JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b01340 • Publication Date (Web): 21 Aug 2017

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Design, Sustainable Synthesis, and Programmed Reactions of Templated *N*-Heteroaryl Fused Vinyl Sultams

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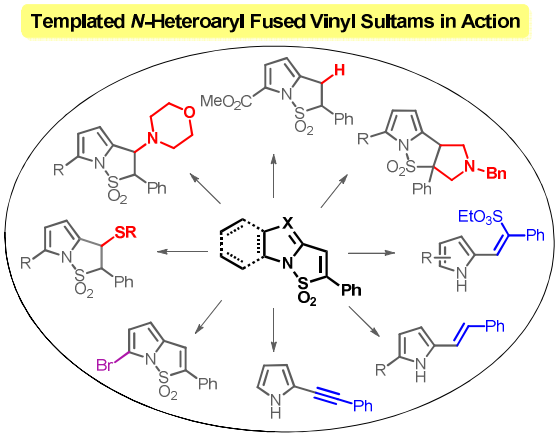
ABSTRACT



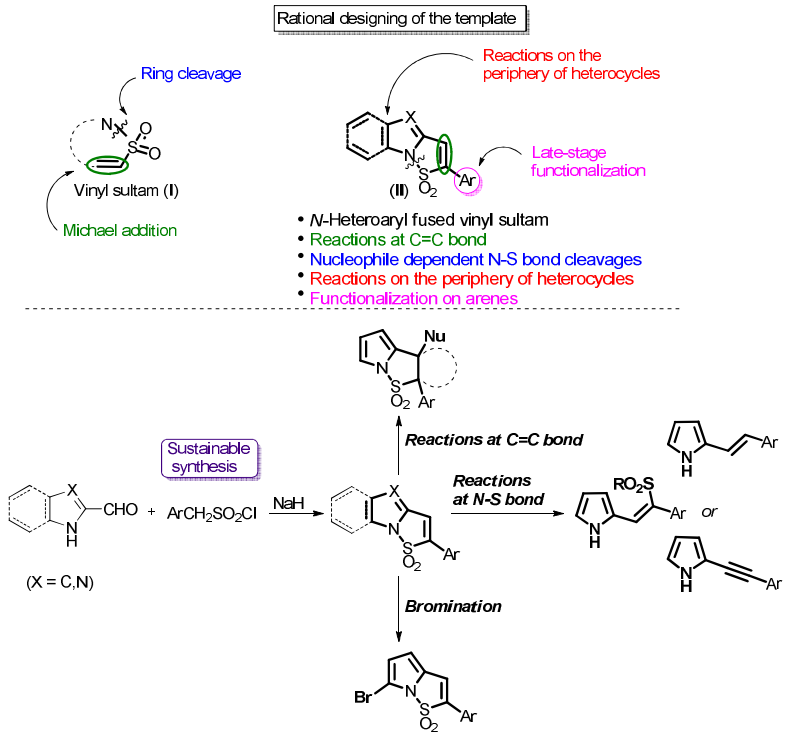
A de novo design and synthesis of *N*-heteroaryl fused vinyl sultams as templates for programming chemical reactions on vinyl sultam periphery or (hetero)aryl ring is described. The key features include rational designing and sustainable synthesis of the template, customized reactions of vinyl sultams at C=C bond or involving N-S bond cleavage, and reactions on the periphery of the heteroaryl ring for late-stage diversification. The simple, easy access to the template coupled with opportunities for the synthesis of diversely functionalized heterocyles from a single template constitutes a rare study in contemporary organic synthesis.

INTRODUCTION

Template designing for programming chemical synthesis has received increasing attention over the last two decades.[1] Rational design of templates, their convenient access in fewest possible steps, and employing them in sustainable chemical synthesis have brought the evolution of sophisticated architectures of synthetic molecules closer to realization. Templates of various origin including small organic molecules[2] or bio-macromolecules[3] have been developed to perform a defined chemical task with remarkable fidelity. However, use of a template in diverse chemical synthesis has been limited.[3d]

Vinyl sulfonamides are privileged chemotypes employed in peptidomimetics,[4] anti-infammatory drugs and other medicinal agents,[5] and biomaterials.[6] Despite poor reactivity of C=C bond in vinyl sulfonamides as compared to that in vinyl sulfones or sulfonates,[7] vinyl sulfonamides have a remarkable biomedical significance owing to their innate ability to act as irreversible inhibitors of cysteine proteases through conjugate addition of the thiol group of the active site of cysteine residue.[8] While sulfonamide functionality has been demonstrated as carbonyl bioisostere making key interactions with receptor proteins,[9] it imparts, unlike carbonyl group, improved aqueous solubility.[10] Despite the presence of two key functional groups, chemical reactivity as Michael acceptors although demonstrated less proficiently,[8,11] and abilities to perform as agents for probing biological systems,[12] strategic design and development of vinyl sulfonamides has been the study of limited investigations.[13]

Scheme 1. Rational Design, Synthesis and Reactions of Templated *N*-Heteroaryl Fused Vinyl Sultams



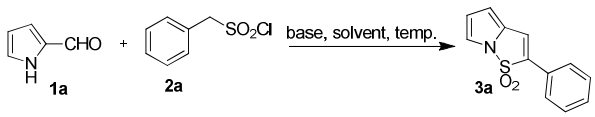
Therefore, a de novo design of vinyl sulfonamides, especially cylic vinyl sulfonamides (vinyl sultams), their expedient access, and subsequent use in diversity organic synthesis could be an aspiring object. The structural feature of a vinyl sultam **I** could include an endo-cyclic double bond adopting a syn-geometry as platform for conjugate Michael addition, pharmacophoric linchpin sulfonamide functionality, and chemoselective cleavage of N-S bond via hydrolytic or nucleophilic cleavage (Scheme 1). These aspects could secure extensive functionalizations, opportunities for the preparation of acyclic vinyl sulfonyl compounds, and preparation of transposed acyclic vinyl sulfonamides by nucleophilic cleavage of N-S bond with amines. Moreover, vinyl sultam **I** when fused to a heterocycle could display additional feature including reactions on the periphery of the heterocycle and late-stage functionalization on the substituted

arenes. Our previous experiences on palladium-catalyzed domino or convergent synthesis of five-,[14] six-,[15] or seven-membered aryl-(hetero)aryl fused sultams[16] and nucleophilic ring-opening reactions of a highly reactive indole-aryl fused sultam[14] provided a strong impetus to strategic designing of templated sultams that are while elusive could execute programmed chemical synthesis. Herein, we describe rational designing of an unprecedented template *N*-heteroaryl fused vinyl sultam **II**, its sustainable synthesis, and multi-faceted reactivity affording diverse functionalized *N*-heterocycles. The programmed reactions of vinyl sultams at C=C bond, sultam ring-opening reactions via N-S bond cleavage, and reactions on the periphery of the (hetero)aryl ring for further functionalization are the key demonstrations presented herein.

RESULTS AND DISCUSSION

Based on our design, *N*-heterocycles bearing an aldehyde group at the 2-position and arylmethanesulfonyl chloride deemed viable substrates for tandem *N*-sulfonylation followed by intramolecular Knoevenagel condensation to form structurally distinct *N*-heterocycle fused vinyl sultams. Our study began with the reaction of model substrates, pyrrole-2-carboxaldehyde (**1a**) and phenylmethanesulfonyl chloride (**2a**), in the presence of a base forming pyrrole-fused vinyl sultam **3a** (Table 1). Reaction of **1a** and **2a** in the presence of 3 equiv of bases including $NaNH_2$, MHMDS (M = Li or K), and organic bases[17] did not produce any product (entries 1-3). However, the screening of other inorganic bases produced dissimilar results (entries 4-5). Interestingly, NaOEt proved effective for N-S bond cleavages in sultams.

Table 1. Optimization Studies[a]



Entry	Base	Solvent	°C	%**3a**[b]
1	$NaNH_2$	THF	75	N.R
2[c]	MHMDS	THF	75	N.R
3[d]	org. base	THF	75	N.R
4[e]	MOBu-*t*	THF	75	25-28
5[e]	NaOEt	EtOH	75	11
6[f]	NaH	THF	70	66
7[g]	NaH	THF	70	72
8[h]	NaH	THF	70	59
9[g]	NaH	DMF	110	N.R
10[g]	NaH	1,4-dioxane	110	Trace
11[g]	NaH	THF	rt	Trace
12[g]	NaH	THF	50 °C	27

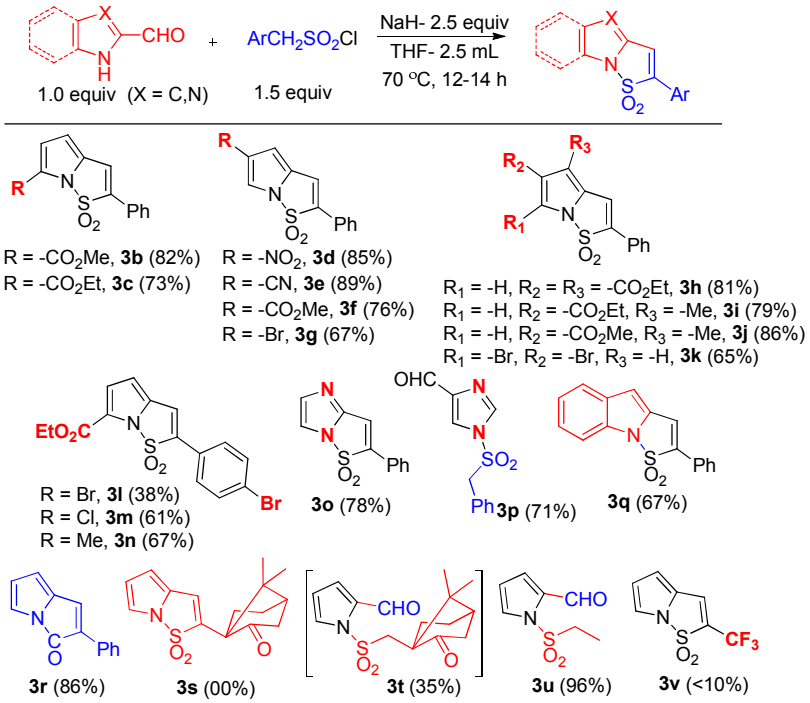
[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), base (1.5 equiv), solvent (2.5 mL), temp. 12 h. [b]Isolated yields. [c]LiHMDS and KHMDS (3.0 equiv). [d]DBU and DBN (3 equiv). [e]LiOBu-*t*, KOBu-*t*, and NaOEt (3.0 equiv). [f]NaH (3.0 equiv). [g]NaH (2.5 equiv). [h]NaH (2.0 equiv).

Among various inorganic bases, NaH in THF proved effective forming **3a** in 66% yield (entry 6). While reducing the amount of NaH to 2.5 equiv had a positive impact in improving the yield, further reduction to 2.0 equiv produced inferior result (entries 7-8). The other solvents such as DMF or dioxane had detrimental effect on the yield of **3a** (entries 9-10). In the attempts to isolate the intermediate, on lowering the reaction temperature (entries 11-12), detrimental effects on the yield of the product was observed. The best result was obtained when **1a** (1 equiv) and **2a** (1.5

equiv) reacted in the presence of NaH (2.5 equiv) in THF (2.5 mL) at 70 °C for 12 h providing **3a** in 72% isolated yield. The central challenge in this investigation was to find an optimum condition that secured formation of vinyl sultam **3a**.

To expand the scope of the strategy, we utilized commercial or readily accessible pyrrole-2-carboxaldehydes and arylmethanesulfonyl chlorides that could participate in the one-pot tandem synthesis of pyrrole-fused vinyl sultams under the optimized conditions (Scheme 2).

Scheme 2. Synthesis of the Designed *N*-Heteroaryl Fused Vinyl Sultams



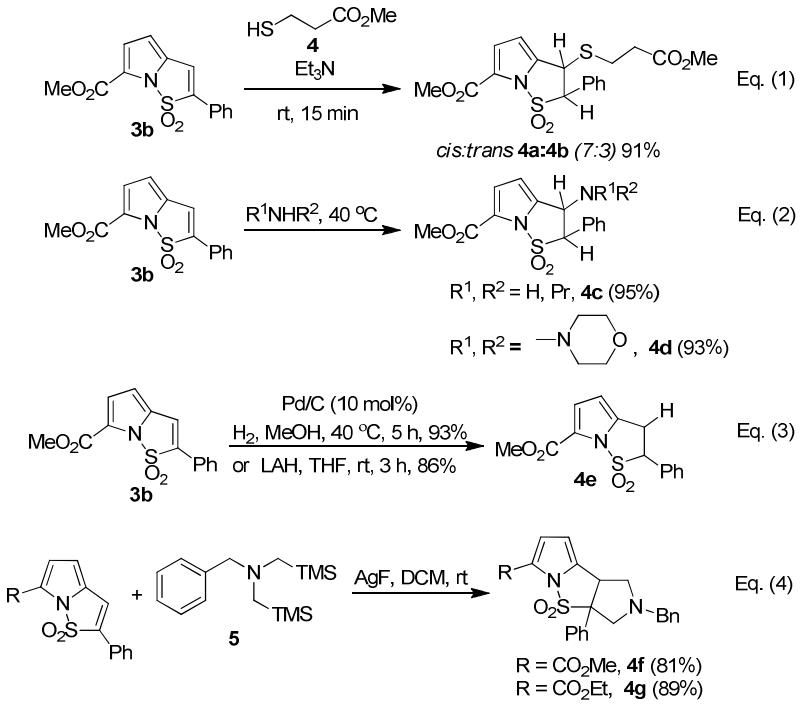
Pyrrole-2-carboxaldehydes containing a functional group at 5- or 4-position were viable substrates affording pyrrole-fused vinyl sultams **3b-3g** in varying yields. Similarly, di-substituted pyrrole-2-carboxaldehydes happened to be evenly competent producing sultams **3h-3k** in good yields. Notably, a di-bromo substituted vinyl sultam **3k** could augur interesting post-synthetic application. 4-substituted-phenylmethanesulfonyl chlorides (**2b-d**) also afforded the

corresponding sultam **3l-n** in moderate yields. Importantly, a bromo/chloro group could serve as a synthetic handle for subsequent functionalization on arene ring. Other heterocycles, imidazole-2-carboxaldehyde and indole-2-carboxaldehyde were subjected to the optimized condition gratifyingly furnishing respective imidazole (**3o**) and indole-fused (**3q**) vinyl sultams in excellent yields. However, imidazole-4-carboxaldehyde did not give a tandem fused vinyl sultam. Only *N*-sulfonylated derivative of imidazole-4-carboxaldehyde **3p** was isolated in this reaction. We next set out to extend the methodology to synthesize kindred lactam. Reaction of phenylacetyl chloride and pyrrole-2-carboxaldehyde gave the corresponding lactam **3r** in 86% yield. Our study indicates that use of an aliphatic methanesulfonyl chloride including (1S)-(+)-10-camphorsulfonyl chloride or ethanesulfonyl chloride could exert a crucial challenge yielding *N*-sulfonyl derivative **3t** or **3u** as the only isolable product. Only a limited success in the reaction of **1a** and 2,2,2-trifluroethanesulfonyl chloride under the optimized condition was realized in the synthesis of **3v**. This experiment suggests that poor acidity of the methylene group in $-NCH_2SO_2-$ could explain the difficulty in intramolecular cyclization in **3t** or **3u**. The central challenge in the preparation of *N*-heteroaryl fused vinyl sultams was to identify an optimized condition, which yielded a sustainable synthesis of the vinyl sultams. Both the electron-withdrawing and -donating groups screened in our study were well-tolerated to give sultams in good to excellent yields.

Next, we investigated the reactions of vinyl sultams at C=C bond (Scheme 3). Michael addition of thiol **4** to the vinyl sultam **3b** gave a diasteromeric mixture **4a** and **4b** which are easily separable by column chromatography, furnishing cis- (J = 9.4 Hz) and trans- (J = 6.8 Hz) isomers respectively in a ratio (7:3) as determined by the isolated yields (eq. 1). However, reaction of aliphatic amines, such as *n*-propylamine or morpholine and **3b** yielded only trans-

isomer (J = 7.3 Hz) of 1,4-conjugate addition product, **4c** and **4d**, respectively (eq. 2). It is noteworthy here that our template shows complete control of chemical reactivity at the vinyl bond in the presence of sulfonamide bond. Hydrogenation or LAH reduction of vinylic C=C bond in **3b** gave reduced pyrrole-fused sultam **4e** (eq. 3). 1,3-Dipolar cycloaddition reaction of azomethine ylide, generated in situ from **5**, was explored with vinyl sultams **3b-c**, which yielded novel pyrrolidine fused sultams bearing a quaternary center (**4f-g**) in good to excellent yields (eq. 4). The key discovery in this study was to uncover previously unexplored reactions of C=C double bond of vinyl sultam template. The reduced pyrrole fused sultam **4e** would have distinct reactivity to that of **3b**.

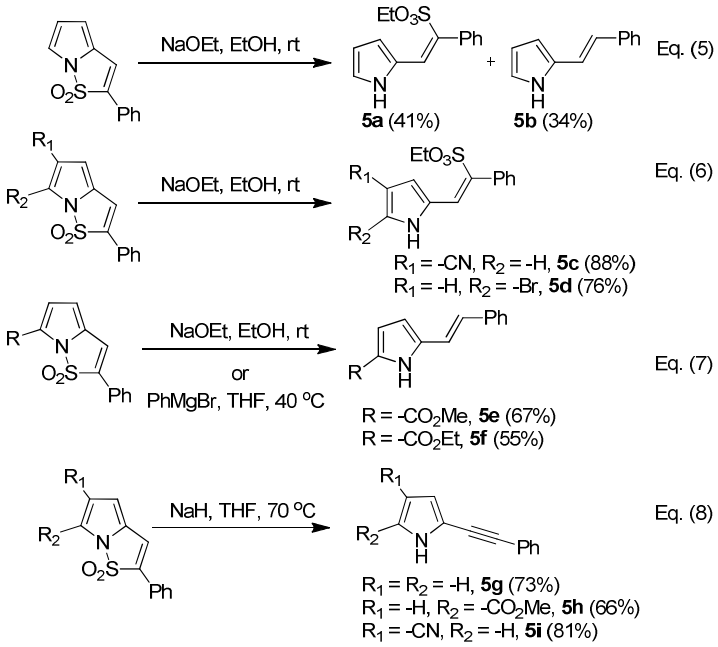
Scheme 3. Reactions Explored at the C=C Bond of Pyrrole Fused Vinyl Sultam



During the course of our current study, one of our defined objectives was to uncover previously unexplored chemoselective N-S bond cleavage (*N*-desulfonylation) [18] in vinyl sultams

with a suitable nucleophile. Unlike our previous study on ring-cleavage of biaryl sultam,[14] the chemoselective N-S bond cleavage in vinyl sultams posed an intrinsic challenge due to the presence of vinyl sulfonamide, a Michael acceptor. Predictably, the amine nucleophiles were unsuccessful in N-S bond cleavage in pyrrole-fused sultams (*cf.* eq. 2, Scheme 3). However, treatment of sultam **3a** with excess NaOEt resulted N-S bond cleavage affording diarylvinyl sulfonate (**5a)** and *(E)*-diarylalkene (**5b**) (eq. 5, Scheme 4).

Scheme 4. Reactions explored at the N-S bond of vinyl sultam



Under a similar condition reaction of **3e** and **6** gave diarylvinyl sulfonates **5c-d** (eq. 6). Importantly, the preparation of a vinyl sulfonate from vinyl sultam could complement the literature protocol. However, reaction of **3b-c** containing an ester group at C-5 position and NaOEt furnished *(E)*-diarylalkenes **5e-f** (eq. 7). Interestingly, phenylmagnesium bromide also produced the similar results (eq 7). The formation of desulfonylated product **5e-f** in the presence of two different nucleophiles is especially noteworthy. Notably, the chemoselective N-S bond

cleavage in pyrrole-fused sultams appears to be primarily dependent upon the substituents present on the pyrrole ring.

For studying the mechanism of the substituent dependent N-S bond cleavage, based on the formation of products **5a** and **5b**, we carried out a control experiment for the synthesis of diaryl alkene from diarylvinyl sulfonate in the presence of NaOEt. However, only a trace amount of **5b** was observed in 2 h suggesting slow desulfonylation. Based on our previous experiences on nucleophilic ring opening of sultams via N-S bond cleavage, it may be stated that alkoxide reacts with the pyrrole sultam to give vinyl sulfonate via ring opening of the sultam. The vinyl sulfonate could undergo desulfonylation to yield the corresponding alkene.[18a] A plausible mechanism could be the NaOEt mediated N-S bond cleavage followed by subsequent desulfonylation from the anionic intermediate prior to proton abstraction. In the presence of an electron-withdrawing group, the negative charge on pyrrole nitrogen is stabilized facilitating fast desulfonylation resulting in diaryl alkenes, whereas in case of other substituents diarylvinyl sulfonates are obtained.

In contrast to these results, reaction of pyrrole-fused vinyl sultams **3a-b,e** and NaH at an elevated temperature (70 °C) produced synthetically useful diarylalkynes **5g-i**, demonstrating the simple, yet rapid efficient synthesis of C2-alkynyl(NH)pyrroles (eq. 8). The formation of alkynes from pyrrole sultam could follow a different pathway. In this case, a β-elimination could occur on pyrrole sultam, which upon subsequent SO_2 extrusion could form alkynes.[18b] However, mechanism for the formation of alkenes or alkynes from pyrrole sultams is a subject of further investigation. The key distinctive features of the pyrrole-fused vinyl sultam template include ability to be diversified affording vinyl sulfonates, diarylalkenes, and diarylalkynes under N-S bond cleavage conditions.

We also explored the chemical reactivity of the pyrrole-fused sultam **3a** towards aromatic electrophilic substitution. Mono-bromination of pyrrole-fused sultam **6** using NBS occurred exclusively at the C-5 position providing a synthetic handle for late-stage diversification (eq. 9).

3a **6** (92%) Eq. (9)

In conclusion, we have demonstrated, for the first time, that *N*-heterocycle fused vinyl sultams could be a useful template for programming chemical synthesis. The sustainable synthesis of the templates from *N*-heterocycles bearing an aldehyde group and arylmethanesulfonyl chlorides employing only sodium hydride as the reagent is especially noteworthy. The template presents a formidable framework that enables a variety of previously unexplored paradigm of reactions. The operational simplicity to prepare the templates and explicit use of classical reactions on the designed templates are the central features of this study. Future strides in this area could unveil many formidable templates that could reveal boundless importance of these templates in diversity organic synthesis.

EXPERIMENTAL SECTION

General Methods: Unless noted otherwise, all reagents and solvents were purchased from commercial sources and used as received. All palladium-catalyzed reactions were performed in a screw-cap sealed tube. The ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ as solvent using a 400 MHz spectrometer with Me_4Si as an internal standard. Coupling constants (*J* values) are reported in Hz. Column chromatography was performed using silica gel (100-200 mesh). High

resolution mass spectra (HRMS) were obtained using electron spray ionisation (ESI) technique and as TOF mass analyser. All melting points were taken using a melting point apparatus equipped with a calibrated thermometer and are uncorrected. New compounds were characterized by melting point, IR, ^{1}H NMR, ^{13}C NMR, and HRMS data.

1. Typical Procedure for Substituted Pyrrole synthesis (1aa-1ae)[19]

Following a literature procedure, to a solution of sodium hydride (2 equiv) in THF (10 mL), solution of *p*-toluenesulfonylmethylisocyanide (10 mmol) and michael acceptor (10 mmol) in THF (10 mL) was added dropwise. As reaction mixture turned brownish upon addition,reaction was allowed to continue overnight. Following which water (10 mL) was added and it was extracted with EtOAc (3 x 10 mL). The combined organic layer was concentrated under reduced pressure and washed with hexane to give substituted pyrrole.

2. General Procedure for Formylation of Pyrroles (1b-c, 1e-f, 1h-j)[20]

The Vilsmeier reagent was prepared by adding $POCl_3$ (5.0 mmol) dropwise to ice cold dry DMF (5 mL) under stirring. The mixture was then stirred for 10-15 min at 0 °C. To the above Vilsmeier reagent was added substituted pyrrole (1.0 mmol) as a solution in DCE (5.0 mL). Then the mixture was allowed to warm to 100 °C and was stirred for 1.0 h. After the staring material was consumed (monitored by TLC), the reaction mixture was poured into saturated sodium chloride aqueous (50 mL). The mixture was extracted with dichloromethane (3 × 20 mL), the combined organic phase was washed with water (3 × 20 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, Ethyl acetate: Hexanes = 2:8 to 1:1) to give desired product.

3. Standard Procedure for Nitration of Pyrrole (1d)[21]

In an oven-dried screw cap vial equipped with a magnetic stir bar, the solution of Pyrrole-2-carboxaldehyde (0.5 mmol) in carbon tetrachloride (2.5 mL) was treated with copper nitrate trihydrate (1.5 equiv) and acetic anhydride (5 equiv) and heated at 50 °C. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (20 mL X 2). The organic layer was dried (Na_2SO_4) and concentrated, which upon chromatography [silica, EtOAc: Hexanes = 1:9] gave the desired product.

4. Standard Procedure for Bromination of Pyrroles (1g, 1k, 6)[22]

To the solution of substrate (0.5 mmol) in DMF (4.0 mL) at 0 °C was added recrystallized *N*-Bromosuccinimide (1.1 equiv) which gave rusty solution. After completion of the reaction (monitored by TLC), the mixture turned light yellow and was quenched with saturated solution of sodium sulfite (10 mL) and extracted with EtOAc (10 mL X 2). The organic layer was dried (Na_2SO_4) and concentrated, which upon chromatography [silica, EtOAc: Hexanes = 0.5:9.5] gave the corresponding brominated product.

5. General procedure for the synthesis of arylmethanesulfonyl chloride (2b-d)[23]

4-substituted benzyl bromide (5.0 mmol) were added dropwise to a solution of sodium sulfite (5.0 mmol) in aqueous NaOH (10%, 5 mL) and the reaction mixture was heated at reflux for 4 h. After cooling the solution in an ice bath, the corresponding sodium arylmethanesulfonates were purified by recrystallization from CH_3OH (95%). The intermediate (2.5mmol) was then treated with thionyl chloride (10.0mmol) in DMF (2.5 mL) for 3 h at room temperature. The residue was subsequently poured into the ice-water mixture and the solid was then extracted with diethyl ether (3-20 mL). After removing the solvent under reduced pressure, desired product was obtained.

6. Synthesis of *N*-Heteroaryl-fused Vinyl Sultams (3a-v)

In an oven-dried screw cap vial equipped with a magnetic stir bar, sodium hydride (2.5 equiv) was added portion wise to an ice cold solution of formylated pyrrole substrate (0.5mmol) in freshly distilled anhydrous THF (2.5 mL). To this reaction mixture was added phenyl methane sulfonyl chloride (1.5 equiv) portion wise and was heated at 70 °C for 12 h. The reaction mixture was allowed to cool to room temperature and neutralized by the addition of saturated solution of NaCl (10 mL). Then, it was extracted with ethyl acetate (2 x 10 mL). The combined organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and purified by column chromatography on silica using (EtOAc: Hexanes = 1:9 to 3:7) as an eluent to give the desired product.

7. General Procedure for Michael Addition at Vinyl Sulfonamide using Thiols and Amines (4a-d)

In an oven-dried screw cap vial equipped with a magnetic stir bar, substrate (0.2 mmol) was treated with methyl 3-mercaptopropanoate (0.26 mmol) in the presence of triethylamine (1.2 equiv) in methanol (1 mL) at room temperature for 15min. The solvent was removed under reduced pressure and the reaction mixture was then diluted with H_2O (5 mL) and extracted with EtOAc (10 mL X 2). The organic layer was dried (Na_2SO_4) and concentrated, which upon chromatography [silica, EtOAc: Hexanes = 3:7] gave the corresponding michael addition product.

In an oven-dried screw cap vial equipped with a magnetic stir bar, substrate (0.2 mmol) was treated with amine (1 mL) at 40 °C for 1 h. After completion of the reaction (monitored by TLC),Thesolvent was removed under reduced pressure and the reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (10 mL X 2). The organic layer was dried (Na_2SO_4) and

concentrated, which upon chromatography [silica, EtOAc: Hexanes = 2:8] gave the corresponding michael addition product.

8. General Procedure for Hydrogenation of Vinyl Sultams (4e)

The vinyl sultam substrate (0.2 mmol), Pd/C (10 mol%) and methanol were added in the reaction tube and then sealed. The reaction tube was thrice evacuated and flushed with hydrogen and heated at 40 °C under hydrogen atmosphere. After the staring material was consumed (monitored by TLC), the reaction mixture was diluted with methanol and passed through celite.The combined organic layer was concentrated under reduced pressure and washed with hexane to get reduced product.

In a perfectly dried two-necked flask, an ice-cold solution of substrate (0.2 mmol) and freshly distilled THF (3.0 mL) under nitrogen was treated with LAH (4 equiv) portion wise. The reaction was allowed to warm at room temperature and after the starting material was consumed (monitored by TLC),the reaction was quenched with sodium hydroxide and extracted withEtOAc (20 mL X 2). The organic layer was dried (Na_2SO_4) and concentrated, which upon flash chromatography [silica, EtOAc: Hexanes = 2:8] gave the corresponding reduced product.

9. General Procedure for Cycloaddition with AzomethineYlide Precursor (4f-g)[24]

In an oven-dried aluminium foil coated screw-cap vial with a magnetic bar, vinyl sultam (0.2 mmol, 1 equiv) and Ag(I)F (2.2 equiv) were taken. [Note: Ag(I)F was completely dried under vacuum at 55-60 °C at least for 30 min with aluminium foil coating before use]. The vial was purged three times with nitrogen and kept under ice bath. A solution of the azomethineylide precursor (1.1 equiv) in anhydrous DCM (1 mL) was added dropwise . The ice-bath was removed, and the reaction mixture was stirred at room temperature for 10-15 min under nitrogen

atmosphere. The reaction mixture was then diluted with 5 mL DCM and passed through a celite bed. The filtrate was concentrated in vacuo and purified by column chromatography (100-200# silica, ethyl acetate: hexane) to give the desired spirocyclic compound.

10. General Procedure for Cleavage of N-S bond to form Sulfonate Ester and/orDiaryl Alkene using NaOEt(5a-f)

In an oven-dried screw cap vial equipped with a magnetic stir bar, a solution of substrate (0.2 mmol) in THF (2 mL) was treated with freshly prepared sodium ethoxide solution in ethanol (0.25mmol) at room temperature. After the staring material was consumed (monitored by TLC), the reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (20 mL X 2). The organic layer was dried (Na_2SO_4) and concentrated, which upon chromatography [silica, EtOAc: Hexanes = 1:9] gave the corresponding sulfonate ester and/ordiaryl alkene.

11. General Procedure for Cleavage of N-S bond using Phenylmagnesiumbromide (5e-f)

In an oven-dried screw cap vial equipped with a magnetic stir bar, a solution of substrate (0.2 mmol) in THF (1 mL) was treated with phenylmagnesiumbromide (0.5 mL, 1M solution in THF) at 60 °C for 2 h. After the staring material was consumed (monitored by TLC), saturated solution of ammonium chloride (2 mL) was added and the mixture was diluted with H_2O (10 mL) and extracted with EtOAc (20 mL X 2). The organic layer was dried (Na_2SO_4) and concentrated, which upon chromatography [silica, EtOAc: Hexanes = 1:9] gave the desulfonylated product.

12. General Procedure for Synthesis of Diaryl Alkynes using NaH (5g-i)

In an oven-dried screw cap vial equipped with a magnetic stir bar, a solution of substrate (0.2mmol) in THF (2 mL) was treated with sodium hydride (1.2 equiv) and allowed to heat at 70 °C. After the staring material was consumed (monitored by TLC), the reaction mixture was

quenched with H_2O (10 mL) and extracted with EtOAc (20 mL X 2). The organic layer was dried (Na_2SO_4) and concentrated, which upon chromatography [silica, EtOAc: Hexanes = 0.5:9.5] gave the correspondingdiaryl alkynes.

COMPOUNDS CHARACTERIZATION DATA

1*H*-Pyrrole-3-carbonitrile (1aa): Colorless liquid (71 mg, 77%); IR (DCM, cm^{-1}): 3307, 2961, 2249, 1423, 1058, 729; ^1H NMR ($CDCl_3$): δ 9.35 (bs, 1H), 7.33-7.32 (m, 1H), 6.83 (dd, J = 2.3, 2.5 Hz, 1H), 6.49 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 126.0, 119.4, 117.3, 111.6; HRMS (ESI) m/z calcd for $C_5H_5N_2$ $[M+H]^+$ 93.0453, found 93.0451.

Methyl 1*H*-pyrrole-3-carboxylate (1ab): Colorless solid (114 mg, 89%); mp.87-89 °C; IR (KBr, cm^{-1}): 3382, 2952, 1687, 1335, 1161, 765; ^1H NMR ($CDCl_3$): δ 8.52 (bs, 1H), 7.44 (s, 1H), 6.77 (d, J = 2.2 Hz, 1H), 6.66 (s, 1H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 165.4, 123.4, 118.7, 116.3, 109.8, 51.1; HRMS (ESI) m/z calcd for $C_6H_8NO_2$ $[M+H]^+$ 126.0555, found 126.0550.

Diethyl 1*H*-pyrrole-3,4-dicarboxylate (1ac): Colorless solid (194 mg, 92%); ^1H NMR ($CDCl_3$): δ 9.59 (bs, 1H), 7.37 (s, 2H), 4.33 (d, J = 7.1 Hz, 4H), 1.36 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 164.0, 164.2, 125.6, 115.9, 60.2, 28.2, 14.3; HRMS (ESI) m/z calcd for $C_{10}H_{14}NO_4$ $[M+H]^+$ 212.0923, found 212.0927.

Ethyl 4-methyl-1*H*-pyrrole-3-carboxylate (1ad): Colorless solid (126 mg, 83%); mp.61-62 °C; IR (KBr, cm^{-1}): 3325, 2925, 1685, 1323, 1154, 778, 600; ^1H NMR ($CDCl_3$): δ 8.64 (bs, 1H), 7.39 (dd, J = 2.3, 3.0 Hz, 1H), 6.55 (dd, J = 0.9, 2.0 Hz, 1H), 4.31 (d, J = 7.2 Hz, 2H), 2.30 (d, J = 0.9 Hz, 3H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 165.8, 124.4, 121.0, 117.3, 114.8, 59.4, 14.5, 11.7; HRMS (ESI) m/z calcd for $C_8H_{12}NO_2$ $[M+H]^+$ 154.0868, found 154.0872.

Methyl 4-methyl-1*H*-pyrrole-3-carboxylate (1ae): Colorless solid (128 mg, 92%); mp.125-126 °C; IR (KBr, cm^{-1}): 3326, 2920, 1688, 1325, 1154, 702; ^1H NMR ($CDCl_3$): δ 8.87 (bs, 1H), 7.38 (dd, J = 2.2, 3.1 Hz, 1H), 6.54 (dd, J = 1.0, 2.0 Hz, 1H), 3.81 (s, 3H), 2.30 (d, J = 0.9 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 165.6, 124.3, 121.0, 117.2, 115.0, 59.3, 11.6; HRMS (ESI) m/z calcd for $C_7H_{10}NO_2$ $[M+H]^+$ 140.0712, found 140.0711.

Methyl 5-formyl-1*H*-pyrrole-2-carboxylate (1b): Colorless solid (116 mg, 76%); mp.100-101 °C; IR (KBr, cm^{-1}): 3300, 2959, 1730, 1675, 1264, 761; ^1H NMR ($CDCl_3$): δ 10.04 (bs, 1H), 9.68 (s, 1H), 6.96 (dd, J = 1.6, 2.2 Hz, 2H), 3.93 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 180.4, 160.8, 134.4, 128.1, 119.7, 115.2, 52.2; HRMS (ESI) m/z calcd for $C_7H_8NO_3$ $[M+H]^+$ 154.0504, found 154.0509.

Ethyl 5-formyl-1*H*-pyrrole-2-carboxylate (1c): Colorless solid (146 mg, 87%); mp.78-79 °C; IR (KBr, cm^{-1}): 3134, 2958, 1730, 1269, 994, 765; ^1H NMR ($CDCl_3$): δ 10.28 (bs, 1H), 9.68 (s, 1H), 6.96-6.93 (m, 2H), 4.42 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 180.5, 160.4, 134.4, 128.6, 119.7, 115.6, 61.4, 14.2; HRMS (ESI) m/z calcd for $C_8H_{10}NO_3$ $[M+H]^+$ 168.0661, found 168.0665.

4-Nitro-1*H*-pyrrole-2-carbaldehyde (1d): Colorless solid (74 mg, 53%); mp.131-132 °C; IR (KBr, cm^{-1}): 3444, 2079, 1666, 1392, 1073, 752; ^1H NMR ($CDCl_3$): δ 10.29 (bs, 1H), 9.61 (s, 1H), 7.90 (s, 1H), 7.48 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 186.4 (d, J = 7 Hz),142.3, 137.1, 131.5, 119.5;HRMS (ESI) m/z calcd for $C_5H_5N_2O_3$ $[M+H]^+$ 141.0300, found 141.0302.

5-Formyl-1*H*-pyrrole-3-carbonitrile (1e): Colorless solid (78 mg, 65%); mp.143-145 °C; IR (KBr, cm^{-1}): 3304, 2917, 2224, 1667, 1422, 1057, 728; ^1H NMR (DMSO-D_6): δ 13.05 (bs, 1H), 9.55 (d, J = 0.7 Hz, 1H), 7.99 (s, 1H), 7.48 (d, J = 1.3 Hz, 1H); ^{13}C NMR (DMSO-D_6): δ 180.7,

133.7, 133.5, 123.0, 116.2, 94.2; HRMS (ESI) m/z calcd for $C_6H_5N_2O$ $[M+H]^+$ 121.0402, found 121.0407.

Methyl 5-formyl-1*H*-pyrrole-3-carboxylate (1f): Colorless solid (120 mg, 79%); mp.135-136 °C; IR (KBr, cm^{-1}): 3255, 1664, 1398, 1185, 1001, 764; ^1H NMR ($CDCl_3$): δ 10.53 (bs, 1H), 9.57 (d, J = 0.9 Hz, 1H), 7.74-7.73 (m, 1H), 7.42 (dd, J = 1.4, 2.4 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 180.1, 164.0, 133.0, 130.0, 121.6, 118.7, 51.5; HRMS (ESI) m/z calcd for $C_7H_8NO_3$ $[M+H]^+$ 154.0504, found 154.0506.

4-Bromo-1*H*-pyrrole-2-carbaldehyde (1g): Colorless solid (79 mg, 46%); mp.122-124 °C; IR (KBr, cm^{-1}): 3252, 3108, 2923, 1667, 1357, 770; ^1H NMR ($CDCl_3$): δ9.96 (bs, 1H), 9.47 (s, 1H), 7.13 (s, 1H), 6.98 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 178.9, 132.6, 126.1, 122.2, 98.8; HRMS (ESI) m/z calcd for C_5H_5BrNO $[M+H]^+$ 173.9555, found 173.9558.

Diethyl 2-formyl-1*H*-pyrrole-3,4-dicarboxylate (1h): Colorless solid (164 mg, 69%); mp.149-151 °C; IR (KBr, cm^{-1}): 34433, 2825, 2067, 1667, 1285, 1190, 766; ^1H NMR ($CDCl_3$): δ 10.48 (bs, 1H), 9.90 (d, J = 0.5 Hz, 1H), 7.61-7.60 (m, 1H), 4.46 (q, J = 7.1 Hz, 2H), 4.35 (q, J = 7.1 Hz, 1H), 1.42-1.33 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 180.9, 163.2, 162.7, 132.4, 128.7, 124.3, 118.3, 61.8, 60.8, 14.2, 14.1; HRMS (ESI) m/z calcd for $C_{11}H_{14}NO_5$ $[M+H]^+$ 240.0872, found 240.0871.

Ethyl 5-formyl-4-methyl-1*H*-pyrrole-3-carboxylate (1i): Colorless solid (135 mg, 75%); mp.118-120 °C; IR (KBr, cm^{-1}): 3325, 2855, 1685, 1451, 1154, 778; ^1H NMR ($CDCl_3$): δ 10.37 (bs, 1H), 9.71 (s, 1H), 7.69 (d, J = 3.3 Hz, 1H), 4.34 (d, J = 7.1 Hz, 2H), 2.62 (s, 3H), 1.38 (d, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 178.5, 164.2, 134.5, 130.7, 130.5, 117.2, 59.9, 14.4, 10.0; HRMS (ESI) m/z calcd for $C_9H_{12}NO_3$ $[M+H]^+$ 182.0817, found 182.0814.

Methyl 5-formyl-4-methyl-1*H*-pyrrole-3-carboxylate (1j): Colorless solid (131 mg, 79%); mp.137-138 °C; IR (KBr, cm^{-1}): 3246, 2927, 1638, 1264, 1171, 805; ^1H NMR ($CDCl_3$): δ 10.18 (bs, 1H), 9.72 (s, 1H), 7.67 (d, J = 3.4 Hz, 1H), 3.85 (s, 3H), 2.62 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 178.5, 164.5, 134.3, 130.5, 130.5, 116.9, 51.2, 9.9; HRMS (ESI) m/z calcd for $C_8H_{10}NO_3$ $[M+H]^+$ 168.0661, found 168.0659.

4,5-Dibromo-1*H*-pyrrole-2-carbaldehyde (1k): Colorless solid (164 mg, 69%); mp.144-146 °C; IR (KBr, cm^{-1}): 3434, 3108, 2860, 1661, 1357, 770; ^1H NMR ($CDCl_3$): δ 10.56 (bs, 1H), 9.35 (s, 1H), 6.98 (s, 1H);^{13}C NMR ($CDCl_3$): δ 181.0, 132.4, 129.1, 124.3, 118.1; HRMS (ESI) m/z calcd for $C_5H_4Br_2NO$ $[M+H]^+$ 251.8660, found 251.8663.

(4-Bromophenyl)methanesulfonyl chloride (2b): Colorless solid (126 mg, 83%); mp.110-112 °C; IR (KBr, cm^{-1}): 3397, 2921, 1770, 1371, 1246, 749; ^1H NMR (DMSO-D_6): δ 7.44 (dd, J = 1.8, 6.5 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H), 3.69 (s, 2H); ^{13}C NMR (DMSO-D_6): δ 139.6, 137.6, 135.6, 124.8, 61.7; HRMS (ESI) m/z calcd for $C_7H_7BrClO_2S$ $[M+H]^+$ 268.9039, found 268.9033.

(4-Chlorophenyl)methanesulfonyl chloride (2c): Colorless solid (85 mg, 77%); ^1H NMR ($CDCl_3$): δ 7.48-7.43 (m, 4H), 4.85 (s, 2H).

***p*-Tolylmethanesulfonyl chloride (2d):** Colorless solid (82 mg, 81%); ^1H NMR ($CDCl_3$): δ 7.39 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 4.85 (s, 2H).

2-Phenylpyrrolo[1,2-b]isothiazole 1,1-dioxide (3a): Colorless solid (16 6 mg, 72%); mp.118-120 °C; IR (KBr, cm^{-1}): 2924, 1588, 1323, 1170, 756, 651; ^1H NMR ($CDCl_3$): δ 7.72-7.69 (m, 2H), 7.51-7.44 (m, 3H), 7.26 (s, 1H), 7.22 (d, J = 3.0 Hz, 1H), 6.43 (t, J = 3.2 Hz, 1H), 6.37 (dd, J = 0.7 Hz, 3.3 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 140.2, 129.9, 129.3, 128.6, 127.1, 125.7, 118.5, 118.4, 116.9, 109.4; HRMS (ESI) m/z calcd for $C_{12}H_{10}NO_2S$ $[M+H]^+$232.0432, found 232.0428.

Methyl 2-phenylpyrrolo[1,2-b]isothiazole-6-carboxylate 1,1-dioxide (3b): Yellowish solid (118 mg, 82%); mp.154-155 °C; IR (KBr, cm^{-1}): 3418, 2924, 2853, 1645, 1154, 749; ^1H NMR ($CDCl_3$): δ 7.74-7.71 (m, 2H), 7.48-7.47 (m, 3H), 7.19 (s, 1H), 7.01 (d, J = 3.6 Hz, 1H), 6.32 (d, J = 3.6 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 159.1, 142.7, 133.0, 130.6, 129.4, 126.7, 126.4, 126.1, 122.6, 116.4, 108.6, 52.4; HRMS (ESI) m/z calcd for $C_{14}H_{12}NO_4S$ $[M+H]^+$ 290.0487, found 290.0492.

Ethyl 2-phenylpyrrolo[1,2-b]isothiazole-6-carboxylate 1,1-dioxide (3c): Yellowish solid (110 mg, 73%); mp.125-127 °C; IR (KBr, cm^{-1}): 3421, 2924, 1289, 1182, 751; ^1H NMR ($CDCl_3$): δ 7.75-7.73 (m, 2H), 7.50-7.47 (m, 3H), 7.20 (s, 1H), 7.03 (d, J = 3.6 Hz, 1H), 6.33 (d, J = 3.6 Hz, 1H) 4.47 (q, J = 7.1 Hz, 2H), 1.46 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 158.6, 142.5, 132.9, 130.5, 129.4, 126.9, 126.7, 126.1, 122.6, 116.4, 108.6, 61.7, 14.1; HRMS (ESI) m/z calcd for $C_{15}H_{14}NO_4S$ $[M+H]^+$ 304.0644, found 304.0648.

5-Nitro-2-phenylpyrrolo[1,2-b]isothiazole 1,1-dioxide (3d): Yellowish solid (117 mg, 85%); mp.187-188 °C; IR (KBr, cm^{-1}): 3269, 2882, 1508, 1310, 1104, 749; ^1H NMR ($CDCl_3$): δ 8.05 (s, 1H), 7.72-7.70 (m, 2H), 7.54-7.53 (m, 3H), 7.30 (s, 1H), 6.92 (d, J = 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 141.8, 131.2, 129.7, 127.1, 126.2, 125.7, 117.9, 117.0, 103.3; HRMS (ESI) m/z calcd for $C_{12}H_9N_2O_4S$ $[M+H]^+$ 277.0283, found 277.0285.

2-Phenylpyrrolo[1,2-b]isothiazole-5-carbonitrile 1,1-dioxide (3e): Off-white solid (113 mg, 89%); mp.138-140 °C; IR (KBr, cm^{-1}): 3433, 3124, 2232, 1634, 1342, 1158, 749; ^1H NMR ($CDCl_3$): δ 7.71-7.68 (m, 3H), 7.53 (t, J = 3.2 Hz, 3H), 7.28 (s, 1H), 6.58 (d, J = 0.9, 1H); ^{13}C NMR ($CDCl_3$): δ 131.0, 129.6, 128.6, 126.1, 125.9, 124.6, 117.1, 113.7, 109.8, 101.6; HRMS (ESI) m/z calcd for $C_{13}H_9N_2O_2S$ $[M+H]^+$ 257.0385, found 257.0379.

Methyl 2-phenylpyrrolo[1,2-b]isothiazole-5-carboxylate 1,1-dioxide (3f): Yellowish solid (109 mg, 76%); mp.183-184 °C; IR (KBr, cm^{-1}): 3439, 2924, 2091, 1644, 1206, 750; ^1H NMR (DMSO-D_6): δ 8.53 (s, 1H), 8.11 (s, 1H), 7.77 (d, J = 7.1 Hz, 2H), 7.59-7.52 (m, 3H), 6.87 (s, 1H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 163.3, 140.8, 130.5, 129.5, 128.4, 126.4, 125.9, 123.9, 122.4, 118.1, 108.9, 51.8; HRMS (ESI) m/z calcd for $C_{14}H_{12}NO_4S$ $[M+H]^+$ 290.0487, found 290.0482.

5-Bromo-2-phenylpyrrolo[1,2-b]isothiazole 1,1-dioxide (3g): Off-white solid (103mg, 67%); mp.138-139 °C; IR (KBr, cm^{-1}): 3420, 1445, 1216, 1143, 921, 754, 569; ^1H NMR ($CDCl_3$): δ 7.70-7.68 (m, 2H), 7.52-7.47 (m, 3H), 7.23 (s, 2H), 6.39 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 140.6, 130.4, 129.4, 128.3, 126.5, 125.9, 117.6, 117.4, 111.5, 104.6; HRMS (ESI) m/z calcd for $C_{12}H_9BrNO_2S$ $[M+H]^+$ 309.9537, found 309.9533.

Diethyl 2-phenylpyrrolo[1,2-b]isothiazole-4,5-dicarboxylate 1,1-dioxide (3h): Colorless solid (164 mg, 81%); mp.231-233 °C; IR (KBr, cm^{-1}): 3272, 2975, 1710, 1667, 1255, 1066, 752; ^1H NMR ($CDCl_3$): δ 7.75-7.73 (m, 2H), 7.70 (d, J = 0.3 Hz, 1H), 7.62 (s, 1H), 7.53-7.52 (m, 3H), 4.44 (q, J = 7.1 Hz, 2H), 4.44 (q, J = 7.1 Hz, 2H), 1.44 (t, J = 7.1 Hz, 3H), 1.40 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 161.7, 161.4, 130.6, 130.0, 129.3, 127.7, 126.6, 124.8, 119.5, 114.4, 61.6, 61.2, 14.3, 14.1; HRMS (ESI) m/z calcd for $C_{18}H_{18}NO_6S$ $[M+H]^+$ 376.0855, found 376.0857.

Ethyl 4-methyl-2-phenylpyrrolo[1,2-b]isothiazole-5-carboxylate 1,1-dioxide (3i): Colorless solid (125 mg, 79%); mp.290-292 °C; IR (KBr, cm^{-1}): 3421, 1711, 1637, 1355, 1150, 1070, 763, 568; ^1H NMR ($CDCl_3$): δ 7.78 (s, 1H), 7.70-7.68 (dd, J = 1.7, 8.1 Hz, 2H), 7.50-7.45 (m, 3H), 7.30 (s, 1H), 4.35 (q, J = 7.1 Hz, 2H), 2.38 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ

163.1, 130.2, 130.1, 129.4, 128.9, 127.7, 127.6, 125.7, 124.6, 123.3, 122.6, 120.5, 120.2, 60.3, 14.2, 11.4; HRMS (ESI) m/z calcd for $C_{16}H_{16}NO_4S$ $[M+H]^+$ 318.0800, found 318.0797.

Methyl 4-methyl-2-phenylpyrrolo[1,2-b]isothiazole-5-carboxylate 1,1-dioxide (3j): Colorless solid (130 mg, 86%); mp.143-145 °C; IR (KBr, cm^{-1}): 3444, 2924, 1634, 1332, 1161, 749, 562; ^1H NMR ($CDCl_3$): δ 7.77 (s, 1H), 7.70 (dd, J = 1.6, 7.8 Hz, 2H), 7.51-4.45 (m, 3H), 7.30 (s, 1H), 3.86 (s, 3H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 163.8, 138.9, 130.1, 129.4, 126.8, 126.6, 125.7, 123.3, 122.5, 121.5, 117.2, 51.5, 10.2; HRMS (ESI) m/z calcd for $C_{15}H_{14}NO_4S$ $[M+H]^+$ 304.0644, found 304.0648.

5,6-Dibromo-2-phenylpyrrolo[1,2-b]isothiazole 1,1-dioxide (3k): Colorless solid (125 mg, 65%); mp.193-196 °C; IR (KBr, cm^{-1}): 3432, 2924, 2075, 1638, 1247, 749; ^1H NMR ($CDCl_3$): δ 7.68-7.66 (m, 2H), 7.50-7.48 (m, 3H), 7.11 (s, 1H), 6.38 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 140.3, 130.5, 129.8, 129.5, 126.3, 126.0, 116.5, 112.1, 107.2, 103.3; HRMS (ESI) m/z calcd for $C_{12}H_8Br_2NO_2S$ $[M+H]^+$ 387.8642, found 387.8649.

Ethyl 2-(4-bromophenyl)pyrrolo[1,2-b]isothiazole-6-carboxylate 1,1-dioxide (3l): Colorless solid (72 mg, 38%); mp.189-191 °C; IR (KBr, cm^{-1}): 3434, 2923, 1638, 1459, 1329, 749; ^1H NMR ($CDCl_3$): δ 7.65-7.60 (m, 4H), 7.21 (s, 1H), 7.04 (d, J = 3.7 Hz, 1H), 6.36 (d, J = 3.7 Hz, 1H), 4.48 (q, J = 7.1 Hz, 2H), 1.46 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 158.6, 141.5, 132.7, 127.5, 127.2, 125.7, 125.0, 122.6, 116.8, 109.0, 107.5, 61.8, 14.1; HRMS (ESI) m/z calcd for $C_{15}H_{13}BrNO_4S$ $[M+H]^+$ 381.9749, found 381.9744.

Ethyl 2-(4-chlorophenyl)pyrrolo[1,2-b]isothiazole-6-carboxylate 1,1-dioxide (3m): Yellow solid (103 mg, 61%); mp.174-176 °C; IR (KBr, cm^{-1}): 3439, 2925, 1656, 1459, 743; ^1H NMR ($CDCl_3$): δ 7.69 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.19 (s, 1H), 7.04 (d, J = 3.6 Hz,

1H), 6.35 (d, *J* = 3.6 Hz, 1H), 4.48 (q, *J* = 7.0 Hz, 2H), 1.46 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 158.5, 141.5, 136.7, 132.6, 129.7, 127.4, 127.1, 125.2, 122.6, 116.8, 108.9, 61.8, 14.1; HRMS (ESI) m/z calcd for $C_{15}H_{13}ClNO_4S$ $[M+H]^+$ 338.0254, found 338.0250.

Ethyl 2-(*p*-tolyl)pyrrolo[1,2-b]isothiazole-6-carboxylate 1,1-dioxide (3n): Off-white solid (106 mg, 67%); mp.143-144 °C; IR (KBr, cm^{-1}): 3429, 2918, 1638, 1329, 566; ^{1}H NMR ($CDCl_3$): δ 7.65 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.14 (s, 1H), 7.03 (d, *J* = 3.6 Hz, 1H), 6.30 (d, *J* = 3.6 Hz, 1H), 4.47 (q, *J* = 7.1 Hz, 2H), 2.42 (s, 3H), 1.46 (q, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 158.7, 142.8, 141.1, 133.1, 130.1, 126.7, 126.1, 123.9, 122.5, 115.3, 108.2, 61.7, 22.6, 14.1; HRMS (ESI) m/z calcd for $C_{16}H_{16}NO_4S$ $[M+H]^+$ 318.0800, found 318.0804.

6-Phenylimidazo[1,2-b]isothiazole 5,5-dioxide (3o): Yellow solid (90 mg, 78%); mp.140-141 °C; IR (KBr, cm^{-1}): 3428, 3032, 1348, 1173, 757, 558; ^{1}H NMR ($CDCl_3$): δ 7.77-7.74 (m, 2H), 7.55-7.53 (m, 3H), 7.40 (d, *J* = 1.0 Hz, 1H), 7.36 (s, 1H), 7.30 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 148.0, 144.3, 136.0, 131.4, 129.6, 126.5, 125.9, 116.6, 115.2; HRMS (ESI) m/z calcd for $C_{11}H_9N_2O_2S$ $[M+H]^+$ 233.0385, found 233.0383.

1-(Benzylsulfonyl)-1*H*-imidazole-4-carbaldehyde (3p): Colorless solid (88 mg, 71%); mp.167-168 °C; IR (KBr, cm^{-1}): 3284, 3131, 1680, 1423, 1204, 763, 526; ^{1}H NMR ($CDCl_3$): δ 9.87 (s, 1H), 7.63 (d, *J* = 1.1 Hz, 1H), 7.52 (s, *J* = 1.0 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.10 (d, *J* = 7.3 Hz, 2H), 4.62 (s, 2H); ^{13}C NMR (DMSO-D_6): δ 181.8, 138.6, 135.6, 132.8, 130.7, 128.9, 127.9, 126.6, 57.9; HRMS (ESI) m/z calcd for $C_{11}H_{11}N_2O_3S$ $[M+H]^+$ 251.0490, found 251.0494.

2-Phenylisothiazolo[2,3-a]indole 1,1-dioxide (3q): Yellow solid (164 mg, 67%); mp.152-154 °C; IR (KBr, cm^{-1}): 2925, 2854, 1731, 1458, 1273, 758; ^{1}H NMR ($CDCl_3$): δ 7.81 (dd, *J* = 1.6,

7.8 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.53-7.48 (m. 3H), 7.44-7.37 (m, 1H), 7.37 (s, 1H), 7.28-7.24 (m, 1H), 6.69 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 143.5, 134.0, 132.8, 132.7, 130.5, 129.4, 126.9, 126.7, 126.1, 123.4, 122.9, 118.0, 111.5, 105.4; HRMS (ESI) m/z calcd for $C_{16}H_{12}NO_2S$ $[M+H]^+$ 282.0589, found 282.0586.

2-Phenyl-3*H*-pyrrolizin-3-one (3r): Reddish solid (83 mg, 86%); mp.110-111 °C; IR (KBr, cm^{-1}): 3443, 1728, 1377, 1240, 779; ^{1}H NMR ($CDCl_3$): δ 7.80-7.77 (m, 2H), 7.43-7.39 (m, 2H), 7.36-7.32 (m, 1H), 7.23 (s, 1H), 6.98-6.97 (m 1H), 6.07-6.05 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 165.0, 135.9, 133.1, 131.2, 129.8, 128.6, 128.4, 126.3, 118.8, 115.8, 111.5;HRMS (ESI) m/z calcd for $C_{13}H_{10}NO$ $[M+H]^+$ 196.0762, found 196.0754.

1-((((1R)-7,7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methyl)sulfonyl)-1*H*-pyrrole-2-carbaldehyde (3t): Colorless solid (54 mg, 35%); mp.93-94 °C; IR (KBr, cm^{-1}): 3148, 2924, 2857, 1713, 1568, 1386, 1089, 757, 675; ^{1}H NMR ($CDCl_3$): δ 9.73 (d, *J* = 0.7 Hz, 1H), 7.62-7.61 (m, 1H), 7.24 (dd, *J* = 1.7, 3.7 Hz, 1H), 6.43 (t, *J* = 3.5 Hz, 1H), 4.11 (d, *J* = 14.7 Hz, 1H), 3.98 (d, *J* = 14.6 Hz, 1H), 2.55-2.38 (m, 2H), 2.18-2.06 (m, 2H), 1.99 (d, *J* = 18.5 Hz, 1H), 1.83-1.76 (m, 1H), 1.52-1.48 (m, 1H), 1.21 (s, 3H), 0.96 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 214.0, 178.2, 133.0, 130.8, 129.1, 111.3, 58.9, 52.5, 48.3, 42.6, 42.5, 27.0, 25.2, 19.8, 19.6; HRMS (ESI) m/z calcd for $C_{15}H_{20}NO_4S$ $[M+H]^+$ 310.1113, found 310.1110.

1-(Ethylsulfonyl)-1*H*-pyrrole-2-carbaldehyde (3u): Viscous oil (89 mg, 96%); IR (DCM, cm^{-1}): 3127, 2926, 1726,1364, 1167, 908, 611; ^{1}H NMR ($CDCl_3$): δ 9.74 (s, 1H), 7.59-7.58 (m, 1H), 7.26 (dd, *J* = 1.7, 3.4 Hz, 1H), 6.45 (t, *J* = 3.4 Hz, 1H), 3.86 (q, *J* = 7.4 Hz, 2H), 1.38 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 178.4, 133.2, 131.2, 128.5, 111.6, 49.6, 7.9; HRMS (ESI) m/z calcd for $C_7H_{10}NO_3S$ $[M+H]^+$ 188.0381, found 188.0388.

2-(Trifluoromethyl)pyrrolo[1,2-b]isothiazole 1,1-dioxide (3v): Semi-solid (10 mg, 9%); IR (DCM, cm^{-1}):2928, 1645, 1030, 774, 630; ^1H NMR ($CDCl_3$): δ 7.56 (s, 1H), 7.27 (d, J = 2.9 Hz, 1H), 6.62 (d, J = 3.4 Hz, 1H), 6.50 (t, J = 3.2 Hz, 1H);^{13}C NMR ($CDCl_3$): δ 128.9, 128.9, 128.5, 125.5, 121.0, 117.9, 114.5; HRMS (ESI) m/z calcd for $C_7H_5F_3NO_2S$ $[M+H]^+$ 223.9993, found 223.9989.

Methyl 3-((3-methoxy-3-oxopropyl)thio)-2-phenyl-2,3-dihydropyrrolo[1,2-b]isothiazole-6-carboxylate 1,1-dioxide (4a): Yellow Semi-solid (52 mg, 64%); IR (DCM, cm^{-1}): 2953, 2852, 1723, 1482, 1366, 1166, 753, 571, 529; ^1H NMR ($CDCl_3$): δ 7.58-7.50 (m, 5H), 7.14 (d, J = 3.6 Hz, 1H), 6.37 (d, J = 3.6 Hz, 1H), 5.10 (d, J = 9.4 Hz, 1H), 4.79 (d, J = 9.4 Hz, 1H), 3.92 (s, 3H), 3.67 (s, 3H), 2.69-2.66 (m, 2H), 2.48-2.44 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 171.6, 159.1, 135.9, 130.6, 130.1, 129.4, 127.3, 123.2, 121.8, 106.9, 52.1, 52.0, 44.0, 34.2, 25.9; HRMS (ESI) m/z calcd for $C_{18}H_{20}NO_6S_2$ $[M+H]^+$ 410.0732, found 410.0734.

Methyl 3-((3-methoxy-3-oxopropyl)thio)-2-phenyl-2,3-dihydropyrrolo[1,2-b]isothiazole-6-carboxylate 1,1-dioxide (4b): Yellow Semi-solid (22 mg, 28%); IR (DCM, cm^{-1}): 2926, 2844, 1721, 1478, 1369, 1170, 775, 580; ^1H NMR ($CDCl_3$): δ 7.45-7.38 (m, 3H), 7.24 (d, J = 7.3 Hz, 2H), 7.13 (d, J = 3.7 Hz, 1H), 6.36 (d, J = 3.6 Hz, 1H), 5.30 (d, J = 6.8 Hz, 1H), 5.09 (d, J = 6.8 Hz, 1H), 3.91 (s, 3H), 3.69 (s, 3H), 2.79-2.64 (m, 2H), 2.56 (t, J = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 171.8, 159.1, 137.8, 130.2, 130.1, 128.9, 128.8, 123.2, 122.5, 106.7, 52.2, 52.0, 43.4, 34.5, 27.8;HRMS (ESI) m/z calcd for $C_{18}H_{20}NO_6S_2$ $[M+H]^+$ 410.0732, found 410.0734.

Methyl 2-phenyl-3-(propylamino)-2,3-dihydropyrrolo[1,2-b]isothiazole-6-carboxylate 1,1-dioxide (4c): Viscous oil (66 mg, 95%); IR (DCM, cm^{-1}): 3332, 2927, 1706, 1497, 1497, 1353, 1167, 751, 598; ^1H NMR ($CDCl_3$): δ 7.48 (s, 5H), 7.14 (d, J = 3.7 Hz, 1H), 6.33 (q, J = 0.8, 3.6

Hz, 1H), 4.99 (d, *J* = 7.3 Hz, 1H), 4.85 (dd, *J* = 0.8, 7.3 Hz, 1H), 3.91 (s, 3H), 2.64-2.53 (m, 2H), 1.49-1.40 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 159.2, 138.7, 130.1, 129.7, 129.3, 128.7, 123.2, 121.2, 105.7, 58.1, 52.0, 47.9, 23.3, 11.5; HRMS (ESI) m/z calcd for $C_{17}H_{21}N_2O_4S$ $[M+H]^+$ 349.1222, found 349.1218.

Methyl 3-morpholino-2-phenyl-2,3-dihydropyrrolo[1,2-b]isothiazole-6-carboxylate 1,1-dioxide (4d): Colorless solid (69 mg, 93%); mp.178-180 °C; IR (KBr, cm^{-1}):3390, 2928, 2852, 1705, 1493, 1353, 1154, 1083, 856, 750, 574; ^{1}H NMR ($CDCl_3$): δ 7.50-7.47 (m, 5H), 7.15 (d, *J* = 3.6 Hz, 1H), 6.29 (d, *J* = 3.6 Hz, 1H), 5.18 (d, *J* = 7.2 Hz, 1H), 4.90 (d, *J* = 7.2 Hz, 1H), 3.89 (s, 3H), 3.67-3.61 (m, 4H), 2.59-2.53 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 159.1, 136.0, 130.1, 129.7, 129.7, 129.4, 123.5, 121.4, 106.5, 70.3, 66.9, 65.5, 52.1, 49.2; HRMS (ESI) m/z calcd for $C_{18}H_{21}N_2O_5S$ $[M+H]^+$ 377.1171, found 377.1165.

Methyl 2-phenyl-2,3-dihydropyrrolo[1,2-b]isothiazole-6-carboxylate 1,1-dioxide (4e): Colorless solid (54 mg, 93%); mp.148-149 °C; IR (KBr, cm^{-1}): 2953, 1712, 1483, 1360, 1170, 754, 585; ^{1}H NMR ($CDCl_3$): δ 7.52-7.48 (m, 5H), 7.11 (d, *J* = 3.6 Hz, 1H), 6.16 (d, *J* = 3.6 Hz, 1H), 5.21 (t, *J* = 8.8 Hz, 1H), 3.91 (s, 3H), 3.76-3.61 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 159.2, 134.8, 130.2, 129.3, 129.3, 129.0, 123.2, 121.1, 105.5, 71.2, 52.0, 28.0; HRMS (ESI) m/z calcd for $C_{14}H_{14}NO_4S$ $[M+H]^+$ 292.0644, found 292.0645.

Methyl 2-benzyl-3a-phenyl-2,3,3a,8b-tetrahydro-1*H*-dipyrrolo[1,2-b:3',4'-d]isothiazole-6-carboxylate 4,4-dioxide (4f): Yellow solid (68 mg, 81%); mp.126-127 °C; IR (KBr, cm^{-1}): 2924, 2853, 1713, 1441, 1157, 954, 753; ^{1}H NMR ($CDCl_3$): δ 7.42-7.41 (m, 2H), 7.34-7.29 (m, 8H), 7.20 (d, *J* = 3.6 Hz, 1H), 6.12 (d, *J* = 3.5 Hz, 1H), 4.43-4.38 (m, 2H), 3.89 (s, 3H), 3.81 (d, *J* = 13.5 Hz, 1H), 3.70 (d, *J* = 13.5 Hz, 1H), 3.24 (d, *J* = 8.8 Hz, 1H), 2.99 (d, *J* = 10.8 Hz, 1H),

2.82 (t, *J* = 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 159.2, 138.5, 137.2, 134.8, 129.4, 129.0, 128.4, 128.3, 127.9, 127.3, 124.8, 120.6, 104.1, 83.2, 62.1, 60.8, 58.3, 51.9, 45.8; HRMS (ESI) m/z calcd for $C_{23}H_{23}N_2O_4S$ $[M+H]^+$ 423.1379, found 423.1373.

Ethyl 2-benzyl-3a-phenyl-2,3,3a,8b-tetrahydro-1*H*-dipyrrolo[1,2-b:3',4'-d]isothiazole-6-carboxylate 4,4-dioxide (4g): Colorless solid (77 mg, 89%); mp.111-112 °C; IR (KBr, cm^{-1}): 2924, 2853, 1713, 1485, 1175, 698, 585; ^{1}H NMR ($CDCl_3$): δ 7.43-7.27 (m, 10H), 7.21 (d, *J* = 3.6 Hz, 1H), 6.11 (d, *J* = 3.6 Hz, 1H), 4.42-4.31 (m, 4H), 3.79 (q, *J* = 13.5 Hz, 2H), 3.22 (d, *J* = 8.8 Hz, 1H), 3.01 (d, *J* = 10.7 Hz, 1H), 2.81 (dd, *J* = 6.8, 8.6 Hz, 1H), 1.39 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 158.7, 137.2, 134.7, 129.5, 129.0, 128.5, 127.8, 124.6, 121.1, 104.2, 83.2, 68.5, 61.1, 60.6, 58.4, 45.7, 14.1; HRMS (ESI) m/z calcd for $C_{24}H_{25}N_2O_4S$ $[M+H]^+$ 437.1535, found 437.1538.

(*Z*)-Ethyl 1-phenyl-2-(1*H*-pyrrol-2-yl)ethenesulfonate (5a): Off-white solid (22 mg, 41%); mp.85-87 °C; IR (KBr, cm^{-1}): 3351, 3107, 2339, 1655, 1187, 825, 623; ^{1}H NMR ($CDCl_3$): δ 7.63 (s, 1H), 7.57-7.50 (m, 5H), 6.71 (d, *J* = 0.9 Hz, 1H), 6.45 (s, 1H), 6.20-6.18 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 131.5, 130.7, 130.0, 130.0, 129.7, 126.6, 125.8, 123.7, 118.7, 110.4, 66.8, 14.8; HRMS (ESI) m/z calcd for $C_{14}H_{16}NO_3S$ $[M+H]^+$ 278.0851, found 278.0854.

(*E*)-2-styryl-1*H*-pyrrole (5b): Colorless solid (13 mg, 34%); mp.128-130 °C; IR (KBr, cm^{-1}): 3297, 2971, 1639, 1385, 1102; ^{1}H NMR ($CDCl_3$): δ 8.38 (bs, 1H), 7.47 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.03 (d, *J* = 16.4 Hz, 1H), 6.84 (d, *J* = 1.1 Hz, 1H), 6.71 (d, *J* = 16.4 Hz, 1H), 6.40 (s, 1H), 6.30-6.28 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 137.5, 130.8,

128.7, 126.9, 125.8, 123.3, 119.2, 119.0, 110.0, 109.2; HRMS (ESI) m/z calcd for $C_{12}H_{12}NO$ $[M+H]^+$ 170.0970, found 170.0972.

(*Z*)-Ethyl 2-(4-cyano-1*H*-pyrrol-2-yl)-1-phenylethenesulfonate (5c): Off-white solid (53 mg, 88%); mp.161-162 °C; IR (KBr, cm^{-1}): 3258, 2923, 2229, 1632, 1348, 1167, 908, 611; ^1H NMR ($CDCl_3$): δ 8.19 (bs, 1H), 7.60-7.58 (m, 4H), 7.48-7.46 (m, 2H), 7.15 (s, 1H), 6.50 (s, 1H), 4.20 (q, J = 7.0 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 132.1, 130.6, 130.5, 130.2, 130.0, 129.0, 128.8, 127.8, 126.8, 126.7, 118.9, 115.2, 95.4, 67.6, 14.8; HRMS (ESI) m/z calcd for $C_{15}H_{15}N_2O_3S$ $[M+H]^+$ 303.0803, found 303.0807.

(*Z*)-Ethyl 2-(5-bromo-1*H*-pyrrol-2-yl)-1-phenylethenesulfonate (5d): Yellowish solid (54 mg, 76%); mp.136-138 °C; IR (KBr, cm^{-1}): 3247, 2165, 1478, 1298, 911, 586; ^1H NMR ($CDCl_3$): δ 7.59-7.58 (m, 3H), 7.51-7.49 (m, 3H), 7.45 (bs, 1H), 6.34 (t, J = 3.6 Hz, 1H), 6.14 (dd, J = 2.4, 3.7 Hz, 1H), 4.20 (q, J = 7.12 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 131.1, 130.9, 130.4, 130.2, 129.8, 128.7, 127.1, 119.7, 112.6, 61.6, 14.1; HRMS (ESI) m/z calcd for $C_{14}H_{15}BrNO_3S$ $[M+H]^+$ 355.9956, found 355.9961.

Methyl (*E*)-5-styryl-1*H*-pyrrole-2-carboxylate (5e): Colorless solid (30 mg, 67%); mp.158-160 °C; IR (KBr, cm^{-1}): 3382, 2956, 1685, 1489, 1159, 758, 611; ^1H NMR ($CDCl_3$): δ 9.35(bs, 1H), 7.49 (d, J = 7.4 Hz, 2H); 7.39 (t, J = 7.4 Hz, 2H); 7.30 (t, J = 7.3 Hz, 1H), 6.95-6.93 (m, 3H), 6.41 (t, J = 2.7 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 161.5, 136.6, 135.3, 128.8, 128.1, 127.9, 126.3, 122.7, 117.6, 116.7, 110.1, 51.6; HRMS (ESI) m/z calcd for $C_{14}H_{14}NO_2$ $[M+H]^+$ 228.1025, found 228.1019.

Ethyl (*E*)-5-styryl-1*H*-pyrrole-2-carboxylate (5f): Colorless solid (26 mg, 55%); mp.140-141 °C; IR (KBr, cm^{-1}): 3325, 2855, 1715, 1649, 1082, 727, 539; ^1H NMR ($CDCl_3$): δ 9.30 (bs, 1H),

7.49 (d, *J* = 7.3 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 2H), 7.30 (t, *J* = 8.8 Hz, 1H), 6.95-6.92 (m, 3H), 6.41 (dd, *J* = 2.7, 3.6 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 161.1, 136.6, 135.2, 128.7, 127.9, 127.8, 126.3, 123.1, 117.7, 116.5, 110.1, 60.5, 14.5; HRMS (ESI) m/z calcd for $C_{15}H_{16}NO_2$ $[M+H]^+$ 242.1181, found 242.1175.

2-(Phenylethynyl)-1*H*-pyrrole (5g): Colorless solid (24 mg, 73%); mp.93-94 °C; IR (KBr, cm^{-1}): 3435, 2952, 2853, 1743, 1463, 755; ^{1}H NMR ($CDCl_3$): δ 8.43 (bs, 1H), 7.49-7.46 (m, 2H), 7.35-7.25 (m, 3H), 6.80 (d, *J* = 1.0 Hz, 1H), 6.54 (s, 1H), 6.24 (q, *J* = 3.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 131.1, 128.3, 128.0, 123.2, 119.6, 114.9, 112.9, 109.4, 90.3, 81.8; HRMS (ESI) m/z calcd for $C_{12}H_{10}N$ $[M+H]^+$ 168.0813, found 168.0818.

Methyl 5-(phenylethynyl)-1*H*-pyrrole-2-carboxylate (5h): White solid (36 mg, 81%); mp.116-117 °C; IR (KBr, cm^{-1}): 3317, 3304, 2284, 1672, 1491, 1226, 773; ^{1}H NMR ($CDCl_3$): δ 9.01 (bs, 1H), 7.33-7.30 (m, 2H), 7.26-7.18 (m, 3H), 6.85 (dd, *J* = 2.7, 0.9 Hz, 1H), 6.01 (t, *J* = 3.1 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 161.6, 140.8, 137.8, 128.5, 128.3, 126.3, 121.0, 115.9, 108.4, 51.3; HRMS (ESI) m/z calcd for $C_{14}H_{12}NO_2$ $[M+H]^+$ 226.0868, found 226.0865.

5-(Phenylethynyl)-1*H*-pyrrole-3-carbonitrile (5i): Buff solid (25 mg, 66%); mp.93-94 °C; IR (KBr, cm^{-1}): 3310, 3307, 2961, 2249, 2210, 1767, 1223, 798; ^{1}H NMR ($CDCl_3$): δ 8.81 (bs, 1H), 7.52-7.50 (m, 2H), 7.39-7.38 (m, 3H), 7.30-7.29 (m, 1H), 6.75 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 131.4, 128.9, 128.5, 126.2, 121.9, 116.8, 115.7, 94.5, 91.6; HRMS (ESI) m/z calcd for $C_{13}H_9N_2$ $[M+H]^+$ 193.0766, found 193.0761.

6-Bromo-2-phenylpyrrolo[1,2-b]isothiazole 1,1-dioxide (6): Colorless solid (56 mg, 92%); mp.123-125 °C; IR (KBr, cm^{-1}): 3430, 2960, 1723, 1286, 744; ^{1}H NMR ($CDCl_3$): δ 7.68 (d, *J* = 7.5 Hz, 2H), 7.51-7.45 (m, 3H), 7.12 (s, 1H), 6.34 (d, *J* = 3.4 Hz, 1H), 6.27 (d, *J* = 3.5 Hz, 1H);

^{13}C NMR ($CDCl_3$): δ 139.9, 130.5, 130.1, 129.4, 126.8, 125.8, 118.7, 117.3, 110.5, 102.1; HRMS (ESI) m/z calcd for $C_{12}H_9BrNO_2S$ $[M+H]^+$ 309.9537, found 309.9540.

ASSOCIATED CONTENT

Supporting Information

Copies of 1H and 13C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

The financial support from the SERB, New Delhi is greatly appreciated. SS and SK thank to the NIPER S.A.S. Nagar and DBT, New Delhi for the award of Senior Research Fellowships, respectively.

REFERENCES

(1) (a) Li, X.; Liu, D. R. *Angew. Chem. Int. Ed.* **2004**, *43*, 4848-4870. (b) Van Bommel, K. J. C.; Friggeri, A.; Shinkai, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 980-999.

(2) Ref for small organic molecule template: (a) Yao, H.; Gao, M.; Yu, S. *Nanoscale* **2010**, *2*, 322-334. (b) Joseph, C. G.; Wilson, K. R.; Wood, M. S.; Sorenson, N. B.; Phan, D. V.; Xiang, Z.; Witek, R. M.; Haskell-Luevano, C. *J. Med. Chem.* **2008**, *51*, 1423-1431.

(3) (a) Du, M.; Bu, Y.; Zhou, Y.; Zhao, Y.; Wang, S.; Xu, H. *RSC Adv.* **2017**, *7*, 12711-12718. (b) Kanan, M. W.; Rozenman, M. M.; Sakurai, K.; Synder, T. M.; Liu, D. R. *Nature* **2004**, *431*, 545-549. (c) Greenwell, D. R.; Ibnouzaki, A. F.; Warriner, S. L. *Angew. Chem. Int. Ed.* **2002**, *41*, 1215-1218. (d) Gartner, Z. J.; Liu, D. R. *J. Am. Chem. Soc.* **2001**, *123*, 6961-6963.

(4) (a) Gennari, C.; Nestler, H. P.; Salom, B.; Still, W. C. *Angew. Chem. Int. Ed.* **1995**, *34*, 1765-1768. (b) Gennari, C.; Salom, B.; Potenza, D.; Williams, A. *Angew. Chem. Int. Ed.* **1994**, *33*, 2067-2069.

(5) (a) Azevedo, C. M. G.; Watterson, K. R.; Wargent, Ed T.; Hansen, S. V. F.; Hudson, B. D.; Kępczyńska, M. A.; Dunlop, J.; Shimpukade, B.; Christiansen, E.; Milligan, G.; Stocker, C. J.; Ulven, T. *J. Med. Chem.* **2016**, *59*, 8868-8878. (b) Kiefer, L.; Gorojankina, T.; Dauban, P.; Faure, H.; Ruat, M.; Dodd, R. H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7483-7487. (c) Lapierre, J.; Rotstein, D. M.; Sjogren, E. B. PCT Int. Appl. WO0228810, **2002**. (d) Roush, W. R.; Cheng, J.; Knapp-Reed, B.; Alvarez-Hernandez, A.; McKerrow, J. H.; Hansell, E.; Engel, J. C. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2759-2762. (e) Chapman, J. M.; Cocolas, Jr. G. H.; Hall, I. H. *J. Med. Chem.* **1983**, *26*, 243-246.

(6) Ref for biomaterials: (a) Swinnen, D.; Jorand-Lebrun, C.; Grippi-Vallotton, T.; Gerber, P.; Gonzalez, J.; Shaw, J.; Jeyaprakashnarayanan, S. PCT Int. Appl. 2010100144, **2010**. (b) Shan, W.; Balog, J. A.; Nation, A. J.; Gavai, A. V.; Han, W.; Salvati, M. E. PCT Int. Appl. 2008030902, **2008**. (c) Na, K.; Bae, Y. H. *Pharm. Res*. **2002**, *19*, 681-688.

(7) (a) Lopez-Jaramillo, F. J.; Hernandez-Mateo, F.; Santoyo-Gonzalez, F. *Vinyl sulfone: a multi-purpose function in proteomics in Integrative proteomics,* InTech, **2012**, p. 301. (b) Meadows, D. C.; Gervay-Hague, J. *Med. Res. Rev.* **2006**, *26*, 793-814.

(8) (a) Reddick, J. J.; Cheng, J.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1967-1970. (b) Roush, W. R.; Gwaltney II, S. L.; Cheng, J.; Scheidt, K. A.; McKerrow, J. H.; Hansell, E. *J. Am. Chem. Soc.* **1998**, *120*, 10994-10995.

(9) (a) Lima, L. M.; Barreiro, E. J. *Curr. Med. Chem.* **2005**, *12*, 23-49. (b) Thornber, C. W. *Chem. Soc. Rev.* **1979**, *8*, 563-580.

(10) (a) Kalgutkar, A.; Jones, R.; Sawant, A. In Metabolism Pharmacokinetics and Toxicity of Functional Groups; Smith, D. A., Ed.; RSC: Cambridge, UK, **2010**; RSC Drug Discovery Series No. 1, Chapter 5. (b) Hansch, C.; Sammes, P. G.; Taylor, J. B. Comprehensive Medicinal Chemistry; Pergamon Press: Oxford, UK, **1990**; Vol. 2, Chapter 7.1.

(11) For selected references, see: (a) Asad, N.; Samarakoon, T. B.; Zang, Q.; Loh, J. K.; Javed, S.; Hanson, P. R. *Org. Lett.* **2013**, *16*, 82-85. (b) Ji, T.; Wang, Y.; Wang, M.; Niu, B.; Xie, P.; Pittman Jr., C. U.; Zhou, A. *ACS Comb. Sci.* **2013**, *15*, 595-600. (c) Zhou, A.; Rayabarapu, D.; Hanson, P. R. *Org. Lett.* **2009**, *11*, 531-534. (d) Zhao, M. M.; Qu, C.; Lynch, J. E. *J. Org. Chem.* **2005**, *70*, 6944-6947. (e) Makara, G. M.; Ma, Y. *Tetrahedron Lett.* **2001**, *42*, 4123-4125.

(12) (a) Suh, E. H.; Liu, Y.; Connelly, S.; Genereux, J. C.; Wilson, I. A.; Kelly, J. W. *J. Am. Chem. Soc*. **2013**, *135*, 17869–17880. (b) Lu, X.; Olsen, S. K.; Capili, A. D.; Cisar, J. S.; Lima, C. D.; Tan, D. S. *J. Am. Chem. Soc.* **2010**, *132*, 1748-1749.

(13) (a) Schmidt, B.; Wolf, F.; Brunner, H. *Eur. J. Org. Chem.* **2016**, *2016*, 2972-2982. (b) Reuter, D. C.; McIntosh, J. E.; Guinn, A. C.; Madera, A. M. *Synthesis,* **2003**, 2321-2324.

(14) Laha, J. K.; Dayal, N.; Jethava, K. P.; Prajapati, D. V. *Org. Lett.* **2015**, *17*, 1296-1299.

(15) Laha, J. K.; Jethava, K. P.; Dayal, N. *J. Org. Chem.* **2014**, *79*, 8010-8019.

(16) Laha, J. K.; Sharma, S.; Dayal, N. *Eur. J. Org. Chem.* **2015**, *2015*, 7885-7891.

(17) Singh, G.; Kumar, R.; Swett, J.; Zajc, B. *Org. Lett.* **2013**, *15*, 4086-4089.

(18) (a) Nájera, C.; Yus, V. *Tetrahedron* **1999**, *55*, 10547-10658. (b) Mandai, T.; Yanagi, T.; Araki, K.; Morisaki, Y.; Kawada, M.; Otera, J. *J. Am. Chem. Soc.* **1984**, *106*, 3670-3672.

(19) Van Leusen, M.; Siderius, H.; Hoogenboom, B. E.; van Leusen, D. *Tetrahedron Lett*. **1972**, *52*, 5337-5340.

(20) Chen, C. Y.; Bocian, D. F.; Lindsey, J. S. *J. Org. Chem.* **2014**, *79*, 1001–1016.

(21) Yanga, S.; Suna, B.; Ou, Z.; Menga, D.; Lua, G.; Fangb, Y.; Kadish, K. M. *J. Porphyrins Phthalocyanines* **2013**,*17*, 1-13.

(22) Gilow, H. M.; Burton, D. E. *J. Org. Chem.* **1981**, *46*, 2221-2225.

(23) Sadeghzadeh, M.; Sheibani, S.; Ghandi, M.; Daha, F. J.; Amanlou, M.; Arjmand, M.; Bozcheloie, A. H. *Eur. J. Med. Chem.* **2013**, *64*, 488-497.

(24) Pandey, G.; Laha, J. K.; Mohanakrishnan, A. *Tetrahedron Lett.* **1999**, *40*, 6065-6068.