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Original article

Hybrids of privileged structures benzothiazoles and pyrrolo[2,1-*c*] [1,4] benzodiazepin-5-one, and diversity-oriented synthesis of benzothiazoles

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ABSTRACT

Privileged structures like Benzothiazole and Pyrrolobenzodiazepine offer wonderful opportunity to explore in anti-cancer drug discovery as a mean to counter drug-resistance problem. BT-PBD hybrids and diverse BT derivatives have been synthesized and their in vitro cytotoxic activities were screened against five cancer cell lines have been discussed. The novel compounds showed promising results as compared with the marketed drug etoposide and could well be used in future anti-cancer drug development studies.

1. Introduction

Vast number of chemotherapeutic anti-cancer drugs are presently available for clinical use which are broadly classified into three major groups based on their mode of action; genotoxic agents, antimetabolites, and mitotic spindle inhibitors [1]. However, there is a continuous demand for the development of new anti-cancer drugs due to the development of drug resistance among cancer cells [2]. In this scenario, privileged structures [3] in medicinal chemistry offer a hugely explorable platform in the development of new chemical entities for future perspective. Among several privileged structures known, we have been involved in the development of expeditious synthetic methods and applications related to benzothiazoles (BT), pyrrolobenzodiazepines (PBD), quinolines, dihydropyrimidinones and few others [4]. Noteworthy among them are BT and PBD for their recent anti-cancer profile. Exploration of BT bicyclic system has resulted in the successful generation of biologically active compounds across a wide range of therapeutics [5]. Especially after the recognition of DF 203 and 5F 203 (Phortess prodrug) [6] as novel anti-cancer drug candidates (Fig. 1), attracted our interest to explore BT chemical space. The mode of action of DF 203 and 5F 203 is unique in nature as they are potent AhR (aryl hydrocarbon receptor) binders in sensitive tumor cells leading to DNA damage by reactive intermediates generation through a sequence of complex processes. Similarly, the anti-cancer profile of natural and synthetic PBDs due to their inherent ability to bind DNA minor groove is well known and explored in the field [7]. On the other hand, diversity-oriented synthesis (DOS) has gained considerable interest to explore chemical space in the discovery of new drugs and targets for chemotherapy [8] and DOS around privileged structures have been termed as '*rationale DOS*' [9]. The present article describes molecular hybridization of BT-PBD systems (Fig. 2) and diversity-oriented synthesis of BT leading to the generation of few potent anti-cancer candidates.

2. Results

2.1. Chemistry

Retrosynthetic analysis for molecules **1a**, **1b**, and **1c** (Scheme 1) reveals that the approach towards the key intermediate 4-(6-substituted-1,3-benzothiazol-2-yl)-2-nitrobenzoic acids (**2a**, **2b** and **2c**) for A-ring and (2*S*)-2-[di(ethylsulfanyl)methyl]tetrahydro-1*H*-pyrrole (**3**) another key intermediate for the construction of C-ring of benzothiazolopyrrolo[2,1-*c*] [1,4]benzodiazepines (**1a**, **1b**, and **1c**).

We began our study on the preparation of key intermediates benzothiazolyl-2-nitrobenzoic acids **2a**–**c** (Scheme 2) by the

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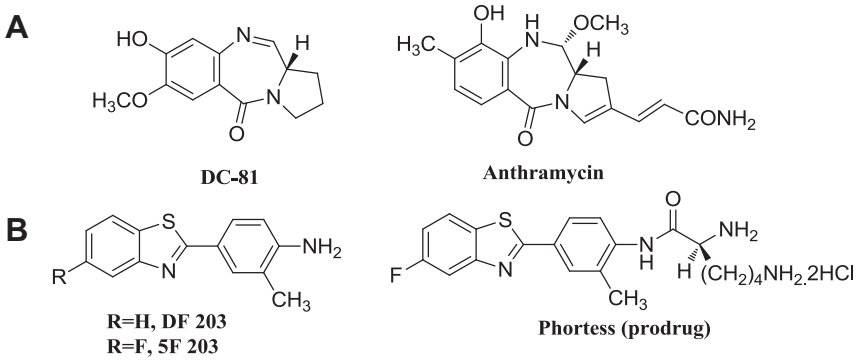
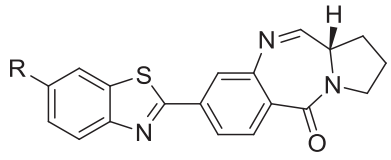


Fig. 1. (A) Naturally occurring PBDs (B) BTA, anti-cancer drug candidates.



Benzothiazole-pyrrolobenzodiazepine hybrids

R= OMe (**1a**), F (**1b**), H (**1c**)

Fig. 2. BTA-PBD hybrids.

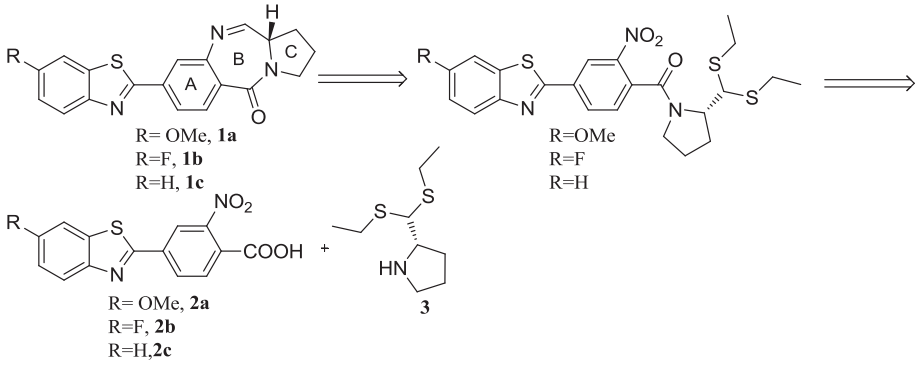
nitration of readily available *p*-toluic acid by using a modified version of the method reported in the literature where trifluoroacetic anhydride was used along with ammonium nitrate [10]. Thus, *p*-toluic acid was treated with ammonium nitrate in the presence of conc. H_2SO_4 in dichloromethane at 0 °C to afford nitro compound **4** in 92% yield as a light yellow solid. Compound **4** was treated with thionyl chloride to obtain acid chloride, which was coupled with *p*-anisidine in the presence of triethylamine to afford amide **4a** in 85% yield as light yellow crystals. Amide **4a** was then treated with Lawesson's reagent [11] in dry toluene under reflux conditions to afford thioamide **5a** as pale yellow prism in 88% yield. Intramolecular cyclization of thioamide **5a** using Dess-Martin periodinane (DMP) [4b], in CH_2Cl_2 at room temperature within 15 min resulted in the formation of 2-arylbenzothiazole **6a** as a light yellow solid in 90% yield. Compound **6a** upon treatment with tetrabutylammonium permanganate, TBAP [12] in dry pyridine at room temperature afforded benzothiazolyl-2-nitrobenzoic acid **2a** as a free flowing light yellow solid in 87% yield. The rest of the benzothiazolyl-2-nitrobenzoic acids **2b** and **2c** were synthesized by using the same reaction sequences.

(2*S*)-2-[Di(ethylsulfanyl)methyl]tetrahydro-1*H*-pyrrole, **3** [13] aliphatic skeleton was synthesized by a modified route to improve the yield and optical purity. This route afforded maximum yields with excellent optical purity (as it avoids reagents like DIBAL-H). The synthesis of protected tetrahydro-1*H*-pyrrole (**3**) was started with the treatment of (*S*)-proline with benzyl chloroformate in the presence of aqueous sodium bicarbonate giving *N*-carbobenzoxy derivative (**7**) in 97% yield as a colorless sticky compound (Scheme 3). Compound **7** was reacted with sodium borohydride and iodine in dry THF [14] to give Cbz-(*S*)-prolinol **8** as a colorless gummy liquid in 74% yield. Oxidation of primary alcohol present in compound **8** led to aldehyde **9** within 1 h in 90% yield using cyanuric chloride and stoichiometric dry DMSO in THF [15].

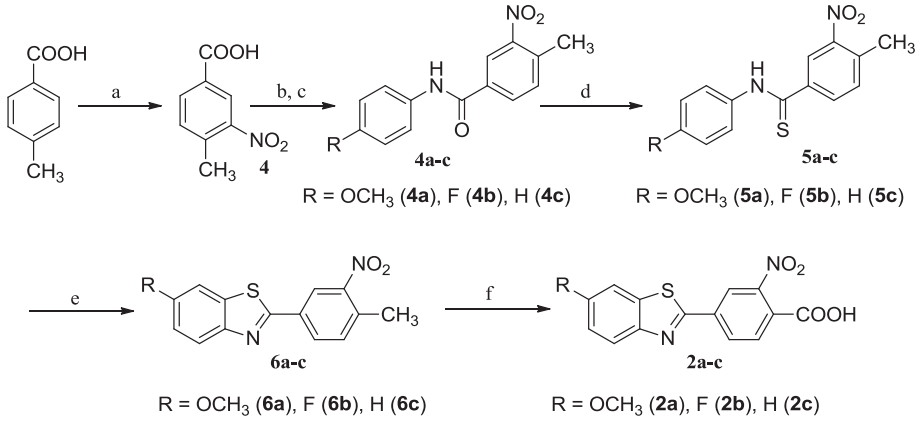
Aldehyde **9** was immediately converted to diethylthioacetal derivative (**10**) by treating with ethanethiol in the presence of Lewis acid trimethylsilyl chloride (TMSCl), in dry dichloromethane. Free amine (**3**) was generated from the ethanethiol protected *N*-carbobenzoxy derivative (**10**) using TMSI (*insitu* generated from NaI and TMSCl in CH_3CN) in 85% yield. Coupling of nitro acids **2a**–**c** with (*S*)-pyrrolidine-2-carbaldehyde diethyl dithioacetal **3** afforded the key intermediate amides **11a**–**c** (Scheme 4). Reduction of nitro group in compounds **11a**–**c** were carried out by treating with $SnCl_2 \cdot 2H_2O$ in methanol for 1 h afforded the corresponding aminodiethylthioacetal derivatives, **12a**–**c** around 50–55% yields. Finally, the crucial step of deprotection of thioacetal group of compounds **12a**–**c** was performed using $HgCl_2/CaCO_3$ in CH_3CN/H_2O (4:1) resulting in the *insitu* formation of the intermediate amino-aldehyde which upon subsequent ring closure to afford target BTA-PBD compounds **1a**–**c** in 55–38% yields.

2.1.1. DOS of benzothiazoles

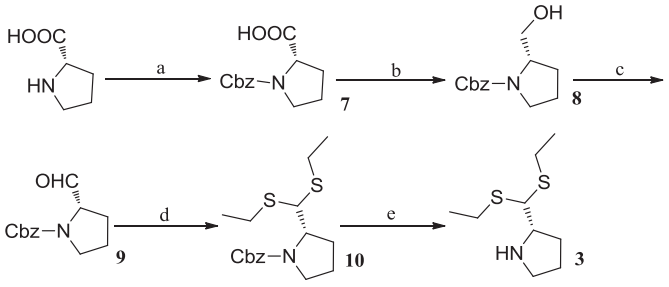
This diversity-oriented synthesis of benzothiazoles was classified into two series of forward synthetic schemes (i) synthesis of



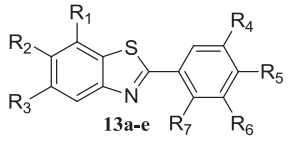
Scheme 1. Retrosynthetic analysis of BTA-PBD hybrids.



Scheme 2. (a) NH_4NO_3, conc. H_2SO_4, CH_2Cl_2, 0 °C-R. T., 4–5 h (b) $SOCl_2$, cat. DMF, benzene, reflux (c) 4-R-aniline, Et_3N, dry THF, 0 °C-R. T., 2 h (d) Lawesson's reagent, toluene, reflux, 1–2 h (e) DMP, CH_2Cl_2, R.T., 15 min (*f*) tetrabutylammonium permanganate (TBAP), dry pyridine, R.T., 12 h.



Scheme 3. (a) Benzyl chloroformate, aq. $NaHCO_3$, 16 h, 0 °C-R. T. (b) $NaBH_4/I_2$, THF, reflux, 18 h (c) cyanuric chloride/DMSO, THF, −30 °C, 1 h (d) EtSH, TMSCl, CH_2Cl_2, 16–24 h, R. T. (e) TMSCl/NaI, CH_3CN, 0 °C-R.T.



13a: R_1= H, R_2= OCH_3, R_3= H
R_4= NH_2, R_5= CH_3, R_6= H, R_7= H

13b: R_1= H, R_2= F, R_3= H
R_4= NH_2, R_5= CH_3, R_6= H, R_7= H

13c: R_1= H, R_2= H, R_3= H
R_4= NH_2, R_5= CH_3, R_6= H, R_7= H

13d: R_1= OCH_3, R_2= OCH_3, R_3= OCH_3
R_4= H, R_5= H, R_6= NH_2, R_7= CH_3

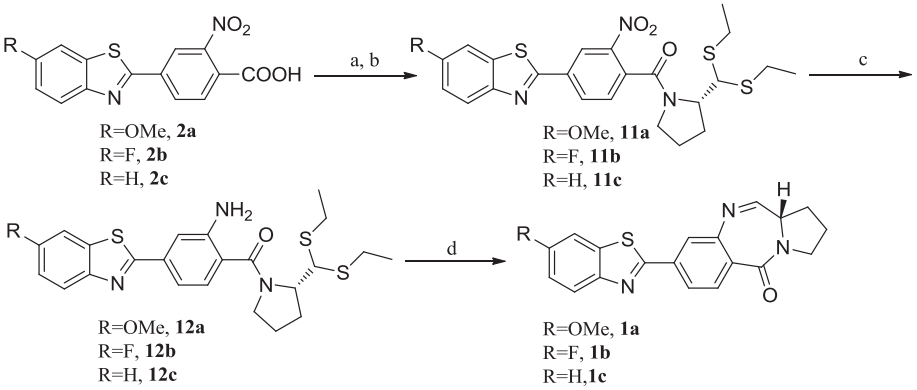
13e: R_1= H, R_2= OCH_3, R_3= H
R_4= H, R_5= NH_2, R_6= H, R_7= H

Fig. 3. Substituted benzothiazole amines.

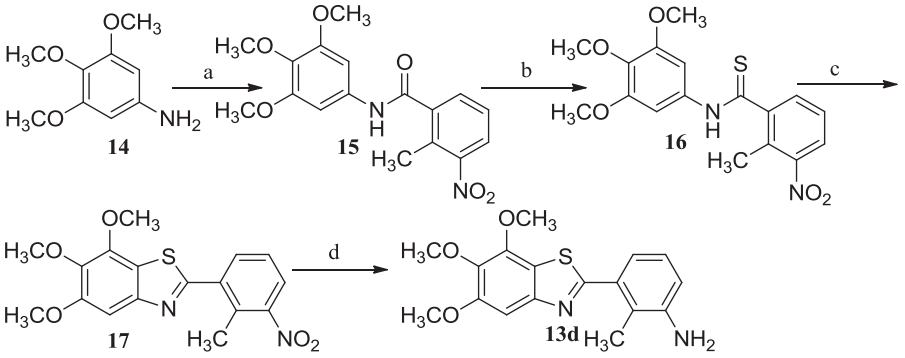
diverse benzothiazole amines (BTA amines, Fig. 3) (ii) diversification of 6-fluoro-2-[4-methylphenyl]benzothiazole.

A typical synthetic scheme of BTA-amine **13d** was started with the reaction between 3,4,5-trimethoxyaniline **14** and 2-methyl-3-nitrobenzoyl chloride using triethylamine in THF to obtain amide **15** in 85% yield as colorless solid (Scheme 5). Amide **15** was converted to thioamide **16** using Lawesson's reagent in toluene under reflux conditions in 85% yield. Thioamide **16** was reacted with Dess-Martin periodinane in CH_2Cl_2 at room temperature leading to the formation of 2-arylbenzothiazole **17** (BTA **17**) in 90% yield as pale yellow solid. BTA **17** was finally reduced with $SnCl_2{\cdot}2H_2O$ in methanol under reflux conditions afforded the benzothiazole amine **13d** in 58% yield. By adopting the similar strategy described above, the other benzothiazole amines (**13a**–**c** and **13e**) were synthesized.

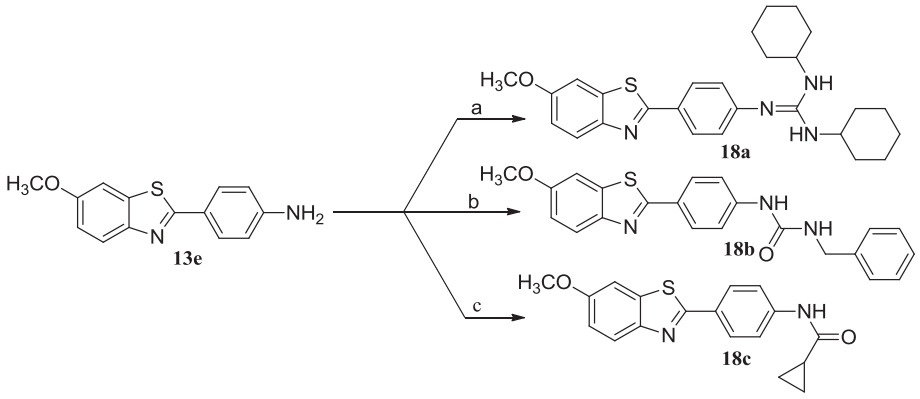
Next, we turned our attention to diversify BTA-amine **13e** in three different ways (Scheme 6). Medicinally important guanidine pharmacophore (found in a vast number of drugs, drug candidates and antiproliferative natural products like lucentamycins A–D, clethramycin, pyrronamycins A and B, Cimipronidine etc.) [16] was incorporated in BTA-amine **13e** by coupling primary amine with *N*,*N*-1,3-dicyclohexylcarbodiimide in dry THF in the presence of catalytic *N*-hydroxybenzotriazole for about 18 h at room temperature. The guanidine-BTA derivative **18a** was obtained as a colorless solid upon column chromatography in 75% yield. BTA-amine **13e** was further diversified by the incorporation of urea



Scheme 4. (a) $SOCl_2$, cat. DMF, benzene, 80 °C, 2 h (b) (2*S*)-pyrrolidine-2-carboxaldehyde diethyl dithioacetal (**3**), Et_3N, THF, 0 °C-R.T., 2 h (c) $SnCl_2{\cdot}2H_2O$, MeOH, 1 h, Reflux (d) $HgCl_2$, $CaCO_3$, CH_3CN/H_2O (4:1), R.T., 12–24 h.



Scheme 5. (a) 2-methyl-3-nitrobenzoyl chloride, Et_3N, THF, 0 °C-R.T. (b) Lawesson's reagent, toluene, reflux, 2 h (c) DMP, CH_2Cl_2, 15 min, R.T. (d) $SnCl_2{\cdot}2H_2O$, MeOH, reflux, 2 h.

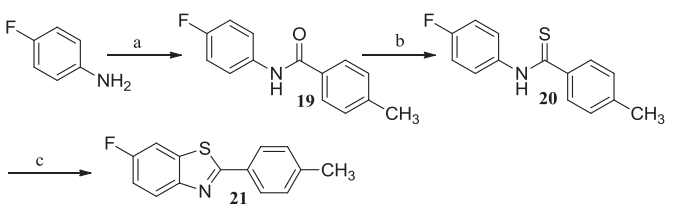


Scheme 6. (a) *N*,*N*-dicyclohexylcarbodiimide (DCC), HOBt, THF, R. T., 12 h (b) benzylisocyanate, Et_3N, THF, R.T., 12 h (c) cyclopropane carbonylchloride, Et_3N, THF, R.T.

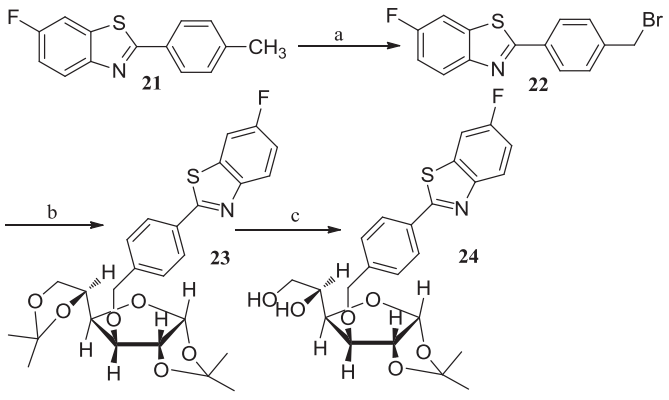
pharmacophore by reacting it with benzylisocyanate in Et_3N using dry THF as the solvent at room temperature for 12 h to afford BTA-urea compound **18b** in 88% yield as colorless solid. Finally, a cyclopropyl amide **18c** was prepared by the reaction between BTA-amine **13e** and cyclopropane carbonylchloride in the presence of Et_3N in dry THF for 1–2 h in 82% yield.

Diversification of 6-fluoro-2-[4-methylphenyl]benzothiazole **21** was performed to synthesize benzothiazole-D-glucose and benzothiazole-*S*-proline hybrid molecules. Initially, the parent molecule 6-fluoro-2-[4-methylphenyl]benzothiazole **21** was synthesized (Scheme 7) by the method described for the synthesis of compound **6a**. Bromination of compound **21** at benzylic position was carried out by using NBS (*N*-bromosuccinimide) and catalytic amount of benzoyl peroxide in CCl_4 but resulted in bromination at an unidentified position in the aromatic ring. Similarly, it was studied with $Br_2/CHCl_3$ but the required monobromo compound was formed in very little amount beside a number of byproducts. However, side-chain bromination with $NaBrO_3$ and $NaHSO_3$ mixture in ethyl acetate/H_2O solvent system at room temperature for 4–5 h gave a good yield (92%) of the monobromo compound **22** exclusively without any side products (Scheme 8) [17].

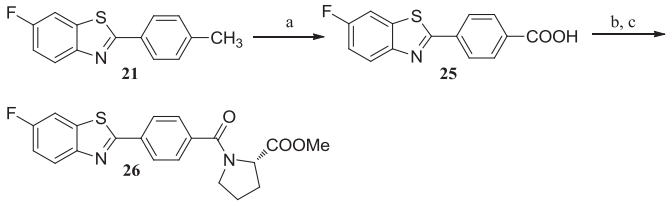
Compound **22** was reacted with D-glucose diacetonide (prepared by the treatment of D-glucose in dry acetone using anhydrous $ZnCl_2$ and catalytic H_3PO_4 at room temperature for 24 h) using NaH in CH_3CN to afford the benzothiazoles-D-glucose diacetonide **23**. Selective deprotection of acetonide group at 5,6 position in compound **23** with 0.8% H_2SO_4 in methanol at room temperature for 12 h to afford monodeprotected acetonide compound **24** in 80% yield. This approach of utilization of carbohydrates especially D-glucose is reported in literature (relating to the exploitation of Warburg effect in cancer cells) [18]. Compound **21** was further diversified by oxidizing the benzylic methyl group to the corresponding carboxylic functionality followed by the amide bond formation with *S*-proline methyl ester to produce a benzothiazole-amino acid hybrid molecule (Scheme 9). We first examined the oxidation of compound **21** using periodic acid (H_5IO_6) and catalytic chromic acid (CrO_3) in CH_3CN at room temperature [19] to afford benzothiazole carboxylic acid **25** in 90% yield. Compound **25**



Scheme 7. (a) 4-methylbenzoyl chloride, Et_3N, TH, 0 °C-R. T. (b) Lawesson's reagent, toluene, reflux, 2 h (c) DMP, CH_2Cl_2, 15 min, R.T.



Scheme 8. (a) $NaBrO_3/NaHSO_3$, ethyl acetate/H_2O, 4–5 h, R. T. (b) *d*-glucose diacetonide, NaH, CH_3CN, R.T. (c) 0.8% H_2SO_4, MeOH, R.T.



Scheme 9. (a) H_5IO_6/cat. CrO_3, CH_3CN, 1–2 h, R. T (b) $SOCl_2$, benzene, reflux (c) (*S*)-proline methyl ester HCl, Et_3N, THF, 2 h, 0 °C-R.T.

was converted to acid chloride by reacting with $SOCl_2$ in reflux benzene for 1–2 h using catalytic DMF followed by the reaction with (*S*)-proline methyl ester hydrochloride in dry THF and Et_3N to give the amide **26** in 82% yield.

2.2. Biological assay

Cytotoxic activities of the synthesized compounds (**1a**–**c**, **13a**–**e**, **18a**–**c**) have been evaluated in vitro against five tumor cell lines: THP-1 (human acute monocytic leukemia), U-937 (human histiocytic lymphoma), HL-60 (human promyelocytic leukemia), Jurkat (Human T-cell leukemia) and A-549 (lung carcinoma). All leukemia cell lines (THP-1, U-937, HL-60, and Jurkat) were cultured in RPMI-1640 and A-549 were cultured in DMEM. Both media were supplemented with 10% heat-inactivated FCS, 1 mM $NaHCO_3$, 2 mM L-glutamine and penicillin–streptomycin in a humidified atmosphere of 95%, 5% CO_2 at 37 °C. Initially, the stock concentrations were prepared by dissolving 8 mg of each test compound in 1 mL of DMSO and further diluted to obtain required experimental stock solution from 0.1 to 100 ppm and obtained the final volume of 200 μL. In all the experiments, HL-60, THP-1, U-937, Jurkat and A-549 cells were seeded at a final density of 2×10^4 cells per well in 96 well microtiter plates. The cells were treated with different test concentrations of **1a**–**c**, **13a**–**e**, and **18a**–**c** and their cytotoxicities were compared with the activity of positive controls, Camptothecin and Etoposide at identical conditions with five replicates each. Cytotoxicity was measured using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) as described by Mosmann [20]. In brief, the cells (2×10^4) were seeded in each well containing 0.1 mL of RPMI medium or DMEM in 96 well plates. After 24 h, different test concentrations were added and cell viability was assessed after 2 days, by adding 10 μl per well of MTT (3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide; 5 mg/mL; stock solution, Sigma). The plates were incubated at 37 °C for additional 4 h. The medium was discarded and the formazan blue, formed in the cells, was dissolved with 100 μL of DMSO. The rate of color production was measured at 570 nm in a spectrophotometer (Spectra MAX Plus; Molecular Devices; supported by SOFT max PRO-3.0). All experiments were conducted under the standard laboratory illumination. The percent inhibition of cell viability was determined with reference to the control values (without test compound). The data were subjected to linear regression analysis and the regression lines were plotted for the best straight-line fit. The IC_{50} (inhibition of cell viability) concentrations were calculated using the respective regression equation. Among the 12 compounds tested in this series, only 6 compounds **1a**–**c**, **13d**, **18a** and **24** showed significant cytotoxic activities (the remaining compounds showed IC_{50} values more than 50 μM). Based on the regression equation, IC_{50} values of the selected potent compounds were calculated and the results are presented (Table 1).

3. Discussion and conclusions

In the present work, we have disclosed new anti-cancer compounds having BT as core privileged sub-structure. Our approach consisted syntheses of BT-PBD hybrids (combining two privileged structures known to have different mechanism of action for cytotoxicity) and diversity-oriented synthesis of benzothiazoles. All the BT-PBD hybrids showed potent activities; however, the fluoro analogue **1b** showed better activities on an average and specifically showed more potent activity on THP-1 cancer cell line. Higher activity by the fluoro analogue **1b** could be attributed to the cell-permeability factor which is usually enhanced by fluoro compounds. Among DOS generated BT molecules, noteworthy are BT amine **13d** and 5,6-deprotected BT-glucose derivative **24**. Interestingly, the diacetonide BT-glucose derivative **23** did not show any significant anti-cancer activity (more than 50 μM) in the tested cancer cell lines. Here we assume that membrane penetration and accumulation is facilitated when 5,6-position of glucose moiety is free and hence particularly compound **24** is showing anti-cancer activity. The new BT compounds **13d** and **23** provided wonderful leads for further SAR studies and our future directions could lead us into their optimization, mechanistic and modeling studies.

In conclusion, we describe herein the coupling of two different pharmacophores, each endowed with different biological properties, afforded the hybrid compound, whose biological profile was markedly improved. In this initial study, our aim was to identify few new anti-cancer leads having BT system which could be developed further by SAR and optimization. Accordingly, novel BT-PBD hybrids and diverse BT derivatives have been synthesized and evaluated for their in vitro cytotoxic activities against five cancer cell lines. Overall the activities are in the range of the marketed drug etoposide and in the case of U-937 cell lines, few compounds showed similar activities as camptothecin. We anticipate that the hybrid BT-PBD synthesis and the DOS strategies described in the manuscript could be explored further to have interesting implications in the fields of chemistry-driven drug discovery and combinatorial chemistry.

Table 1
In vitro cytotoxicity data of compounds **1a**–**c**, **13d**, **18a**, and **24** on THP-1, A-549, HL-60, Jurkat and U-937 tumor cell lines.

Compound	IC_{50} (μM) ± SE				
	THP-1	A-549	HL-60	Jurkat	U-937
1a	2.14 ± 0.18	N/T	6.39 ± 2.12	11.27 ± 1.40	6.03 ± 0.51
1b	0.49 ± 0.11	N/T	4.13 ± 1.57	6.58 ± 1.05	3.44 ± 0.29
1c	3.09 ± 0.26	N/T	7.27 ± 3.15	9.43 ± 1.56	5.41 ± 0.44
13d	3.56 ± 0.48	4.56 ± 0.38	5.63 ± 0.35	9.75 ± 0.85	N/T
18a	3.1 ± 0.26	3.23 ± 0.27	7.15 ± 0.60	2.23 ± 0.12	N/T
24	3.0 ± 0.22	5.01 ± 0.42	22.28 ± 5.68	3.20 ± 0.27	N/T
Etoposide	2.16 ± 0.15	9.51 ± 1.33	1.83 ± 0.20	5.35 ± 0.63	17.94 ± 1.19
Camptothecin	0.071 ± 0.0053	0.008 ± 0.006	0.600 ± 0.03	0.026 ± 0.002	1.980 ± 0.11

N/T=Not Tested.

4. Experimental section

4.1. Chemistry

All reactions were monitored by analytical Thin Layer Chromatography (TLC) performed on E-Merck 0.25 mm precoated silica gel glass plates (60 F_{254}). Visualization of the spots on TLC plates was achieved either by exposure to UV light or iodine vapor or by dipping the plates in ethanolic solution of phosphomolybdic acid (PMA) and heating the plates at 120 °C. Column chromatography was performed using silica gel (Acme, 60–120 mesh). Solvents were dried according to conventional methods and purified by distillation prior to use. Solvents for chromatography (*n*-hexane and EtOAc) were distilled prior to use. Evaporations were carried out under reduced pressure on Buchi rotary evaporator below 40–44 °C. Melting points were obtained using a precision digital melting point Veego VMP-DS apparatus and are uncorrected. IR spectra were obtained on a Perkin–Elmer 683 or 1310 spectrophotometer with sodium chloride optics or KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker Avance 300 (300.132 MHz for ^{1}H, 75.473 MHz for ^{13}C), or Varian FT-200 MHz (Gemini) spectrometer in $CDCl_3$ or DMSO-d_6. Chemical shifts have been expressed in parts per million (δ) relative to tetramethylsilane ($\delta = 0.0$) as an internal standard and coupling constants (*J*) in Hertz. Optical rotations were measured using JASCO DIP-370 digital polarimeter at 20 °C. Elemental analyses were performed using an Elementar Vario EL microanalyzer. Microanalysis of all the synthesized compounds agreed within ±0.3% of calculated values. Low-resolution mass spectra (ESI-MS) and HRMS were recorded on Quattro LC, Micromass and Q STAR XL, Applied Biosystems respectively.

4.1.1. 4-Methyl-3-nitrobenzoic acid (**4**)

To a stirred solution of 4-methylbenzoic acid (13.61 g, 0.1 mol) in CH_2Cl_2 (100 mL) was added NH_4NO_3 (7.60 g, 0.1 mol) and stirred for 10 min. To the above mixture conc. H_2SO_4 (18.5 mL, 0.35 mol) was added drop wise at 0 °C for a period of 15 min while stirring. Stirring was continued at room temperature for a period of 2–5 h till TLC showed the completion of the reaction. The reaction mixture was quenched with cold water (200 mL) and then allowed to return to room temperature. The organic layer was washed several times with water to remove acidic impurities and evaporated under reduced pressure to afford crude solid. Recrystallization using EtOAc: petroleum ether mixture to give **4** as light yellow prisms (16.66 g) in 92% yield. m.p. 178–180 °C (lit. 184–185 °C [21]); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.65 (s, 3H, Ar-CH_3), 7.41–7.49 (d, 1H, $J = 7.73$ Hz, Ar-H), 8.08–8.16 (dd, 1H, $J_1 = 8.50$ Hz, $J_2 = 1.55$ Hz, Ar-H), 8.51–8.54 (d, 1H, $J = 1.55$ Hz, Ar-H).

4.1.2. N1-(4-Methoxyphenyl)-4-methyl-3-nitrobenzamide (**4a**)

Nitro acid **4** (5.5 g, 30.38 mmol) was converted to 4-methyl-3-nitrobenzoyl chloride (6.06 g, 30.38 mmol) using $SOCl_2$ and dry benzene at 80 °C in the presence of catalytic amount of DMF (2 drops). Freshly prepared acid chloride was added drop wise to a stirred solution of *p*-anisidine (3.816 g, 31.00 mmol) and Et_3N (10 mL) in dry THF (35 mL) at 0 °C and the stirring was continued at room temperature for a period of 2–3 h. Solvent THF was evaporated under reduced pressure. The crude solid was washed with a saturated solution of $NaHCO_3$, 1N HCl and cold water to remove if any unreacted starting materials were present. The crude solid was filtered through Buchner funnel and recrystallized using MeOH to afford **4a** (7.30 g) as a light yellow crystalline solid in 85% yield. m.p. 150–152 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.69 (s, 3H, Ar-CH_3), 3.81 (s, 3H, Ar-OCH_3), 6.82–6.90 (d, 2H, $J = 9.06$ Hz, Ar-H), 7.42–7.53 (m, 3H, Ar-H), 7.66–7.72 (br s, CONH), 8.00–8.07 (d, 2H, $J = 7.55$ Hz, Ar-H), 8.38 (s, 1H, Ar-H); MS (ESI): *m*/*z* (%) = 287 (M + H, 100), 309 (M + Na^+, 50); Anal. Calcd. for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. Found: C, 63.10; H, 4.88; N, 9.62.

4.1.3. N-(4-Fluorophenyl)-4-methyl-3-nitrobenzamide (**4b**)

Brownish solid; Yield 83.5%; m.p: 140–141 °C; IR (KBr): *v* 3463, 3014, 2970, 2946, 1740, 1438, 1368, 1215, 1093, 900, 830, 734 cm^{-1}; ^{1}HNMR (300 MHz, DMSO- d_6): δ 2.65 (s, 3H, Ar-CH_3), 7.05–7.10 (m, 2H, Ar-H), 7.5 (d, 1H, $J = 8.1$, Ar-H), 7.74–7.83 (m, 2H, Ar-H), 8.21 (dd, 1H, $J_1 = 8.1$ Hz, $J_2 = 1.7$Hz, Ar-H), 8.65 (d, 1H, $J = 1.7$, Ar-H), 10.4 (br s, 1H, CONH); ^{13}C NMR (300 MHz, DMSO-d_6): δ 19.5, 115.05, 115.3, 122.3, 123.5, 132.0, 133.1, 133.5, 135.0, 136.3, 148.7, 156.8, 160.0, 162.9; MS(ESI): *m*/*z* (%) = 274 (M + H, 100); Anal. Calcd. for $C_{14}H_{11}N_2O_4$: C, 61.31; H, 4.04; N, 6.93. Found: C, 61.38; H, 4.98; N, 6.88.

4.1.4. 4-Methyl-3-nitro-N-phenylbenzamide (**4c**)

Colourless solid; Yield 86.1%; m.p.135–136 °C; IR (KBr): *v* 3460, 3013, 2970, 2946, 1740, 1438, 1368, 1215, 1092, 901 cm^{-1} ^{1}HNMR (300 MHz, DMSO- d_6): δ 2.65 (s, 3H, Ar-CH_3), 7.1 (m, 1H, Ar-H), 7.3 (t, 2H, $J = 7.9$Hz, Ar-H), 7.5 (d, 1H, $J = 7.8$, Ar-H), 7.7 (d, 2H, $J = 7.8$ Hz, Ar-H), 8.2 (d, 1H, $J = 7.8$ Hz, Ar-H), 8.6 (s, 1H, Ar-H), 10.2 (br s, 1H, NH); ^{13}C NMR (300 MHz, DMSO- d_6): δ 19.5, 120.5, 123.5, 124.0, 128.6, 132.0, 133.0, 133.7, 136.2, 138.7, 148.7, 163.1; MS (ESI): *m*/*z* (%) = 257 (M + H, 100).

4.1.5. N1-(4-Methoxylphenyl)-4-methyl-3-nitro-1-benzenecarbothioamide (**5a**)

Lawesson's reagent (5.07 g, 12.55 mmol) was added to the stirred solution of amide **4a** (7.15 g, 25.00 mmol) in dry toluene (50 mL) at 60 °C. The mixture was then refluxed for 1–2 h till TLC showed the completion of the reaction. After the completion of the reaction, solvent toluene was evaporated under reduced pressure. The resulting residue was quenched with 5 mL of Sodium hypochlorite solution (available approx. 4% chlorine). Ice-cubes were added to it to get dark yellow colored crude solid which was filtered through Buchner funnel. Recrystallization (using acetone: water mixture) followed by column chromatography using EtOAc: petroleum ether (2:5) afforded pure pale yellow colored prisms **5a** (6.64 g) in 88% yield. m.p. 132–134 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.67 (s, 3H, Ar-CH_3), 3.84 (s, 3H, Ar-OCH_3), 6.88–6.99 (d, 2H, $J = 8.81$ Hz, Ar-H), 7.36–7.47 (d, 1H, $J = 7.35$ Hz, Ar-H), 7.56–7.69 (d, 2H, $J = 8.08$ Hz, Ar-H), 8.03–8.13 (d, 2H, $J = 7.35$ Hz, Ar-H), 8.33 (s, 1H, Ar-H), 8.97 (br s, 1H, CONH); MS (ESI): *m*/*z* (%) 303 (M + H); Anal. Calcd. for $C_{15}H_{14}N_2O_3S$: C, 59.59; H, 4.67; N, 9.27. Found: C, 59.39; H, 4.55; N, 9.35.

4.1.6. N-(4-Fluorophenyl)-4-methyl-3-nitrothiobenzanilide (**5b**)

pale yellow solid; Yield 85.2%; m.p. 138–139 °C; IR (KBr): *v* 3462, 3346, 2970, 1740, 1509, 1439, 1367, 1215, 1094, 1076, 910, 833, 800, 732, 694, 608 cm^{-1}; ^{1}HNMR (500 MHz, DMSO-d_6): δ 2.53 (s, 3H, Ar-CH_3), 7.14 (t, 2H, $J = 8.89$ Hz, Ar-H), 7.36 (d, 1H, $J = 7.91$ Hz, Ar-H), 7.68–7.73 (m, 2H, Ar-H), 8.02 (d, 1H, $J = 7.91$, Ar-H), 8.38 (d, 1H, $J = 1.7$ Hz, Ar-H), 11.61(br s, 1H, NH); ^{13}C NMR (300 MHz, DMSO-d_6), 19.4, 115.1, 115.4, 123.1, 126.5, 131.7, 132.5, 135.3, 136.0, 140.7, 148.2, 158.2, 161.5, 194.4; MS (ESI): *m*/*z* (%) = 291 (M + H, 100).

4.1.7. 4-Methyl-3-nitro-N-phenylthiobenanilide (**5c**)

Bright yellow crystal; Yield 87.4%; m.p. 124.5–126.0 °C; IR (KBr): *v* 3450, 3308, 3070, 2928, 1617, 1521, 1444, 1398, 1346, 1209, 1069, 1022, 994, 895, 817, 762, 689, 662, 578, 497, 415; ^{1}HNMR (300 MHz, DMSO-d_6): δ 2.63(s, 3H, Ar-CH_3),7.26–7.30 (m, 1H, Ar-H), 7.40–7.46 (m, 3H, Ar-H), 7.80 (d, 2H, $J = 7.9$ Hz, Ar-H), 8.12 (d, 1H, $J = 7.9$ Hz, Ar-H), 8.49 (s, 1H, Ar-H), 11.68 (br s, 1H, NH); ^{13}C NMR (300 MHz, DMSO- d_6), 19.3, 123.1, 124.1, 126.5, 128.5, 131.7, 132.5, 135.2, 139.6, 140.9, 148.2, 194.2. MS (ESI) : *m*/*z* (%) = 273 (M + H, 100).

4.1.8. 6-Methoxy-2-(4-methyl-3-nitrophenyl)-1,3-benzothiazole[4e] (**6a**)

Dess-Martin periodinane (4.66 g, 11.00 mmol) was added to a stirred solution of thioformanilide **5a** (3.00 g, 10 mmol) in CH_2Cl_2 (50 mL) at room temperature. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was quenched with H_2O (2 × 10 mL) and the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was initially dried with anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure, to afford the crude product which was purified by column chromatography on silica gel using EtOAc: petroleum ether (1:3) as eluent to give the 2-arylbenzothiazole **6a** as a light yellow solid (2.682 g) in 90% yield. m.p. 141–142 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.68 (s, 3H, Ar-CH_3), 3.90 (s, 3H, Ar-OCH_3), 7.06–7.11 (dd, 1H, J_1 = 9.06 Hz, J_2 = 3.02 Hz, Ar-H), 7.31–7.33 (d, 1H, J = 2.26 Hz, Ar-H), 7.41–7.46 (d, 1H, J = 8.30 Hz, Ar-H), 7.90–7.94 (dd, 1H, J = 9.06 Hz, Ar-H), 8.12–8.17 (d, 1H, J = 7.55 Hz, Ar-H), 8.58 (s, 1H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 55.8, 104.0, 116.2, 123.0, 124.0, 130.8, 132.9, 133.4, 135.4, 136.4, 148.4, 149.5, 158.1, 162.3; MS (ESI): m/z (%) = 301 (M^++H, 100); Anal. Calcd. for $C_{15}H_{12}N_2O_3S$: C, 59.99; H, 4.03; N, 9.33. Found: C, 60.12; H, 3.98; N, 9.21.

4.1.9. 6-Fluoro-2-(4-methyl-3-nitrophenyl)-1,3-benzothiazole[4e] (**6b**)

m.p. 154–156 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.70 (s, 3H, Ar-CH_3), 7.19–7.30 (m, 1H, Ar-H), 7.44–7.49 (d, 1H, J = 8.6 Hz, Ar-H), 7.56–7.62 (dd, 1H, J_1 = 2.34 Hz, J_2 = 7.81 Hz, Ar-H), 7.97–8.04 (m, 1H, Ar-H), 8.13–8.19 (dd, 1H, J_1 = 1.56 Hz, J_2 = 7.81 Hz, Ar-H), 8.60–8.62 (d, 1H, J = 1.56 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 107.8, 108.1, 115.3, 115.6, 123.3, 124.6, 127.0, 129.5, 131.0, 133.6, 136.0, 150.6, 162.4; MS (EI): m/z (%) = 288 (M^+ 100), 271 (98), 243 (95), 227 (10), 216 (25), 69 (30), 63 (30), 45 (20); Anal. Calcd. for $C_{14}H_9FN_2O_2S$: C, 58.33; H, 3.15; N, 9.72. Found: C, 58.53; H, 3.22; N, 9.66.

4.1.10. 2-(4-Methyl-3-nitrophenyl)-1,3-benzothiazole[4e] (**6c**)

m.p. 169–171 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.69 (s, 3H, Ar-CH_3), 7.37–7.56 (m, 3H, Ar-H), 7.88–7.93 (d, 1H, J = 7.55 Hz, Ar-H), 8.03–8.08 (d, 1H, J = 8.30 Hz, Ar-H), 8.18–8.22 (dd, 1H, J = 1.51 Hz, J = 8.30 Hz, Ar-H) 8.63–8.65 (m, 1H, Ar-H); MS (EI): m/z (%) = 271 (M^++H, 40); Anal. Calcd. for $C_{14}H_{10}N_2O_2S$: C, 62.21; H, 3.73; N, 10.36. Found: C, 62.45; H, 3.80; N, 10.22.

4.1.11. 4-(6-Methoxy-1,3-benzothiazol-2-yl)-2-nitrobenzoic acid (**2a**)

Freshly prepared (see procedure below) tetrabutylammonium permanganate, TBAP (6.31 g, 16.66 mmol) was added to a solution of 2-arylbenzothiazole **6a** (2.50 g, 8.33 mmol) in dry pyridine (50 mL) at room temperature. The reaction mixture became exothermic after stirring for 5 min. The reaction was continued at room temperature for a period of 12 h till TLC showed the completion of the reaction. The reaction mixture was poured into a mixture of $NaHSO_3$ and cold dilute HCl. The yellow solid product resulted was extracted with ethyl acetate (3 × 10 mL). The organic layer was evaporated under reduced pressure to get crude acid. Recrystallization using EtOAc: petroleum ether afforded **2a** (2.39 g) as a pale yellow solid in 87% yield. m.p. 221–222 °C; IR (KBr): ν 2925, 1715, 1601, 1538, 1369, 1225, 1143, 1025, 826, 792 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.91 (s, 3H, Ar-OCH_3), 7.06–7.15 (dd, 1H, J_1 = 8.85 Hz, J_2 = 2.72 Hz, Ar-H), 7.41–7.45 (m, 1H, Ar-H), 7.90–7.98 (m, 2H, Ar-H), 8.20–8.27 (d, 1H, J = 8.17 Hz, AR-H), 8.42 (s, 1H, AR-H); MS (ESI): m/z (%) = 331 (10); Anal. Calcd. for $C_{15}H_{10}N_2O_5S$: C, 54.54; H, 3.05; N, 8.48. Found: C, 55.02; H, 3.22; N, 8.66. The same procedure was followed for the syntheses of compounds **2b** and **2c**.

4.1.12. Procedure for the preparation of tetrabutylammonium permanganate (TBAP) reagent

$KMnO_4$ (4.00 g, 25.32 mmol) dissolved in minimum amount of water was added with stirring to an aqueous solution 150 mL of tetrabutylammonium bromide (9.38 g, 29.10 mmol).[12] Upon stirring for 10–15 min a purple colored precipitate formed in the reaction mixture, which was filtered using Buchner funnel and dried in calcium chloride desiccator for 10–12 h to obtain a purple solid TBAP reagent (8.68 g) in 95% yield.

4.1.13. 4-(6-Fluoro-1,3-benzothiazol-2-yl)-2-nitrobenzoic acid (**2b**)

m.p. 218–220 °C; IR (KBr): ν 3376, 2923, 1725, 1602, 1542, 1367, 1251, 1200, 818, 793 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.24–7.36 (dt, 1H, J_1 = 8.98 Hz, J_2 = 2.76 Hz, Ar-H), 7.70–7.78 (m, 1H, Ar-H), 7.86–8.09 (m, 2H, Ar-H), 8.26–8.32 (m, 1H, Ar-H), 8.48 (s, 1H, Ar-H); MS (ESI): m/z (%) = 319 (M + H, 10); Anal. Calcd. for $C_{14}H_7FN_2O_4S$: C, 52.83; H, 2.22; N, 8.80. Found: C, 53.08; H, 2.40; N, 9.01.

4.1.14. 4-(1,3-Benzothiazol-2-yl)-2-nitrobenzoic acid (**2c**)

m.p. 179–181 °C; IR (KBr): ν 3377, 2924, 1716, 1611, 1539, 1239, 1150, 756 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.36–7.60 (m, 2H, Ar-H), 7.93–8.14 (m, 3H, Ar-H), 8.27–8.34 (m, 1H, Ar-H), 8.50 (s, 1H, Ar-H); MS (ESI): m/z (%) = 301 (M + H, 8), 271 (45), 242 (100); Anal. Calcd. for $C_{14}H_8N_2O_4S$: C, 56.00; H, 2.69; N, 9.33. Found: C, 55.85; H, 2.60; N, 9.27.

4.1.15. (2S)-1-[(Benzyloxy)carbonyl]tetrahydro-1H-2-pyrrolecarboxylic acid (**7**)

To a stirred aqueous solution of *S*-proline (5.0 g, 43.48 mmol, 1.0 equiv) and $NaHCO_3$ (18.26 g, 217.40 mmol, 2.5 equiv) was added drop wise benzylchloroformate (8.16 g, 47.82 mmol, 1.1 equiv) at 0 °C and stirred overnight at room temperature. The reaction mixture was quenched with 1N HCl till pH 2. This solution was extracted with EtOAc (3 × 15 mL) treated with brine and dried over Na_2SO_4. Upon column chromatography using EtOAc: petroleum ether (1:3) afforded a colorless gummy compound **7** (10.5 g, 97% yield). $[\alpha]_D$ −73.57° (c 1.4, $CHCl_3$); IR (Neat): ν 2959, 2887, 1706, 1426, 1358, 1180, 1124, 1089, 765, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.85–2.33 (m, 4H, CH_2), 3.42–3.66 (m, 2H, CH_2), 4.31–4.42 (m, 1H, CH), 5.08–5.17 (m, 2H, Ar-CH_2), 7.20–7.36 (m, 5H, Ar-H); MS (ESI): m/z (%) = 250 (M + H, 55), (M + NH_4^+, 100).

4.1.16. Benzyl (2S)-2-(hydroxymethyl)tetrahydro-1H-1-pyrrolecarboxylate (**8**)

To a solution of Cbz-(*S*)-proline **7** (10.5 g, 46.25 mmol) in dry THF (100 mL) in a two necked round bottom flask was added $NaBH_4$ (3.98 g, 105.3 mmol) in three portions at 0 °C. After stirring the reaction mixture at 0 °C for ½ hour, I_2 (10.70 g, 42.16 mmol) dissolved in dry THF (25 mL) was added drop wise over a period of 30 min. This solution was refluxed for a period of 18 h till the TLC showed complete disappearance of the starting material. The milky reaction mixture was stirred further for 30 min at room temperature followed by the addition of methanol (50 mL) till a clear solution appears. A white paste was obtained after evaporation under reduced pressure. It was further quenched with 1N HCl and extracted with CH_2Cl_2 (3 × 20 mL). Column chromatography afforded a colorless gummy liquid Cbz-(*S*)-prolinol **8** (7.55 g, 74% yield). $[\alpha]_D$ −41.6° (c 1.73, $CHCl_3$) (lit. −41.8° (c 1.4, $CHCl_3$) [22]); IR (Neat): ν 3430, 3033, 2953, 2880, 1680, 1418, 1357, 1192, 1105, 1049, 747, 698 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.60–1.72 (m, 1H), 1.77–2.10 (m, 3H), 3.36–3.45 (m, 1H), 3.50–3.66 (m, 3H), 3.91–4.01 (m, 1H), 4.15–4.27 (br s, 1H), 5.11–5.15 (d, 2H, J = 3.77 Hz), 7.25–7.37 (m, 5H); MS (ESI): m/z (%) = 236 (M + H, 100).

*4.1.17. Benzyl (2S)-2-formyltetrahydro-1H-1-pyrrolecarboxylate (**9**)*

In a 100 mL two-necked round bottom flask was taken cyanuric chloride (5.65 g, 30.62 mmol, 1.2 equiv), and dissolved in dry THF. To this solution was added dry DMSO (10.86 mL, 153.14 mmol, 6.0 equiv), slowly at −30 °C. After 30 min was added Cbz-(*S*)-prolinol **8** (6.0 g, 25.53 mmol, 1.0 equiv) dissolved in dry THF (60 mL) at −30 °C and stirring was continued for further 30 min at −30 °C. Et_3N (21.32 mL, 153.14 mmol, 6.0 equiv), was added to the reaction mixture and the temperature was maintained for further 30 min at −30 °C. Slowly it was allowed to warm-up for room temperature and stirred for further 15 min. The organic solvents were evaporated under reduced pressure to get a white solid. To this was added Et_2O and the suspension was treated with 1N HCl till two clear layers develop. The organic layer was separated and treated with saturated solution of $NaHCO_3$, brine and Na_2SO_4. Flash chromatography using EtOAc: petroleum ether (1:2) afforded a colorless liquid Cbz-(*S*)-prolinal **9** (5.35 g, 90% yield). $[\alpha]_D$ −66.58° (c 1.06, $CHCl_3$) (lit. −74.42° (c 0.1384 $CHCl_3$) [23]); IR (Neat): *ν* 3450, 3033, 2955, 2884, 1705, 1415, 1355, 1204, 1173, 1120, 766, 699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 1.73–2.27 (m, 4H, CH_2), 3.35–3.76 (m, 3H, CH_2, CH), 4.10–4.38 (m, 1H, CH), 5.08–5.16 (d, 1H, *J* = 6.61 Hz, CH), 7.23–7.38 (m, 5H, Ar-H), 9.47 and 9.57 (s, 1H, rotameric C*H*O). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.88; H, 6.42; N, 5.96.

*4.1.18. Benzyl (2S)-2-[di(ethylsulfanyl)methyl]tetrahydro-1H-1-pyrrolecarboxylate (**10**)*

Ethanethiol (2.93 g, 47.18 mmol, 2.2 equiv) was added to a stirred solution of Cbz-(*S*)-prolinal **9** (5.0 g, 21.46 mmol, 1.0 equiv) in dry $CHCl_3$ (50 mL) under nitrogen atmosphere. After stirring for a period of 30 min trimethylsilyl chloride (6.75 mL, 53.66 mmol, 2.5 equiv) was added to it at room temperature. The reaction was continued for further 12–24 h till TLC showed the completion of the reaction. The reaction mixture was carefully neutralized using saturated solution of $NaHCO_3$, extracted with $CHCl_3$ (3 × 20 mL) treated with brine and dried over Na_2SO_4. The crude diethyl thioacetal was purified by column chromatography on silica gel using EtOAc: petroleum ether (1:5) to afford a pale yellow liquid **10** (7.27 g, 100% yield). $[\alpha]_D$ −48.5° (c 1.05, $CHCl_3$) (lit. −50.9° (c 0.2104 $CHCl_3$) [23a]); ^1H NMR (200 MHz, $CDCl_3$): *δ* 1.05–1.39 (m, 6H, $SCCH_3$), 1.70–1.84 (m, 1H, CH), 1.98–2.11 (m, 3H, CH_2, CH), 2.37–2.73 (m, 4H, CH_2), 3.38–3.48 (m, 1H, CH), 3.55–3.70 (m, 1H, CH), 4.16–4.27 (m, 1H, CH), 4.55–4.60 (d, 1H, *J* = 3.77 Hz, CH), 4.96–5.27 (m, 2H, Ar-CH_2), 7.23–7.38 (m, 5H, Ar-H); MS (ESI): *m*/*z* (%) = 340 (M + H, 10), 362 (M + Na, 80), 377 (M + K, 15); Anal. Calcd. for $C_{17}H_{25}NO_2S_2$: C, 60.14; H, 7.42; N, 4.13. Found: C, 60.09; H, 7.22; N, 4.24.

*4.1.19. (2S)-2-[Di(ethylsulfanyl)methyl]tetrahydro-1H-pyrrole (**3**)*

To a solution of TMSCl (3.47 mL, 27.44 mmol, 2.0 equiv) in dry CH_3CN (60 mL) containing molecular sieves at 0 °C was added sodium iodide (4.93 g, 32.89 mmol, 2.4 equiv) in portions over 10 min. Stirring was continued for a period of 1–2 h at room temperature till a brick red color of TMSI persisted. To this solution was added drop wise Cbz-(*S*)-proline diethyl thioacetal **10** (4.65 g, 13.71 mmol, 1.0 equiv) dissolved in dry acetonitrile (40 mL) over a period of 30 min. Stirring is continued for further approximately 1–2 h till the TLC (EtOAc: petroleum ether, 1:1) showed the completion of the reaction. After quenching with methanol (15 mL) and evaporation at 35 °C under reduced pressure, the resulting oil was dissolved in ether (50 mL) and extracted with 0.5 N HCl (3 × 20 mL). The combined aqueous layers, after adjusting to pH 8 with 2N NaOH, were back-extracted with ether (3 × 15 mL), and the combined organic phase was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to afford a pale yellow liquid **3** (2.39 g, 85% yield). $[\alpha]_D$ −32.5° (c 0.66, $CHCl_3$) (lit. −31.8° (c 0.434 $CHCl_3$) [23a]); IR (Neat): *ν* 3447, 2964, 2926, 2868, 1614, 1448, 1378, 1338, 1263, 1183, 1110, 1050, 973, 754, 588 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 1.19–1.31 (m, 6H, $SCCH_3$), 1.59–2.16 (m, 4H, CH_2), 2.54–2.79 (m, 4H, CH_2), 2.86–2.96 (m, 1H, CH), 3.01–3.11 (m, 1H, CH), 3.22–3.31 (q, 1H, *J* = 7.55 Hz, CH), 3.70–3.75 (d, 1H, *J* = 8.3 Hz, CH); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 14.5, 24.2, 24.9–25.0, 29.9, 46.1, 57.0, 62.1; MS (ESI): *m*/*z* (%) = 206 (M + H, 100), 144 (30), 101 (10); HRMS (ESI) calcd. for $C_9H_{19}NS_2$ 205.1037 $[M + H]^+$, found 205.1040.

*4.1.20. (2S)-2-[Di(ethylsulfanyl)methyl]tetrahydro-1H-1-pyrrolyl [4-(6-methoxy-1,3-benzothiazol-2-yl)-2-nitrophenyl]methanone (**11a**)*

N,N-Dimethylformamide (2 drops) was added to a stirred suspension of the nitro acid **2a** (1.5 g, 4.5 mmol, 1.0 equiv) and thionyl chloride (0.80 g, 6.78 mmol, 1.5 equiv) in dry benzene (20 mL) and refluxed for a period of 4–5 h till a transparent solution obtained. After evaporation of benzene under reduced pressure, the resultant yellow solid was dissolved in THF (15 mL) and added drop wise for a period of 10 min to a vigorously stirred mixture of (*S*)-pyrrolidine-2-carbaldehyde diethyl thioacetal **3** (0.93 g, 4.5 mmol, 1.0 equiv), Et_3N (3 mL), and ice/water (4-5 drops) at 0 °C. The reaction mixture was stirred at room temperature for a period of 1.5 h. After removal of the THF by evaporation under reduced pressure, the residue was diluted with water (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with water (2 × 10 mL), brine, dried (Na_2SO_4), and the solvent was removed by evaporation under reduced pressure to afford dark red oil. Purification of the crude product by column chromatography using EtOAc: petroleum ether, (1:2) to afford the corresponding amide as a low melting solid **11a** (1.175 g, 50% yield). $[\alpha]_D$ −84.2° (c 0.5, $CHCl_3$); m.p. 83–85 °C; ^1H NMR (200 MHz, $CDCl_3$): *δ* 1.32–1.43 (dt, 6H, J_1 = 7.35 Hz, J_2 = 2.20 Hz, $SCCH_3$), 1.78–2.43 (m, 4H, CH_2), 2.65–2.91 (m, 4H, CH_2), 3.28–3.38 (m, 2H, CH_2), 3.91 (s, 3H, Ar-OCH_3), 4.64–4.75 (m, 1H, CH), 4.79–4.83 (d, 1H, *J* = 3.67 Hz, CH), 7.08–7.15 (dd, 1H, J_1 = 8.81 Hz, J_2 = 2.20 Hz, Ar-H), 7.32–7.36 (d, 1H, *J* = 2.20 Hz, Ar-H), 7.51–7.56 (d, 1H, *J* = 8.08 Hz, Ar-H), 7.93–7.99 (d, 1H, *J* = 8.81 Hz, Ar-H), 8.30–8.36 (dd, 1H, J_1 = 8.08 Hz, J_2 = 2.20 Hz, Ar-H), 8.75–8.77 (d, 1H, *J* = 1.47 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 15.0, 24.7, 26.3, 27.2, 29.7, 50.4, 52.8, 55.8, 61.2, 104.0, 116.5, 122.9, 124.4, 128.8, 132.2, 135.7, 136.7, 145.7, 148.5, 158.5, 161.2, 165.8; MS (ESI): *m*/*z* (%) = 518 (M + H, 20), 540 ($M + Na^+$, 25), 556 ($M + K^+$, 100); Anal. Calcd. for $C_{24}H_{27}N_3O_4S_3$: C, 55.68; H, 5.26; N, 8.12. Found: C, 55.45; H, 5.12; N, 8.43. The same procedure was used for the preparation of compound **11b** (1.14 g, 48% yield) and compound **11c** (1.26 g, 52% yield).

*4.1.21. (2S)-2-[Di(ethylsulfanyl)methyl]tetrahydro-1H-1-pyrrolyl [4-(6-fluoro-1,3-benzothiazol-2-yl)-2-nitrophenyl]methanone (**11b**)*

$[\alpha]_D$ −98.0° (c 0.5, $CHCl_3$); m.p. 150–152 °C; IR (Neat): *ν* 3430.14, 2963.46, 2922.42, 2869.58, 1633.49, 1547.41, 1512.06, 1431.89, 1351.42, 1249.19, 1203.00, 856.37, 815.75 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, TMS): *δ* 1.32–1.43 (dt, 6H, J_1 = 7.31 Hz, J_2 = 2.19 Hz, $SCCH_3$), 1.81–2.41 (m, 4H, CH_2), 2.66–2.89 (m, 4H, CH_2), 3.28–3.39 (m, 2H, CH_2), 3.91 (s, 3H, Ar-OCH_3), 4.64–4.75 (m, 1H, CH), 4.79–4.84 (d, 1H, *J* = 3.66 Hz, CH), 7.22–7.34 (dt, 1H, J_1 = 8.77 Hz, J_2 = 2.19 Hz, Ar-H), 7.54–7.65 (m, 2H, Ar-H), 8.01–8.10 (m, 1H, Ar-H), 8.31–8.38 (dd, 1H, J_1 = 8.04 Hz, J_2 = 1.46 Hz, Ar-H), 8.78–8.80 (d, 1H, *J* = 1.46 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 14.9, 24.7, 26.3, 26.6, 27.2, 29.6, 50.4, 52.8, 61.2, 107.9, 108.2, 115.6, 115.9, 123.2, 124.9, 129.0, 132.4, 135.2, 145.7, 150.5, 159.3, 162.6, 165.6; MS (ESI): *m*/*z* (%) = 505 (M + H, 5), 528 ($M + Na^+$, 22), 544 ($M + K^+$, 6).

*4.1.22. [4-(1,3-Benzothiazol-2-yl)-2-nitrophenyl](2S)-2-[di(ethylsulfanyl)methyl]tetrahydro-1H-1-pyrrolylmethanone (**11c**)*

$[\alpha]_D$ −87.6° (c 0.5, $CHCl_3$); m.p. 139–142 °C; IR (Neat): *ν* 3430, 2961, 2923, 2859, 1632, 1545, 1512, 1430, 1350, 756 cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$): δ 1.33–1.42 (dt, 6H, J_1 = 7.55 Hz, J_2 = 3.02 Hz, $SCCH_3$), 1.81–2.18 (m, 3H, CH_2, CH), 2.27–2.39 (m, 1H, CH), 2.67–2.87 (m, 4H, CH_2), 3.30–3.37 (m, 2H, CH_2), 4.66–4.74 (m, 1H, CH), 4.80–4.83 (d, 1H, J = 3.77 Hz, CH), 7.40–7.59 (m, 3H, Ar-H), 7.91–7.96 (d, 1H, J = 7.55 Hz, Ar-H), 8.08–8.12 (d, 1H, J = 7.55 Hz, Ar-H), 8.37–8.41 (dd, 1H, J_1 = 7.55 Hz, J_2 = 1.51 Hz, Ar-H), 8.82–8.84 (d, 1H, J = 1.51 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.0, 24.7, 26.3, 26.5, 27.2, 29.6, 50.4, 52.8, 61.2, 121.8, 123.3, 123.8, 126.2, 126.9, 128.9, 132.5, 135.1, 135.5, 145.6, 153.8, 163.9, 165.7; MS (ESI): m/z (%) = 487 (M + H, 5), 510 (M + Na^+, 15), 526 (M + K^+, 4).

4.1.23. [2-Amino-4-(6-methoxy-1,3-benzothiazol-2-yl)phenyl](2S)-2-[di(ethylsulfanyl)methyl]tetrahydro-1H-1-pyrrolylmethanone (**12a**)

A solution of the thioacetal protected nitro amide **11a** (1.0 g, 1.93 mmol, 1.0 equiv) and $SnCl_2 \cdot 2H_2O$ (1.30 g, 5.76 mmol, 3.0 equiv) in methanol (20 mL) was refluxed for 1 h until TLC (EtOAc: petroleum ether, 1:1) indicated that reaction was complete. The solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (20 mL) and then treated with saturated solution of $NaHCO_3$. The mixture was stirred for a period of 2 h and the suspension was filtered through a short bed of celite. The combined organic phases were evaporated under reduced pressure to afford the corresponding amino thioacetal as dark yellow foam. Purification of the resulting residue by column chromatography (EtOAc) resulted a yellow sticky liquid **12a** (0.518 g, 55% yield). IR (Neat): ν 3449, 3354, 2926, 2857, 1719, 1603, 1433, 1263, 1225, 1059, 1027, 831, 760 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19–1.31 (m, 6H, $SCCH_3$), 1.58–2.07 (m, 3H, CH_2, CH), 2.21–2.33 (m, 1H, CH), 2.58–2.84 (m, 4H, CH_2), 3.57–3.69 (m, 2H, CH_2), 3.89 (s, 3H, Ar-OCH_3), 4.62–4.76 (m, 2H, CH_2), 4.90 (br s, Ar-NH_2), 7.02–7.08 (dd, 1H, J_1 = 9.06 Hz, J_2 = 3.02 Hz, Ar-H), 7.28–7.41 (m, 4H, Ar-H), 7.88–7.93 (d, 1H, J = 9.06 Hz, Ar-H); MS (ESI): m/z (%) = 488 (M + H, 10), 510 (M + Na^+, 20), 526 (M + K^+, 4). The same procedure was followed for the preparation of compound **12b** (0.470 g, 50% yield) and compound **12c** (0.488 g, 52% yield).

4.1.24. [2-Amino-4-(6-fluoro-1,3-benzothiazol-2-yl)phenyl](2S)-2-[di(ethylsulfanyl)methyl]tetrahydro-1H-1-pyrrolylmethanone (**12b**)

IR (Neat): ν 3446, 3345, 2925, 2852, 1736, 1616, 1450, 1330, 1253, 1155, 928, 817 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19–1.31 (m, 6H, $SCCH_3$), 1.56–2.09 (m, 3H, CH_2, CH), 2.20–2.34 (m, 1H, CH), 2.56–2.81 (m, 4H, CH_2), 3.54–3.70 (m, 2H, CH_2), 3.89 (s, 3H, Ar-OCH_3), 4.61–4.76 (m, 2H, CH_2), 7.17–7.25 (m, 2H, Ar-H), 7.26–7.41 (m, 2H, Ar-H), 7.54–7.58 (dd, 1H, J_1 = 7.55 Hz, J_2 = 2.26 Hz, Ar-H), 7.95–8.01 (m, 1H, Ar-H); MS (ESI): m/z (%) = 476 (M + H, 5), 498 (M + Na^+, 20).

4.1.25. [2-Amino-4-(1,3-benzothiazol-2-yl)phenyl](2S)-2-[di(ethylsulfanyl)methyl]tetrahydro-1H-1-pyrrolylmethanone (**12c**)

IR (Neat): ν 3437, 3344, 2925, 2855, 1739, 1618, 1431, 1329, 1157, 760 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 1.19–1.45 (m, 6H, $SCCH_3$), 1.67–2.12 (m, 3H, CH_2, CH), 2.20–2.34 (m, 1H, CH), 2.59–2.85 (m, 4H, CH_2), 3.56–3.70 (m, 2H), 3.89 (s, 3H, Ar-OCH_3), 4.62–4.77 (m, 2H, CH_2), 4.86 (br s, Ar-NH_2), 7.27–7.50 (m, 5H, Ar-H), 7.84–7.90 (d, 1H, J = 7.55 Hz, Ar-H), 8.00–8.06 (d, 1H, J = 8.31 Hz, Ar-H); MS (ESI): m/z (%) = 458 (M + H, 5).

4.1.26. (11aS)-8-(6-Methoxy-1,3-benzothiazol-2-yl)-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one (**1a**)

A suspension of the amino thioacetal **12a** (0.45 g, 0.92 mmol, 1.0 equiv), $HgCl_2$ (0.55 g, 2.04 mmol, 2.2 equiv), and $CaCO_3$ (0.230 g, 2.3 mmol, 2.5 equiv) in CH_3CN/H_2O (4:1, 15 mL) was stirred slowly at room temperature for a period of 18–24 h until TLC (ethyl acetate) indicated the complete disappearance of the starting material. The reaction mixture was diluted with ethyl acetate (10 mL) and filtered through a short bed of celite and the filter cake was washed with ethyl acetate (5 mL). The filtrate was dried by using Na_2SO_4 and directly poured on silica gel column. Column chromatography (EtOAc: petroleum ether, 3:1) afforded a pale yellow gummy syrup **1a** (0.184 g, 55% yield). $[\alpha]_D$ 45.4° (c 0.36, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.00–2.25 (m, 3H, CH_2, CH), 2.31–2.41 (m, 1H, CH), 3.54–3.92 (m, 3H, CH_2, CH), 3.89 (s, 3H, Ar-OCH_3), 7.04–7.10 (dd, 1H, J_1 = 9.06 Hz, J_2 = 3.02 Hz, Ar-H), 7.31–7.34 (d, 1H, J = 2.26 Hz, Ar-H), 7.78–7.82 (d, 1H, J = 4.53 Hz, N=CH), 7.91–7.96 (m, 2H, Ar-H), 8.00–8.04 (m, 1H, Ar-H), 8.09–8.14 (d, 1H, J = 8.30 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.1, 29.2, 46.8, 53.6, 55.8, 84.0, 103.4, 104.0, 115.6, 116.1, 123.4, 123.6, 124.0, 124.7, 125.5, 131.1, 133.0, 136.4, 143.2, 165.2; MS (ESI): m/z (%) = 364 (M + H, 35), 396 (M + MeOH, 100); HRMS (ESI) calcd. for $C_{20}H_{18}N_3O_2S$ 364.1119 $[M + H]^+$, found 364.1118; Anal. Calcd. for $C_{20}H_{17}N_3O_2S$: C, 66.10; H, 4.71; N, 11.56. Found: C, 65.96; H, 4.66; N, 11.23. The same procedure was followed for the preparation of compound **1b** (0.127 g, 43% yield) and compound **1c** (0.110 g, 38% yield).

4.1.27. (11aS)-8-(6-Fluoro-1,3-benzothiazol-2-yl)-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one (**1b**)

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.96–2.42 (m, 4H, CH_2), 3.51–3.96 (m, 3H, CH_2, CH), 7.20–7.37 (m, 2H, Ar-H), 7.57–7.64 (dd, 1H, J_1 = 8.08 Hz, J_2 = 2.20 Hz, Ar-H), 7.85–7.90 (d, 1H, J = 4.40 Hz, N=CH), 7.98–8.09 (m, 2H, Ar-H), 8.15–8.20 (d, 1H, J = 8.81 Hz, Ar-H); MS (ESI): m/z (%) = 352 (M + H, 10), 384 (M + MeOH, 75); HRMS (ESI) calcd. for $C_{20}H_{18}FN_3O_2S$ (methyl ether of carbinolamine generated in ESI mass spectrometer due to the reaction with methanol) 384.1140 $[M + H]^+$, found 384.1143; Anal. Calcd. for $C_{19}H_{14}FN_3OS$: C, 64.94; H, 4.02; N, 11.96. Found: C, 65.11; H, 3.89; N, 11.77.

4.1.28. (11aS)-8-(1,3-Benzothiazol-2-yl)-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one (**1c**)

$[\alpha]_D$ 61.538° (c 0.23, acetone); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.98–2.42 (m, 4H, CH_2), 3.50–3.96 (m, 3H, CH_2, CH), 7.30–7.66 (m, 4H, Ar-H), 7.85–7.90 (d, 1H, J = 4.40 Hz, N=CH), 7.91–8.21 (m, 3H, Ar-H). MS (ESI): m/z (%) = 334 (M + H, 10), 366 (M + MeOH, 100); HRMS (ESI) calcd. for $C_{19}H_{16}N_3OS$ (imine) 334.1014 $[M + H]^+$, found 334.1010 and HRMS (ESI) calcd. for $C_{20}H_{19}N_3O_2S$ (methyl ether of carbinolamine generated in ESI mass spectrometer due to the reaction with methanol) 366.120 $[M + H]^+$, found 366.115; Anal. Calcd. for $C_{19}H_{15}N_3OS$: C, 68.45; H, 4.53; N, 12.60. Found: C, 68.20; H, 4.67; N, 12.44.

4.1.29. 2-Methyl-3-nitro-N-(3,4,5-trimethoxyphenyl)benzamide (**15**)

Brown solid; m.p. 168–169 °C; IR (KBr): ν 3463, 2970, 1740, 1439, 1368, 1215, 1117, 1006, 900 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 2.51(s, 3H, Ar-CH_3), 3.81(s, 3H, Ar-OCH_3), 3.86(s, 6H, Ar-OCH_3), 7.42(t, 1H, J = 7.93 Hz, Ar-H), 7.53 (s, 2H, Ar-H), 7.59–7.65(m, 1H, Ar-H), 7.79(d, 1H, J = 7.93, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ 15.0, 55.8, 60.0, 100.1, 123.4, 126.2, 126.9, 130.7, 135.0, 146.9, 150.1, 152.4, 194.7; MS (ESI): m/z (%) = 347 (M + H, 100).

4.1.30. N1-(3,4,5-Trimethoxyphenyl)-2-methyl-3-nitro-1-benzenecarbothioamide (**16**)

m.p. 165–167 °C; ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 2.55 (s, 3H, Ar-CH_3), 3.82 (s, 3H, Ar-OCH_3), 3.86 (s, 6H, Ar-OCH_3), 7.24–7.41 (m, 3H, Ar-H), 7.53 (m, 1H, Ar-H), 7.76 (m, 1H, Ar-H), 8.85 (br s, CONH); MS (ESI): m/z (%) 363 (M + H, 100); Anal. Calcd. for $C_{17}H_{18}N_2O_5S$: C, 56.34; H, 5.01; N, 7.73. Found: C, 56.43; H, 4.87; N, 7.55.

4.1.31. 5,6,7-Trimetoxy-2[2-methyl-3-nitrophenyl]benzothiazole (**17**)

m.p. 163–165 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 2.68 (s, 3H, Ar-CH_3), 3.92 (s, 3H, Ar-OCH_3), 3.98 (s, 3H, Ar-OCH_3), 4.11 (s, 3H, Ar-OCH_3),

7.33 (s, 1H, Ar-H), 7.41–7.47 (m, 1H, Ar-H), 7.82–7.88 (m, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.7, 56.3, 60.7, 61.5, 100.9, 125.2, 126.6, 131.6, 134.2, 136.1, 140.1, 146.6, 150.0, 151.8, 154.3, 165.1; MS (ESI): *m/z* (%) = 361 (M^+, 100), 101 (80), 79 (35); Anal. Calcd for $C_{17}H_{16}N_2O_5S$: C, 56.66; H, 4.47; N, 7.77. Found: C, 56.59; H, 4.42; N, 7.73.

4.1.32. 2-Methyl-3-(5,6,7-trimethoxy-1,3-benzothiazol-2-yl)aniline (**13d**)

Procedure described for the synthesis of compound **12a** was followed for the syntheses of amines **13a**–**e**. m.p. 125–127 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 2.02 (s, 1H, Ar-CH_3), 2.14 (br s, NH_2), 3.91 (s, 3H, Ar-OCH_3), 3.96 (s, 3H, Ar-OCH_3), 4.08 (s, 3H, Ar-OCH_3), 6.71–6.76 (d, 1H, *J* = 7.55 Hz, Ar-H), 7.01–7.11 (m, 2H, Ar-H), 7.32 (s, 1H, Ar-H); MS (ESI): *m/z* (%) = 331 (M + H, 100); Anal. Calcd. for $C_{17}H_{18}N_2O_3S$: C, 61.80; H, 5.49; N, 8.48. Found: C, 62.02; H, 5.32; N, 8.34.

4.1.33. 5-(6-Methoxy-1,3-benzothiazol-2-yl)-2-methylaniline (**13a**)

m.p. 148–149 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 2.20 (s, 3H, Ar-CH_3), 3.67 (br s, NH_2), 3.87 (s, 3H, Ar-OCH_3), 6.99–7.09 (m, 2H, Ar-H), 7.24–7.37 (m, 3H, Ar-H), 7.84–7.88 (d, 1H, *J* = 9.06 Hz, Ar-H); MS (ESI): *m/z* (%) = 271 (M + H, 100); Anal. Calcd. for $C_{15}H_{14}N_2OS$: C, 66.64; H, 5.22; N, 10.36. Found: C, 66.34; H, 5.38; N, 10.67.

4.1.34. 5-(6-Fluoro-1,3-benzothiazol-2-yl)-2-methylaniline (**13b**)

m.p. 126–128 °C; ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 2.22 (s, 3H, Ar-CH_3), 3.70 (br s, NH_2), 7.07–7.39 (m, 4H, Ar-H), 7.49–7.57 (dd, 1H, J_1 = 7.81, J_2 = 2.34 Hz, Ar-H), 7.89–7.97 (m, 1H, Ar-H). MS (ESI): *m/z* (%) = 259 (M + H, 100); Anal. Calcd. for $C_{14}H_{11}FN_2S$: C, 65.10; H, 4.29; N, 10.84. Found: C, 64.93; H, 4.34; N, 10.95.

4.1.35. 5-(1,3-Benzothiazol-2-yl)-2-methylaniline (**13c**)

m.p. 164–166 °C; ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 2.22 (s, 3H, Ar-CH_3), 3.72 (br s, NH_2), 7.07–7.13 (d, 1H, *J* = 7.57 Hz, Ar-H), 7.27–7.48 (m, 4H, Ar-H), 7.81–7.87 (m, 1H, Ar-H), 7.96–8.02 (d, 1H, *J* = 7.57 Hz, Ar-H); MS (ESI): *m/z* (%) = 241 (M + H, 100); Anal. Calcd. for $C_{14}H_{12}N_2S$: C, 69.97; H, 5.03; N, 11.66. Found: C, 70.10; H, 5.22; N, 11.59.

4.1.36. 4-(6-Methoxy-1,3-benzothiazol-2-yl)aniline (**13e**)

m.p. 186–188 °C; ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ 3.88 (s, 3H, Ar-OCH_3), 6.67–6.74 (d, 1H, *J* = 8.19 Hz, Ar-H), 6.98–7.06 (dd, 1H, J_1 = 8.94 Hz, J_2 = 2.98 Hz, Ar-H), 7.28–7.32 (d, 1H, *J* = 2.98 Hz, Ar-H), 7.79–7.89 (m, 3H, Ar-H); MS (ESI): *m/z* (%) = 257 (M+1, 100); Anal. Calcd. for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.72; H, 4.62; N, 10.88.

4.1.37. N,N′-Dicyclohexyl-N″-[4-(6-methoxy-1,3-benzothiazol-2-yl) phenyl]guanidine (**18a**)

To a stirred solution of compound **13e** (0.256 g, 1.0 mmol) in dry THF (10 mL) (0.206 g, 1.0 mmol) 1,3-dicyclohexylcarbodiimide (DCC), and (0.0135 g, 0.1 mmol) *N*-hydroxybenzotriazole (HOBt) were added and stirred at room temperature for a period of 12 h. TLC (5% MeOH in ethyl acetate) showed the completion of the reaction. THF was evaporated under reduced pressure and the residue was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine (1 × 5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography to give a colorless solid **18a** (0.346 g, 75% yield). m.p. 126–128 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.02–1.98 (m, 20H, CH_2), 3.38–3.59 (m, 2H, CH), 3.89 (s, 3H, Ar-OCH_3), 7.01–7.09 (dd, 1H, J_1 = 9.37, J_2 = 2.34 Hz, Ar-H), 7.22–7.30 (d, 1H, *J* = 8.59 Hz, Ar-H), 7.34–7.39 (d, 1H, *J* = 2.34 Hz, Ar-H), 7.82–8.05 (m, 4H, Ar-H); MS (ESI): *m/z* (%) = 463 (M + H, 100); Anal. Calcd. for $C_{27}H_{34}N_4OS$: C, 70.09; H, 7.41; N, 12.11. Found: C, 69.96; H, 7.49; N, 12.32.

4.1.38. N-Benzyl-N′-[4-(6-methoxy-1,3-benzothiazol-2-yl)phenyl] urea (**18b**)

Benzyl isocyanate (0.066 g, 0.5 mmol) was added to a mixture of compound **13e** (0.128 g, 0.5 mmol) and Et_3N (0.055 g, 0.55 mmol) in dry THF (5 mL) under N_2 atmosphere at room temperature. The reaction was stirred for 12 h at the same temperature until the starting material had been consumed (monitored by TLC). The solution was poured onto hexane and filtered to get crude solid, which upon column chromatography using EtOAc: petroleum ether, (1:2) afforded a colorless solid **18b** (0.170 g, 88% yield). m.p. 241–243 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.88 (s, 3H, Ar-OCH_3), 4.36–4.41 (d, 2H, *J* = 5.85 Hz, Ar-CH_2), 6.40–6.49 (t, 1H, *J* = 5.85 Hz, CNHCO), 6.97–7.04 (dd, 1H, J_1 = 8.77, J_2 = 2.19 Hz, Ar-H), 7.21–7.37 (m, 5H, Ar-H), 7.51–7.58 (d, 2H, *J* = 8.77 Hz, Ar-H), 7.71–7.92 (m, 4H, Ar-H), 8.52 (s, NH, Ar-NHCO); ^{13}C NMR (75 MHz, DMSO-d_6): δ 41.6, 54.0, 102.8, 113.7, 116.1, 121.3, 124.6, 125.2, 125.6, 126.0, 126.7, 134.2, 138.2, 141.4, 146.7, 153.5, 155.7, 163.3; MS (ESI): *m/z* (%) = 390 (M + H, 85); Anal. Calcd. for $C_{22}H_{19}N_3O_2S$: C, 67.84; H, 4.92; N, 10.79. Found: C, 67.76; H, 5.01; N, 10.84.

4.1.39. N1-[4-(6-Methoxy-1,3-benzothiazol-2-yl)phenyl]-1-cyclopropanecarboxamide (**18c**)

Freshly prepared cyclopropyl carbonyl chloride (0.104 g, 1.0 mmol) dissolved in dry THF (3 mL) was slowly added to a solution of compound **13e** (0.256 g, 1.0 mmol) in dry THF (5 mL) at 0 °C. The reaction was continued at room temperature for 1–2 h till TLC showed the completion of the reaction. Solvent was evaporated under reduced pressure and the residue was washed with water, saturated solution of $NaHCO_3$ and 1N HCl solution to remove the excess unreacted starting materials. Column chromatography afforded a pure colorless solid **18c** (0.265 g, 82% yield). m.p. 249–251 °C; ^{1}H NMR (200 MHz, DMSO-d_6, TMS): δ 0.74–0.85 (m, 2H, CH_2), 0.95–1.06 (m, 2H, CH_2), 1.69–1.84 (m, 1H, CH), 3.86 (s, 3H, Ar-OCH_3), 7.00–7.08 (dd, 1H, J_1 = 8.85, J_2 = 2.21 Hz, Ar-H), 7.32–7.37 (d, 1H, *J* = 2.21 Hz, Ar-H), 7.71–7.97 (m, 5H, Ar-H), 9.91 (s, 1H, CONH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 6.60, 13.8, 54.6, 103.2, 114.3, 118.3, 122.0, 126.4, 127.0, 134.9, 140.6, 147.4, 156.4, 163.8, 171.4; MS (ESI): *m/z* (%) = 325 (M + H, 100); Anal. Calcd. for $C_{18}H_{16}N_2O_2S$: C, 66.64; H, 4.97; N, 8.64. Found: C, 66.35; H, 5.03; N, 8.75.

4.1.40. N-(4-Fluorophenyl)-4-methylbenzanilide (**19**)

colourless solid; m.p. 180.5–181.5 °C; IR (Neat): *ν* 2969, 1740, 1652, 1609, 1441, 1368, 1215, 1093, 896, 826, 747, 624 cm^{-1}; ^{1}HNMR (300 MHz, DMSO- d_6): δ 2.43 (s, 3H, Ar-CH_3), 7.02 (m, 2H, Ar-H), 7.27 (d, 2H, *J* = 8.1 Hz, Ar-H), 7.75–7.8 (m, 2H, Ar-H), 7.87 (d, 2H, *J* = 8.87 Hz, Ar-H), 9.95 (br s, 1H, NH); ^{13}C NMR (300 MHz, DMSO-d_6): δ 21.0, 115.0, 115.3, 122.1, 122.2, 127.6, 128.9, 131.8, 135.6, 141.6, 156.6, 159.8, 165.3; MS (ESI): *m/z* (%) = 230 (M + H, 100).

4.1.41. N-(4-Fluorophenyl)-4-methylbenzothioamide (**20**)

pale yellow; m.p. 166–167 °C; IR (Neat): *ν* 2970, 1738, 1435, 1366, 1216, 1093, 993, 822, 760 cm^{-1}; ^{1}HNMR (300 MHz, DMSO-d_6): δ 2.39 (s, 3H, CH_3), 7.09 (m, 2H, 2,6-Ar-H), 7.22 (d, 2H, *J* = 7.9Hz, 3′,5′-Ar-H), 7.77–7.84 (m, 4H, 3,5, 2′,6′-Ar-H), 11.29 (br s, 1H, NH); ^{13}C NMR (300 MHz, DMSO- d_6): δ 20.8, 114.4, 114.7, 125.8, 125.9, 127.2, 128.0, 136.0, 139.5, 140.6, 157.9, 161.2, 197.6; MS (ESI) : *m/z* (%) = 246 (M + H, 100)

4.1.42. 6-Fluoro-2-(4-methylphenyl)-1,3-benzothiazole[4e] (**21**)

Procedure described for the synthesis of compound **6a** was followed. m.p. 128–129 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 3H, Ar-CH_3), 7.15–7.22 (m, 1H, Ar-H), 7.24–7.29 (d, 2H, *J* = 7.55 Hz, Ar-H), 7.52–7.56 (dd, 1H, J_1 = 7.55, J_2 = 2.26 Hz, Ar-H), 7.89–7.98 (m, 3H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 107.5, 107.9,

114.6, 114.9, 123.9, 127.3, 129.7, 130.6, 141.4, 150.7, 158.7, 161.9, 167.9; MS (ESI): *m*/*z* (%) = 244 (M + H, 100); Anal. Calcd for $C_{14}H_{10}FNS$: C, 69.11; H, 4.14; N, 5.76. Found: C, 69.07; H, 4.08; N, 5.72.

4.1.43. 2-[4-(Bromomethyl)phenyl]-6-fluoro-1,3-benzothiazole (**22**)

To a mixture of compound **21** (0.486 g, 2.0 mmol) dissolved in ethyl acetate (15 mL) and $NaBrO_3$ (0.60 g, 4.0 mmol) dissolved in water (10 mL) was added drop wise a solution of $NaHSO_3$ (0.41 g, 4.0 mmol) dissolved in water (5 mL) during a period of 15 min at room temperature. Stirring was continued at room temperature for a period of 4–6 h till the TLC (EtOAc: petroleum ether, 1:9) showed completion of the reaction. Organic layer was evaporated under reduced pressure and the solid formed in aqueous layer was back extracted with CH_2Cl_2 (2 × 20 mL) treated with brine, dried over Na_2SO_4 and column purified (using EtOAc: petroleum ether, 1:5) to get a cream colored solid compound **22** (0.59 g, 92% yield). m.p. 115–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.50 (s, 2H, Ar-CH_2Br), 7.16–7.30 (m, 1H, Ar-H), 7.46–7.60 (m, 3H, Ar-H), 7.89–8.06 (m, 3H, Ar-H); MS (ESI): *m*/*z* (%) = 322 (M + H, 20), 324 (M+3, 20); Anal. Calcd for $C_{14}H_9BrFNS$: C, 52.19; H, 2.82; N, 4.35. Found: C, 52.33; H, 3.00; N, 4.22.

4.1.44. 2-(4–(((3aR,5S,6aS)-5–((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-dihydro-5H-furo[3,2-d][1,3]dioxol-6-yloxy) methyl)phenyl)-6-fluorobenzo[d]thiazole (**23**)

To a solution of *d*-glucose diacetonide (0.26 g, 1.0 mmol) in dry CH_3CN (10 mL) was added NaH 60% w/w (0.060 g, 1.5 mmol) in portions at 0 °C. After stirring for 30 min compound **22** (0.321 g, 1.0 mmol) was added and stirring was continued for further 2–4 h at room temperature till TLC showed complete disappearance of the starting materials. The reaction mixture was then diluted with EtOAc (30 mL) and washed with H_2O (2 × 5 mL) and brine (1 × 10 mL). The organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was passed through a thin layer of silica gel chromatography using EtOAc: petroleum ether (1:3) as eluent to afford a colorless gummy material **23** (0.446 g, 89% yield). $[\alpha]_D$ 32.4° (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24–1.53 (m, 12H, CH_3), 3.94–4.14 (m, 4H, CH_2, CH), 4.29–4.40 (m, 1H, CH), 4.54–4.57 (d, 1H, *J* = 3.78 Hz, CH), 4.71–4.74 (d, 2H, *J* = 3.02 Hz, Ar-CH_2), 5.84–5.86 (d, 1H, *J* = 3.78 Hz, CH), 7.17–7.25 (m, 1H, Ar-H), 7.42–7.49 (d, 2H, *J* = 8.31 Hz, Ar-H), 7.54–7.59 (dd, 1H, J_1 = 7.55, J_2 = 2.26 Hz, Ar-H), 7.95–8.06 (m, 3H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.4, 26.2, 26.8, 67.5, 71.8, 72.4, 81.3, 82.0, 105.3, 107.6, 108.0, 109.1, 111.9, 114.8, 115.1, 124.0, 127.5, 128.0, 132.8, 140.9, 150.7, 162.1, 167.3; MS (ESI): *m*/*z* (%) = 502 (M + H, 100), 242 (20); Anal. Calcd for $C_{26}H_{28}FNO_6S$: C, 62.26; H, 5.63; N, 2.79. Found: C, 62.14; H, 5.34; N, 2.99.

4.1.45. (R)-1–((3aR,5S,6aS)-6-(4-(6-Fluorobenzo[d]thiazol-2-yl) benzyloxy)-2,2-dimethyl-dihydro-5H-furo[3,2-d][1,3]dioxol-5-yl) ethane-1,2-diol (**24**)

To a stirred solution of benzothiazole glucose diacetonide **23** (0.25 g, 0.5 mmol) in excess of MeOH (15 mL) was added aqueous 0.8% H_2SO_4 solution and stirred for overnight. TLC (EtOAc: petroleum ether, 1:1) showed the completion of the reaction. The reaction was quenched with triethyl amine. Methanol was evaporated under reduced pressure and the resulting residue was washed with saturated solution of $NaHCO_3$ and extracted with ethyl acetate (3 × 5 mL). Column chromatography using EtOAc: petroleum ether (1:2) afforded a colorless solid **24** (0.184 g, 80% yield). m.p. 159–160 °C; $[\alpha]_D$ 22.9° (c 1.0, $CHCl_3$); IR (Neat): *ν* 2970, 1739, 1605, 1568, 1453, 1370, 1216, 1072, 903, 811 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22–1.31 (m, 6H, CH_3), 2.88 (s, OH), 2.96 (s, OH), 3.70–3.87 (m, 2H, CH), 3.96–4.14 (m, 3H, CH_2, CH), 4.57–4.60 (d, 1H, *J* = 3.78 Hz, CH), 4.64–4.81 (m, 2H, Ar-CH_2), 5.87–5.90 (d, 1H, *J* = 3.78 Hz, CH), 7.17–7.25 (m, 1H, Ar-H), 7.42–7.49 (d, 2H, *J* = 8.31 Hz, Ar-H), 7.54–7.59 (dd, 1H, J_1 = 7.55, J_2 = 2.26 Hz, Ar-H), 7.95–8.06 (m, 3H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.2, 26.7, 64.4, 69.0, 80.0, 82.1, 82.4, 105.1, 107.6, 108.0, 111.9, 114.8, 124.0, 127.6, 128.1, 132.9, 140.5, 150.6, 158.8, 167.3; MS (ESI): *m*/*z* (%) = 462 (M + H, 100); Anal. Calcd for $C_{23}H_{24}FNO_6S$: C, 59.86; H, 5.24; N, 3.04. Found: C, 59.76; H, 5.31; N, 3.11.

4.1.46. 4-(6-Fluoro-1,3-benzothiazol-2-yl)benzoic acid (**25**)

H_5IO_6, periodic acid (1.596 g, 7.0 mmol) was dissolved in CH_3CN (15 mL) by vigorous stirring for 15–20 min at room temperature. After complete dissolution of periodic acid, CrO_3 (0.04 g, 0.0004 mmol) was added to it and stirred for 5 min. Now compound **21** (0.486 g, 2 mmol) dissolved in CH_3CN was added to the above mixture slowly and stirring continued for 1–2 h till TLC (ethyl acetate) showed the completion of the reaction. Organic solvent was evaporated under reduced pressure and the resulting solid was washed with water (2 × 10 mL) and extracted with ethyl acetate to afford **25** as a colorless solid (0.491 g, 90% yield). m.p. 243–244 °C; IR (KBr): *ν* 2923, 2851,1681, 1292, 852 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.24–7.36 (m, 1H, Ar-H), 7.70–7.78 (m, 1H, Ar-H), 7.86–8.10 (m, 2H, Ar-H), 8.26–8.32 (m, 1H, Ar-H), 8.48 (s, 1H, Ar-H); Anal. Calcd for $C_{14}H_8FNO_2S$: C, 61.53; H, 2.95; N, 5.13. Found: C, 61.59; H, 2.78; N, 5.23.

4.1.47. Methyl (2S)-1-[4-(6-fluoro-1,3-benzothiazol-2-yl)benzoyl] tetrahydro-1H-2-pyrrolecarboxylate (**26**)

N,N-dimethylformamide (1-2 drops) was added to a stirred suspension of the fluoro benzothiazole acid **25** (0.273 g, 1.0 mmol) and $SOCl_2$ (0.177 g, 1.5 mmol) in benzene (10 mL) and the mixture was refluxed 1–2 h till a transparent solution obtained. After evaporation of benzene under reduced pressure, the resultant yellow solid was dissolved in THF (10 mL) and added drop wise for a period of 10 min to a stirred mixture of (*S*)-proline methyl ester hydrochloride (0.165 g, 1.0 mmol), and Et_3N (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for a period of 1–2 h. After removal of the THF by evaporation under reduced pressure, the residue was diluted with water (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with water (2 × 10 mL), sat. brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (ethyl acetate/hexane, 1:3; TLC: EtOAc/hexane, 1:2) to afford the corresponding amide **26** as a low melting colorless solid (0.315 g, 82% yield). m.p. 163–165 °C; $[\alpha]_D$ −10.66° (c 0.2, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.77–2.43 (m, 4H, CH_2), 3.50–3.73 (m, 2H, CH_2), 3.81 (s, 3H, $COOCH_3$), 4.65–4.75 (m, 1H, CH), 7.19–7.30 (dt, 1H, J_1 = 8.31, J_2 = 2.49 Hz, Ar-H), 7.47–7.64 (m, 1H, Ar-H), 7.67–7.76 (d, 1H, *J* = 8.31 Hz, Ar-H), 7.98–8.14 (m, 3H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.4, 29.3, 49.9, 52.3, 59.2, 107.7, 108.1, 115.0, 115.4, 124.3, 127.3, 128.1, 134.9, 138.4, 150.7, 159.7, 162.3, 172.6; MS (ESI): *m*/*z* (%) = 385 (M + H, 100); Anal. Calcd for $C_{20}H_{17}FN_2O_3S$: C, 59.86; H, 5.24; N, 3.04. Found: C, 60.02; H, 5.22; N, 3.21.

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