target compound was prepared by cbz deprotection compound **10a** (622 mg, 1.0 mmol) by using Pd/C under hydrogen atmosphere afforded deprotected compound (439 mg, 90%). Then this compound (488 mg, 1.0 mmol) undergoes amide bond formation with (E)-3-[5-(4-chlorophenyl)-2-furyl]-2-propenoic acid (248 mg, 1 mmol) in dry DMF, by using coupling agent EDC (77 mg, 0.5 mmol) and hydroxybenzotriazole (13.5 mg, 0.1 mmol). Reaction mixture was stirred at room temperature for 12 h, After completion of reaction as indicated by TLC, the reaction was poured into crushed ice (10 g) and extract with ether and the crude product purified by column chromatography by using chloroform, methanol (10:1) system gives the product (**11a**) (yield 465 mg, 65%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  7.93 (d, 1H, J = 7.9 Hz, BTD-H), 7.65-7.60 (d, 2H, J = 8.4 Hz, Ar–H), 7.54–7.48 (m, 2H, J = 9.6 Hz, BTD–H, –CH=CH–), 7.43 (dd, 1H, J = 14.2, 2.5 Hz, oxa-Ar-H), 7.39-7.29 (m, 3H, BTD-H, Ar-H), 7.12 (d, 1H, J = 8.4 Hz, BTD-H), 7.04 (d, 1H, J = 9.3 Hz, oxa–Ar–H), 6.85 (m, 2H, oxa–Ar–H), 6.68 (d, 1H, J = 8.4 Hz –CH= CH-), 6.62 (d, 1H, furan-H), 6.35 (bs, 1H, -NH), 4.98-5.00 (m, 1H, oxa-CH-), 4.12-4.05 (m, 2H, oxa-CH<sub>2</sub>-), 3.74-3.92 (m, 6H, oxa-CH<sub>2</sub>-, piperazine-CH<sub>2</sub>-), 3.03-3.16 (m, 4H, piperazine-CH<sub>2</sub>-), 2.09 (s, 3H, -NCH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ 159.3, 156.8, 154.7, 153.8, 153.5, 152.5, 150.1, 137.3, 136.4, 132.9, 132.8, 130.0, 128.6, 128.1, 125.4, 125.3, 124.5, 123.9, 118.7, 117.1, 116.1, 115.4, 114.0, 108.6, 107.4, 80.1, 71.4, 50.8, 46.3, 41.4, 39.1; ESIMS: m/z 720 (M + H)<sup>+</sup>, 742  $(M + Na)^+$ ; HRMS: (ESI m/z) for C<sub>35</sub>H<sub>32</sub>ClFN<sub>6</sub>O<sub>6</sub>SNa calcd. 741.1634, found 741.1628  $(M + Na)^+$ ; Anal. calcd. for C<sub>35</sub>H<sub>32</sub>ClFN<sub>6</sub>O<sub>6</sub>S: C, 58.45, H, 4.48, N, 11.69. Found: C, 58.49; H, 4.46, N, 11.70.

5.2.19. (R)-[{N-3-[3-fluoro-4-(4-(4-(E)-3-[5-(4-chlorophenyl)-2furyl]-2-propenyoyl) piperzino)phenyl]-2-oxo-5-oxazolidinyl} methyl]amino-4-ethyl-1,4-dihydro-1,2,4-benzothiadiazine 1,1dioxide (**11b**)

This compound was prepared according to the method described for the compound **11a**, deprotection of compound **10b** (636 mg, 1.0 mmol) gives piperzinyl-oxo-BTD intermediate (446 mg, 89%), then this intermediate (502 mg, 1. mmol) on amide bond formation reaction with (E)-3-[5-(4-chlorophenyl)-2-furyl]-2-propenoic acid (248 mg, 1 mmol) affords the product **11b** (yield 468 mg, 64%).  $^{1}$ H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.95 (d, 1H, J = 7.6 Hz, BTD-H), 7.66-7.64 (m, 2H, J = 8.4 Hz, Ar-H), 7.59-7.42 (m, 3H, BTD-H, oxa-ArH, -CH=CH-), 7.38-7.33 (m, 3H, J = 8.4 Hz, BTD-H, Ar-H), 7.19 (d, 1H, J = 8.5 Hz, BTD-H), 7.04 (d, 1H, J = 9.3 Hz, oxa-Ar-H), 6.92-6.86 (m, 2H, oxa-ArH, -CH=CH-), 6.72-6.69 (d, 1H, J = 3.4 Hz, furan-H), 6.65–6.66 (d, 1H, J = 3.4 Hz, furan–H), 6.36 (bs, 1H, –NH), 4.97–5.00 (m, 1H, oxa-CH-), 4.12-4.08 (m, 2H, oxa-CH<sub>2</sub>-), 4.02 (q, 2H, -N-CH<sub>2</sub>CH<sub>3</sub>), 3.88-3.68 (m, 6H, oxa-CH<sub>2</sub>-, piperazine-CH<sub>2</sub>-), 3.07-3.12 (m, 4H, piperazine-CH<sub>2</sub>-), 1.44 (t, 3H,  $-N-CH_2CH_3$ );  $^{13}C$ NMR (CDCl<sub>3</sub>, 75 MHz): δ 159.3, 156.8, 154.7, 153.8, 153.5, 152.5, 150.1,137.3, 136.4, 132.9, 132.8, 130.0, 128.6, 128.1, 125.4, 125.3, 124.5, 123.9, 118.7, 117.1, 116.1, 115.4, 114.0, 108.6, 107.4, 80.1, 71.4, 50.8, 46.3, 45.3, 41.4, 12.8; ESIMS: *m*/*z* 733 (M + H)<sup>+</sup>, 755 (M + Na)<sup>+</sup>; HRMS: (ESI *m*/*z*) for C<sub>36</sub>H<sub>34</sub>ClFN<sub>6</sub>O<sub>6</sub>S calcd. 733.1933, found 733.1928  $(M + H)^+$ ; Anal. calcd. for C<sub>36</sub>H<sub>34</sub>ClFN<sub>6</sub>O<sub>6</sub>S: C, 58.97, H, 4.67, N, 11.46. Found: C, 58.95; H, 4.65, N, 11.44.

5.2.20. (R)-[{N-3-[3-fluoro-4-(4-(4-(E)-3-[5-(4-chlorophenyl)-2furyl]-2-propenyoyl)piperzino)phenyl]-2-oxo-5-oxazolidinyl} methyl]amino-4-ethyl-1,4-dihydro-1,2,4-benzothiadiazine 1,1dioxide (**11c**)

This compound was prepared according to the method described for the compound **11a**, deprotection of compound **10c** 

(684 mg, 1.0 mmol) gives piperzinyl-oxo-BTD intermediate (500 mg, 91%), then this intermediate (550 mg, 1.0 mmol) on amide bond formation reaction with (E)-3-[5-(4-chlorophenyl)-2-furyl]-2-propenoic acid (248 mg, 1 mmol) affords the product 11c (550 mg, 1 mmol). (Yield 491 mg, 63%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  7.95 (m, 1H, I = 9.4 Hz, BTD-H), 7.72-7.66 (m, 4H, BTD-Ar-H, Ar–H), 7.62 (d, 1H, *J* = 8.6 Hz, –CH=CH–), 7.56 (dd, 1H, *J* = 11.7 Hz, BTD-H), 7.47 (d, 1H, I = 14.8 Hz, oxa-Ar-H), 7.39-7.36 (m, 3H, *J* = 8.6 Hz, BTD–*H*, Ar–*H*), 7.30–7.26 (m, 3H, *J* = 9.4 Hz, BTD–Ar–*H*), 7.24–7.18 (m, 2H, BTD-H, -CH=CH-), 7.01 (dd, 1H, J=8.6 Hz, oxa-Ar-H), 6.84 (d, 1H, J = 14.9 Hz, oxa-Ar-H), 6.76 (d, 1H, I = 3.3 Hz, furan-H), 6.64 (d, 1H, I = 3.3 Hz, furan-H), 6.31 (bs, 1H, -NH), 4.96-4.99 (m, 1H, oxa-CH-), 4.02-4.13 (m, 2H, oxa-CH<sub>2</sub>-), 3.86–3.95 (m, 6H, piperazine–CH<sub>2</sub>–, oxa–CH<sub>2</sub>–), 3.07–3.13 (m, 4H, piperazine–CH<sub>2</sub>–); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ 159.3, 156.8, 153.8, 153.7, 153.5, 150.9, 150.1, 138.0, 136.2, 134.4, 132.9, 132.5, 132.2, 131.7, 131.0, 130.0, 129.3, 128.6, 128.1, 125.4, 124.8, 123.9, 118.7, 117.1, 116.5, 116.1, 113.7, 108.6, 107.3, 80.1, 70.9, 50.8, 46.3, 44.8; ESIMS: m/z 781 (M + H)<sup>+</sup>, 803 (M + Na)<sup>+</sup>; HRMS: (ESI m/z) for  $C_{40}H_{34}ClFN_6O_6SNa$  calcd. 803.1838, found 803.1829 (M + Na)<sup>+</sup>; Anal. calcd. for C<sub>40</sub>H<sub>34</sub>ClFN<sub>6</sub>O<sub>6</sub>S: C, 61.48, H, 4.39, N, 10.76. Found: C, 61.49; H, 4.38, N, 10.78.

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