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SYNTHESIS OF NOVEL 5-ARYL/HETARYLIDENYL 3-(2-METHYL-5,6,7,8-TETRAHYDROBENZO[4,5]THIENO[2,3-*d*]PYRIMIDIN-4-YL)-2-THIOXOTHIAZOLIDIN-4-ONES

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Abstract – The synthesis of a variety of novel 5-substituted titled compounds containing a privileged rhodanine scaffold is described. The synthesis involves a microwave (MW) assisted Knoevenagel condensation of 3-(2-methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4-yl)-2-thioxothiazolidin-4-one with suitably substituted aromatic aldehydes. However, these condensations fail with aliphatic aldehydes. The 2-thioxothiazolidin-4-one (rhodanine) precursor was prepared by the condensation of 2-thioxothiazolidin-4-one-di-(carboxymethyl)trithiocarbonyl and 4,5,6,7-tetrahydrobenzo[4,5]thienyl[2,3-*d*]-2-methylpyrimidin-4-amine in the presence of K₂CO₃.

Thienopyrimidines are biologically important heterocycles that have been attracting attention in medicinal chemistry research over the last two decades due to their diverse range of biological activities. An intensive literature review reveals that several thienopyrimidines possess a wide range of biological activities such as antitumor, antimicrobial, anti-inflammatory, and bronchodilatory activities¹⁻³ as well as inhibitors of enzymes like VEGFR-2 kinase,⁴ tyrosine kinase and phosphodiesterases; several of these drugs have been patented.⁵ Currently, benzothiophenes in combination with other ring systems are being used extensively in pharmaceutical applications such as antiallergic⁶ and analgesic agents.⁷ Raloxifene, a polyhydroxyphenylbenzo[*b*]thiophene antiestrogen, has been approved by the U.S food and Drug Administration for the prevention and treatment of postmenopausal osteoporosis.⁸ In addition, benzo[*b*]thiophenes containing a nitrogen ring system (compound **A** in Figure 1) are potent metabotropic glutamate receptors (mGluRs).⁹ Rhodanines¹⁰ that possess a substituted ring-nitrogen atom are patented as fungicides while those containing an unsubstituted ring nitrogen atom¹¹ are patented as pesticides. Additionally, 2-aryl-5-(4-oxo-3-phenethyl-2-thioxothiazolidinylidene)methyl)furans, (Compound **B** in Figure 1) which possess a rhodanine core, exhibits anti-HIV-1 activity,¹² and 5-benzylidene-

3-phenyl-2-thioxothiazolidin-4-one (Compound **C** in Figure 1) inhibits jun NH₂-terminal kinase (jnk) stimulatory phosphatase-1 (jsp-1).¹³

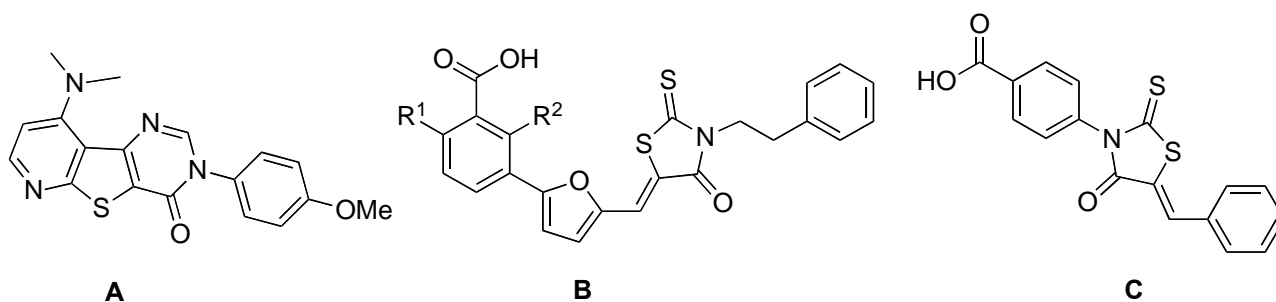
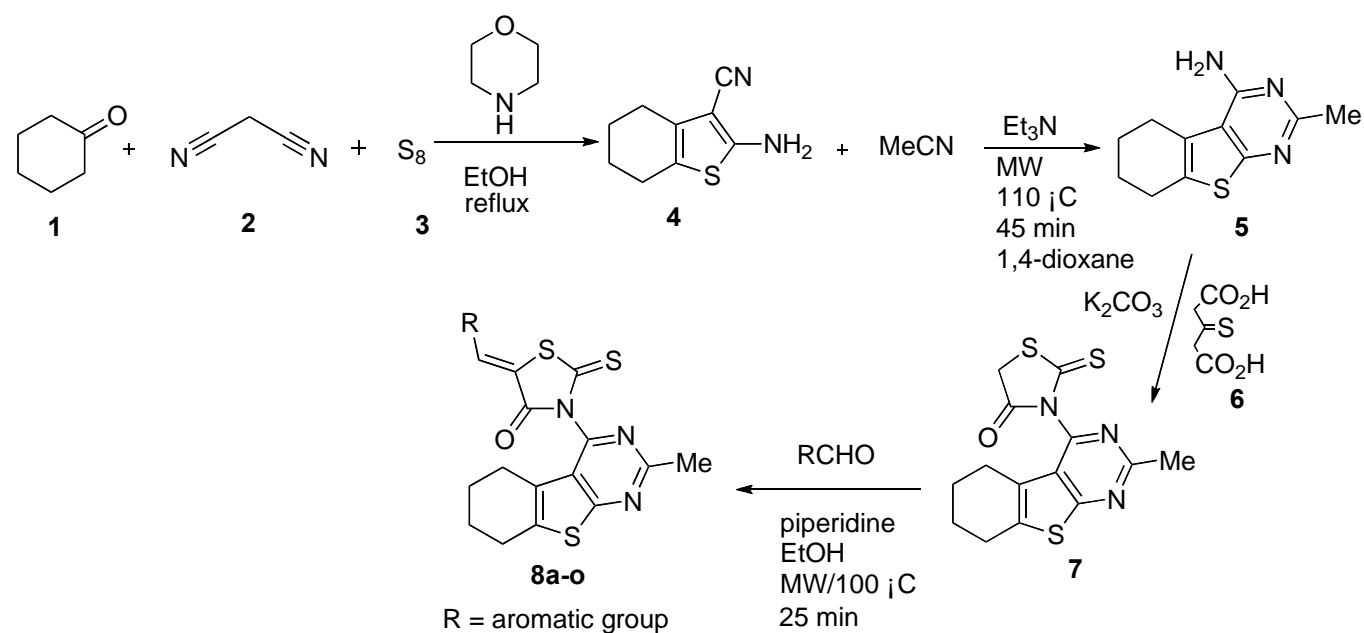


Figure 1. Structures of biologically active benzothiophenes containing a nitrogen ring system (**A**) and heterocycles containing a rhodanine core (**B** and **C**)

In addition, rhodanine-based compounds are popular small molecule inhibitors of numerous targets such as HCVNS3 protease,^{14a} aldose reductase,^{14b,c} β -lactamase,^{14d} UDP-N-acetylmuramate/L-alanine ligase,^{14e} and histidine decarboxylase,^{14f} and can also behave as antidiabetic agents^{14g} and cathepsin D receptors.^{14h}

For the past few years, our group has been carrying out microwave assisted reactions for the preparation of potentially biologically important heterocycles.^{15a-j} Several of these compound exhibit strong neuroprotecting properties.¹⁶ We have now extended the scope of microwave assisted reactions to include the incorporation of potentially biologically active rhodanine cores into a variety of heterocyclic side chains and report the result herein.

As shown in Scheme 1, compounds (**8a-o**) were obtained by a four-step reaction sequence. The first step involves the reaction of cyclohexanone (**1**) and malononitrile (**2**) in presence of sulphur (**3**)¹⁷ to give



Scheme 1. Four-step preparation of titled compounds (**8a-o**)

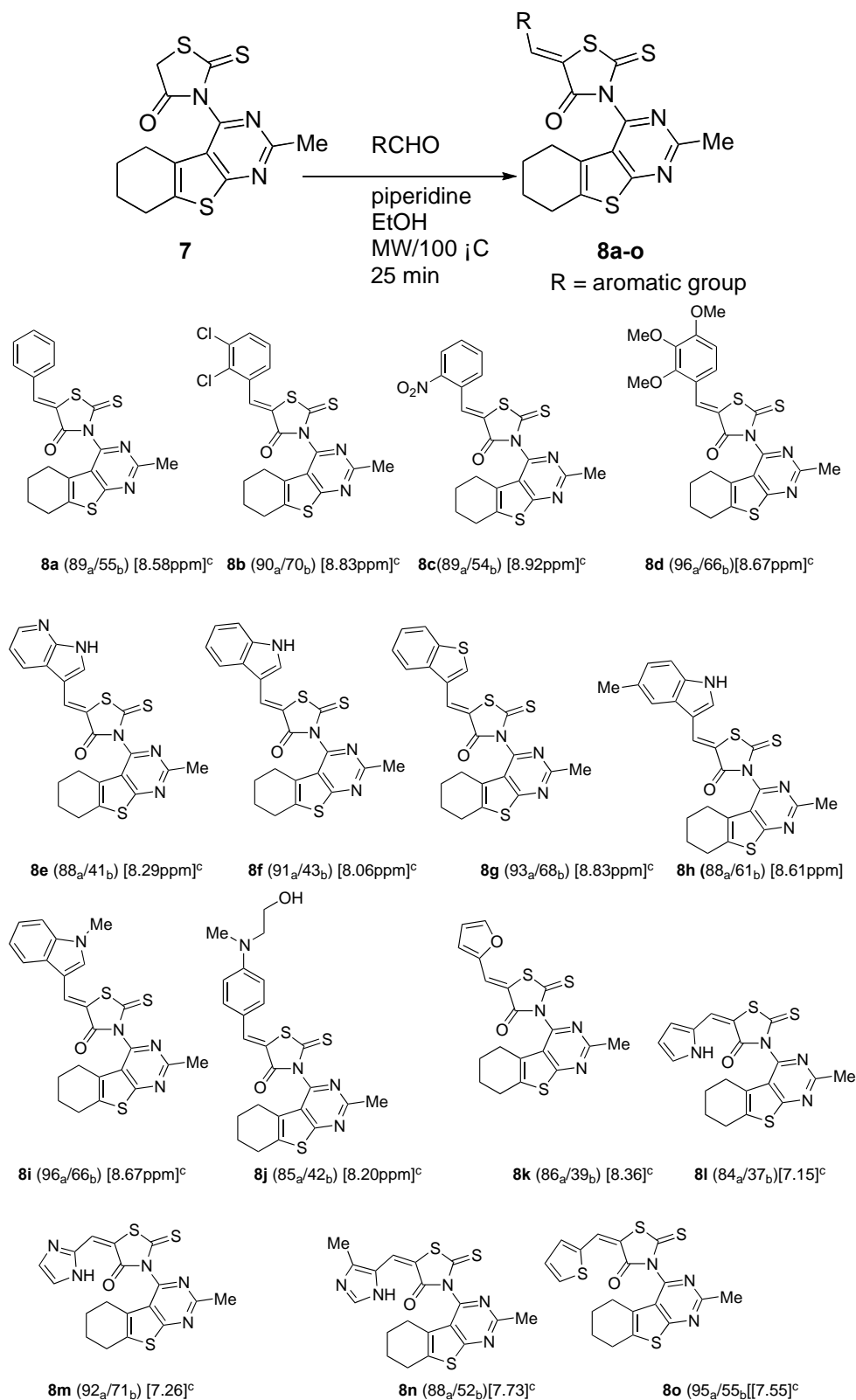
2-amino-4,5,6,7-tetrahydro[1]benzo[*b*]thiophene-3-carbonitrile (**4**) in 92% yield. 2-Methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4-amine (**5**) is next prepared by a microwave assisted intramolecular cyclization of compound **4** with acetonitrile in 1,4-dioxane.¹⁸ The penultimate step involves preparing **7** by treating 4,5,6,7-tetrahydro-3-(2-methylthieno[2,3-*d*]pyrimidin-4-yl) (**5**) and diacid **6** in the presence of K₂CO₃.^{17,18} Lastly, the titled compounds **8a-o** are obtained via the Knoevenagel condensation of 3-(2-methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4-yl)-2-thioxo-thiazolidin-4-one (**7**) with suitably substituted aromatic/heteroaromatic aldehydes using microwave heating. In this step the condensation involves the addition of the 5-carbon of the 2-thioxo-thiazolidin-4,5-enolate to the C=O of the aldehyde.

In order to maximize yields of compounds (**8a-o**), optimum reaction conditions were determined by carrying out a series of reactions of compound **7** and benzaldehyde using various bases. The results, which are summarized in Table 1, indicate that optimum conditions for these reactions involved MW heating at 100 °C for 25 min in ethanol in the presence of a catalytic amount of piperidine.

Table 1. Determination of optimum conditions for synthesis of compound **8a**

Base	Condition	Temp (°C)	Time (min)	Yield (%)
----	no solvent	90	15	trace
----	EtOH	90	15	trace
triethylamine	EtOH	90-110	15-30	59-65
TMP	EtOH	90-110	15-30	60-65
TMP	no solvent	90-110	15-30	trace
piperidine	no solvent	90-110	25	trace
piperidine	EtOH	100	25	89
piperidine	EtOH	110	25-30	85-89
DBU	EtOH	100	25	35
NMP	EtOH	100	25	15
piperidine	water	100	25	trace
piperidine	THF	100	25	41
piperidine	1,4-dioxane	100	25	45
piperidine	benzene/toluene	100	25	10
piperidine	DMF	100	25	61
DBU piperidine	EtOH	100	25	81
pyridine	EtOH	100	25	55
NMP	THF/water	100	25	Trace

The results of synthesis of compounds **8a-o** using MW irradiation and conventional heating are shown in Scheme 2. As shown, the microwave assisted reactions affords compounds **8a-o** in excellent yields



a. Isolated yield from microwave heating b. Isolated yield from conventional heating for 5h at 100 °C. c. δ of C=CH

Scheme 2. Structures, % yields, δ of C=CH compounds **8a-o** using microwave and conventional heating. Attempts to carryout Knoevenagel condensations with alkyl aldehydes under similar conditions were unsuccessful.

(89-94%). The crude products were readily purified by washing with ethyl acetate and hexane (20:80 v/v). The same reaction using conventional refluxing in ethanol solvent gave compounds **8a-o** in lower yields (56-71%), required a longer reaction time (5 h), and the crude products required rigorous purification. The structures of purified compounds **8a-o** were established by LC/MS, GC/MS and NMR analysis. As shown in Scheme 2, compounds **8a-k** were assigned *Z* configurations and **8l-o** were assigned *E* configurations. The configuration about their C-C double bond was assigned on the basis of ¹H-NMR analysis of the vinyl hydrogen chemical shifts. As shown in Scheme 2, the chemical shift of vinyl hydrogen of **8a-k** appears in the range of δ 8.06-8.92 ppm whereas that of **8l-m** is seen in the range of δ 7.15-7.73 ppm. The downfield shift of the former vinyl hydrogens can be explained by the anisotropic effect of the carbonyl group located at carbon atom C-4 of the rhodanine core which is only possible for *Z* but not for *E*-configured pyrimidin-4-ylthioxothiazolidin-4-ones. Similar results have been observed and so rationalized for certain indolones,¹⁶ thiaindirubin-*N*-glycosides,¹⁹ and selenoindirubins and selenoindirubin-*N*-glycosides.²⁰ With the exception of the furan derivative **8k**, the preference of the *Z* over the *E* configurational structure is most likely a steric effect *i.e.* less steric hindrance in the *Z* isomer than in the *E* isomer. The *E* isomers are however structured in such a way to allow intramolecular stabilization via resonance interaction of the heteroatom of the five-membered ring and the oxygen atom of the 4-keto group of the rhodanine core. Thus, in the case of the thiophene derivative **8o**, shown in Figure 2, stabilization of the *E* configuration most likely involves resonance delocalization of the lone pair sulfur electrons (probably d electrons) onto the 4-keto group of the rhodanine core in which the resulting resonance hybrid possesses a favorable electron donor/electron acceptor attraction.

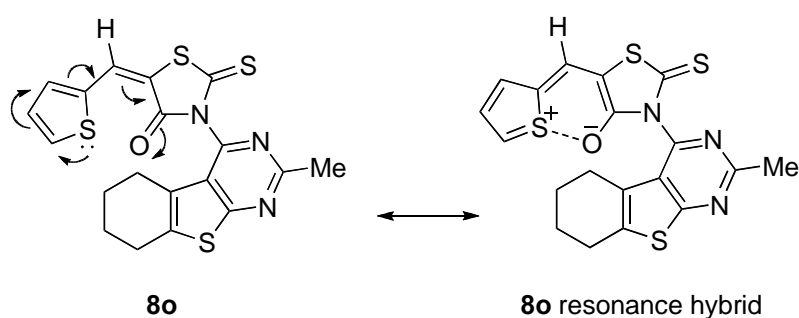


Figure 2. Stabilization of *E*-configuration of **8o** by resonance induced electron donor/ electron acceptor attraction

The pyrrole **8m** and imidazole derivatives **8l** most likely adopt *E* configuration due to intramolecular hydrogen bonding between the NH group of the nitrogen heterocycles and oxygen atom of the O=C group on C-4 of the rhodanine ring. Such NH \cdots O=C interactions have been recently found to be crucial in inducing a high degree of stereochemical control in aza-Morita-Baylis-Hillman reactions.²¹ However, the

vinyl-H chemical shift of the furan derivative **8c** occurs at 8.36 ppm indicating it most likely exist in the *Z*-configuration. Since oxygen is more electronegative than sulfur, its ability to be an electron acceptor in stabilizing the *E* configuration is decreased to such an extent that the molecule adopts the *Z* configuration where the two potential interacting oxygen atoms are removed from each.

Additional support for the necessity of intramolecular stabilization of *E* isomer comes by noting that indol-3-yl **8e**, 5-methyl-1-*H*-imidazol-3-yl **8f**, (benzothiophene-3-yl)methylene **8g** derivatives shown in Figure 3 cannot be stabilized by electron- donor/electron acceptor interactions due to geometrical constraints. Furthermore, **8a-d** and **8i-j** lack functionality needed to interact with the O=C group attached to C-4 of the rhodanine ring to form *E* configured compounds.

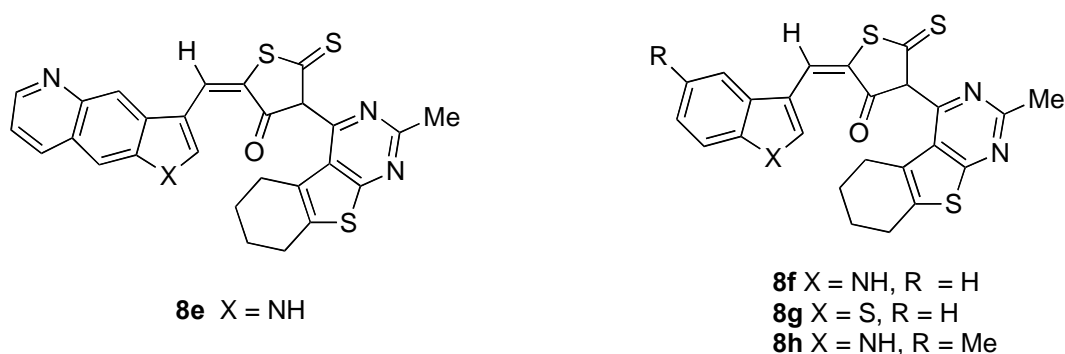


Figure 3. Lack of intramolecular stabilization of *E* isomers (**8e**, **8f**, **8g** and **8h** due to geometrical constraints

We currently are attempting confirm *E* and *Z* isomers assigned structures for selective compounds by X-ray structural analysis. In addition, computational chemical studies on the energetics of *E* and *Z* conformers of titled compounds are being carried out. The results of these studies will be reported in due course.

In conclusion, we have successfully developed an easy practical access to novel thieno[2,3-*d*]pyrimidine derivatives. The mild reaction conditions and easy work up procedure allow the products to be produced in good to excellent yields from readily available starting materials, thus rendering this reaction as an attractive method for the preparation of these biologically important compounds. Efforts towards the microwave-assisted synthesis of other rhodanine moiety are ongoing in our laboratory. Also potential biological activity (anti-bacterial, antifungal, anticancer, and neuroprotective kinase inhibitory activities) of these important compounds are being investigated, the results of which will be reported in due course.

EXPERIMENTAL

General information. The ^1H and ^{13}C NMR spectra were recorded on a 500-MHz Jeol multinuclear NMR spectrometer and chemical shifts were referenced to tetramethylsilane (TMS) as internal standard. Melting points were taken on a Meltemp apparatus. MW reactions were carried out in CEM DiscoverTM

microwave oven which comprises a mono mode (single mode) microwave cavity that operates at a frequency of 2.45 GHz with continuous irradiation power from 0-300 W. The reaction temperature in the microwave cavity was measured by an IR captor (infrared thermometry) and a software algorithm regulates the microwave output power so that the preselected maximum temperature can be maintained during the reaction. High-resolution mass spectra (HRMS) were obtained from Washington University; St. Louis, MO. Column chromatography was carried out on *Combi-Flash* instrument using pre-packed silica gel columns. Mass analysis of products were carried out by Ommscientific Inc, Dallas, Texas.

Materials. All chemicals and reagents were purchased from commercial sources and used as received. 2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (**4**),¹⁸ 4,5,6,7-tetrahydrobenzo[*b*]thieno[2,3-*d*]-2-methylpyrimidin-4-amine (**5**)¹⁸ and 3-(2-methyl-5,6,7,8-hydrobenzo[4,5]-thieno[2,3-*d*]-pyrimidin-4-yl)-2-thioxothiazolidin-4-one (**7**)¹⁷ were prepared by literature procedures.

General microwave-assisted synthesis of 5-aryl/hetarylidenyl-3-(2-methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4-yl)-2-thioxothiazolidin-4-ones (8a-o):

3-(2-Methyl-5,6,7,8-hydrobenzo[4,5]-thieno[2,3-*d*]pyrimidin-4-yl)-2-thioxothiazolidin-4-one **7** (0.2 g, (0.60 mmol, 1 equiv) and aromatic aldehyde (0.77 mmol, 1.3 equiv). were thoroughly mixed then placed into a specially designed microwave test tube containing 5 mL EtOH and three drops of piperidine. The charged tube was heated for 25 min at 100 °C and 250 psi pressure. After cooling, the solid mass was placed in 50 mL cold EtOH and crushed. The slurry was filtered to give a solid that was washed several times with EtOH/hexane mix (20%, v/v), then dried under vacuum to give the corresponding 5-aryl/hetaryl-2-thiocothiazolidine-4-one (**8a-o**) whose structures were identified by IR, LC/MS, GC/MS and NMR analysis. The physical and spectral properties of these compounds are shown later in the experimental section.

General synthesis of compound (8o-m) using conventional heating. Compound **7** (0.2 g, 0.60 mmol) and aromatic aldehyde (0.77 mmol, 1.3 equiv) were thoroughly mixed and place in 25 mL flask containing 10 mL EtOH and three drops of piperidine, then the charged tube was refluxed for 8 h. After cooling, the solid mass was filtered and the filtrate was discarded. After several washing with EtOH/hexane mix (20%, v/v), the crude product **8** was dried under vacuum was then purified by column chromatography carried out on a *Combi-Flash* instrument using a pre-packed silica gel column and MeOH/DCM, 10% (v/v) as elutant.

Physical and spectral data for compounds (8a-8o):

(5*Z*)-5-Benzylidene-3-(2-methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4-yl)-2-thioxothiazolidin-4-one (8a): Isolated as a light orange solid, mp 122.0-122.8 °C; IR (KBr): 1716, 1615 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 8.58 (s, ¹H, vinyl-H), 7.92 (d, *J* = 7.6 Hz, 2H, Ar-CH), 7.55-7.49 (m, 3H, Ar-CH), 2.64-2.52 (m, 2H, CH₂), 2.46 (s, 3H, CH₃), 1.75-1.73 (m, 2H, CH₂). ¹³C NMR (DMSO-*d*₆):

δ 195.6 (C=S), 166.1 (C=O), 161.0 (C), 155.1 (C), 142.5 (C), 143.3 (CH), 137.3 (C), 135.2 (C), 133.3 (CH), 129.7 (CH), 129.5 (CH), 127.1 (C), 122.1 (C), 114.6 (C), 25.1 (CH₂), 24.2 (CH₃), 23.0 (CH₂), 21.9 (CH₂), 21.3 (CH₂).95: HRMS: m/z calculated for C₂₁H₁₇N₃OS₃: 423.0534. Found: 424.0544 (M⁺+1).

(5Z)-5-[(2,3-Dichlorophenyl)methylene]-3-(2-methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-yl)-2-thioxothiazolidin-4-one (8b): Isolated as a golden yellow solid, mp 209.7-211.0 °C; IR (KBr): 1700, 1611 cm⁻¹. ¹H NMR (CDCl₃): δ 8.83 (s, 1H, vinyl-H), 8.26 (d, J = 7.5 Hz, 1H, Ar-CH), 7.55 (d, J = 7.5 Hz, 1H, Ar-CH), 7.30 (dd, J = 7.5, 7.8 Hz, 1H, Ar-CH), 2.71-2.66 (m, 4H, CH₂), 2.43 (s, 3H, CH₃), 1.87-1.85 (m, 4H, CH₂). ¹³C NMR (CDCl₃): δ 195.6 (C=S), 166.3 (C=O), 165.3 (C), 154.6 (C), 145.2 (C), 143.2 (CH), 142.5 (C), 137.2 (C), 135.6 (C), 133.4 (CH), 127.7 (C), 127.5 (CH), 125.3 (CH), 113.2 (C), 118.8 (C), 25.4 (CH₂), 24.3 (CH₂), 24.0 (CH₃), 23.0 (CH₂), 22.1 (CH₂), 22.0 (CH₂). HRMS: m/z calculated for C₂₁H₁₅Cl₂N₃OS₃: 490.9754. Found: 491.9764 [M⁺+1].

(5Z)-3-(2-Methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-yl)-2-thioxo-5-[(2-nitrophenyl)methylene]-2-thioxothiazolidin-4-one (8c): Isolated as a dark brown fine powder, mp 165.1- 167.0 °C. IR (KBr): 1717, 1620 cm⁻¹. ¹H NMR (CDCl₃): δ 8.92 (C, 1H, vinyl-H), 8.45 (d, J = 7.8 Hz, 1H, Ar-CH), 8.04 (d, J = 7.8 Hz, 1H, Ar-CH), 7.63 (dd, J = 7.8, 3.1 Hz, 1H, Ar-CH), 7.62 (dd, J = 7.8, 3.0 Hz, 1H, Ar-CH), 2.72-2.66 (m, 4H, Ar-CH₂), 2.49 (s, 3H CH₃), 1.86-1.84 (m, 4H, CH₂). ¹³C NMR (CDCl₃): δ 195.6 (C=S), 166.2 (C=O), 160.2 (C), 158.4 (C), 149.3 (C), 143.2 (CH), 137.1 (C), 135.7 (CH), 130.0 (CH), 129.7 (CH), 127.2 (C), 124.9 (C), 123.1 (CH), 116.2 (C), 114.2 (C). HRMS: m/z calculated for C₂₁H₁₆N₄O₃S₃: 468.0385. Found: 469.0397 [M⁺+1].

(5Z)-3-(2-Methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-yl)-2-thioxo-5-[(2,3,4-trimethoxyphenyl)methylene]-2-thioxothiazolidin-4-one (8d): Isolated as a bright yellow solid powder, mp 159.5- 160.1 °C. IR (KBr): 1719, 1620 cm⁻¹. ¹H NMR (CDCl₃): δ 8.67 (s, 1H, vinyl-H), 7.98 (d, J = 8.0 Hz, 1H, Ar-CH), 6.74 (d, J = 8.0 Hz, 1H, Ar-CH), 3.97 (s, 3H, OCH₃), 3.92 (s, 3H, OCH₃), 3.87 (s, 3H, OCH₃), 2.67-2.64 (m, 4H, CH₂), 2.43 (s, 3H, CH₃), 1.86-1.84 (m, 4H, CH₂). ¹³C NMR (CDCl₃): δ 197.9 (C=S), 168.3 (C=O), 165.9 (C), 157.6 (C), 155.0 (C), 154.8 (C), 145.2 (C), 143.1 (CH), 141.7 (C), 137.9 (C), 131.6 (C), 123.9 (CH), 121.8 (C), 108.5 (CH), 62.2 (OCH₃), 61.0 (OCH₃), 56.2 (OCH₃), 25.2 (CH₂), 24.4 (CH₂), 24.1 (CH₃), 23.2 (CH₂), 21.1 (CH₂), 22.0 (CH₂). HRMS: m/z calculated for C₂₄H₂₃N₃O₄S₃, 513.0851. Found: 514.0868 [M⁺+1].

(5Z)-3-(2-Methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-yl)-5-(1H-pyrrolo[2,3-b]pyridin-3-ylmethylene)-2-thioxothiazolidin-4-one (8e): Isolated as a mustard yellow fine shiny powder, mp 288.3-289.7 °C. IR (KBr) 3200, 1716, 1615 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 12.64 (brs, ¹H, NH), 8.61 (dd, J = 7.5 Hz, 2.5 Hz, ¹H, Ar-CH), 8.33 (dd, J = 7.5, 2.5 Hz, 1H, Ar-CH), 8.29 (s, 1H, vinyl-H), 7.9-7.27 (m, 2H, Ar-CH), 2.62-2.51 (m, 4H, CH₂), 2.41 (s, 3H, CH₃), 1.75-1.75 (m, 4H, CH₂). ¹³C NMR (DMSO-*d*₆): δ 198.2 (C=S), 165.9 (C=O), 163.2 (C), 155.8 (C), 145.3 (C), 148.3 (C), 143.3 (CH), 142.1 (CH), 137.2

(C), 128.3 (CH), 127.3 (C), 124.3 (C), 122.1 (C), 118.5 (CH), 118.1 (C), 25.1 (CH₂), 24.1 (CH₃), 23.0 (CH₂), 22.0 (CH₂), 21.3 (CH₂). HRMS: m/z calculated for C₂₂H₁₇N₅OS₃: 463.0595. Found: 464.0598 [M⁺+1].

(5Z)-5-[(1H-Indol-3-yl)methylene]-3-(2-methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-yl)-2-thioxothiazolidin-4-one (8f): Isolated as a dark brown solid with tints of purple, mp 204.9-205.4 °C; IR (KBr): 3213, 1718, 1615 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 12.07 (brs, 1H, NH), 8.65 (s, 1H, Ar-CH), 8.36 (dd, *J* = 7.8, 2.9 Hz, 1H, Ar-CH), 8.15 (s, 1H, vinyl-H), 7.47 (dd, *J* = 7.8, 3.0 Hz, 1H, Ar-CH), 7.24-7.21 (m, 2H, Ar-CH), 3.10 (s, 3H, CH₃), 2.59-2.46 (m, 4H, CH₂), 1.73-1.72 (m, 4H, CH₂). ¹³C NMR (DMSO-*d*₆): δ 198.3 (C=S), 166.9 (C=O), 166.3 (C), 163.5 (C), 145.8 (C), 143.2 (CH), 138.0 (C), 137.1 (C), 129.8 (CH), 127.5 (C), 127.1 (C), 124.0 (CH), 122.6 (C), 122.3 (CH), 115.5 (C), 114.8 (CH), 112.9 (CH), 103.1 (C), 25.0 (CH₂), 24.3 (CH₃), 23.1 (CH₂), 22.1 (CH₂), 21.1 (CH₂). Anal. HRMS: m/z calculated for C₂₃H₁₈N₄OS₃: 462.0643. Found 463.0652 [M⁺+1].

(5Z)-5-[(Benzothiophen-3-yl)methylene]-3-(2-methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-yl)-2-thioxothiazolidin-4-one (8g): Isolated as a bright yellow powder, mp 137.1-138.0 °C. IR (KBr): 1700, 1616 cm⁻¹. ¹H NMR (DMSO-*d*₆): 8.90 (d, *J* = 7.5 Hz, 1H, Ar-CH), 8.79 (s, 1H, Ar-CH), 8.65 (s, 1H, vinyl-H), 8.06 (d, *J* = 7.5 Hz, 1H, Ar-CH), 7.51-7.46 (m, 2H, Ar-CH), 2.63-2.52 (m, 4H, CH₂), 2.43 (s, 3H, CH₃), 1.76-1.73 (m, 4H, CH₂). ¹³C NMR (DMSO-*d*₆): 196.8 (C=S), 166.5 (C=O), 165.2 (C), 155.7 (C), 145.2 (C), 143.2 (CH), 141.7 (C), 140.8 (C), 135.8 (C), 134.7 (C), 126.4 (C), 125.5 (C), 124.2 (CH), 123.7 (CH), 122.8 (CH), 114.9 (CH), 25.1 (CH₂), 24.2 (CH₃), 23.0 (CH₂), 22.01 (CH₂), 22.0 (CH₂). Anal. HRMS: m/z calculated for C₂₃H₁₇N₃OS₄: 479.0254. Found 480.0259 [M⁺+1].

(5Z)-5-[(5-Methyl-1H-indol-3-yl)methylene]-3-(2-methyl-5,6,7,8-tetrahydro[4,5]thieno[2,3-d]pyrimidin-4-yl)-2-thioxothiazolidin-4-one (8h): Isolated as a dark yellow flakey solid, mp 207.6- 209.3 °C. IR (KBr): 3312, 1701, 1618 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 11.93 (brs, 1H, NH), 8.61 (s, 1H, vinyl-H), 8.02 (d, *J* = 7.8 Hz, 2H, Ar-CH), 7.81 (s, 1H, Ar-CH), 7.36 (d, *J* = 3.5 Hz, 1H, Ar-CH), 6.84 (d, *J* = 7.8 Hz, 1H, Ar-CH), 3.79 (s, 3H, CH₃), 2.55-2.47 (m, 4H, CH₂), 2.49 (s, 3H, CH₃), 1.71-1.70 (m, 4H, CH₂). ¹³C NMR (DMSO-*d*₆): δ 195.5 (C=S), 168.0 (C=O), 163.2 (C), 155.9 (C), 145.2 (C), 143.2 (CH), 136.6 (C), 132.6 (C), 129.7 (CH), 127.2 (C), 126.0 (C), 122.0 (C), 115.5 (CH), 114.7 (CH), 113.5 (CH), 25.0 (CH₂), 24.3 (CH₂), 24.1 (CH₃), 22.1 (CH₂), 22.0 (CH₂), 19.08 (CH₃). HRMS: m/z calculated for C₂₄H₂₀N₄OS₃: 476.0799. Found: 477.0787] [M⁺+1].

(5Z)-5-[(1-Methyl-1H-indol-3-yl)methylene]-3-(2-methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno-2,3-d-pyrimidin-4-yl)-2-thioxothiazolidin-4-one (8i): Isolated as a orange brown solid powder, mp 171.4-172.8 °C. IR (KBr): 1719, 1619 cm⁻¹. ¹H NMR (CDCl₃): δ 8.55 (dd, *J* = 7.8, 3.1 Hz, 1H, Ar-CH), 8.50 (s, 1H, vinyl- H), 7.49 (s, 1H, Ar-CH), 7.35-7.31 (m, 3H, Ar-CH), 3.81 (s, 3H, CH₃), 2.66-2.63 (m, 4H, CH₂), 2.43 (s, 3H, CH₃), 1.85-1.84 (m, 4H CH₂). ¹³C NMR (CDCl₃): δ 195.9 (C=S), 168.3 (C=O), 166.3 (C),

153.2 (C), 145.2 (C), 144.1 (CH), 138.2 (C), 136.5 (C), 134.3 (C), 129.6 (CH), 127.2 (C), 123.9 (CH), 123.2 (CH), 122.7 (C), 115.4 (CH), 114.1 (C), 109.7 (CH), 33.6 (CH₃), 25.2 (CH₂), 24.4 (CH₃), 23.3 (CH₂), 22.2 (CH₂), 21.9 (CH₂). HRMS: m/z calculated for C₂₄H₂₀N₄O₃S₃: 476.0799. Found: 477.0823 [M⁺+1].

(5Z)-5-{4-[(2-Hydroxyethyl)(methyl)amino]phenylmethylene}-3-(2-methyl-5,6,7,8-tetrahydrobenzo[4,5][2,3-*d*]pyrimidin-4-yl)-2-thioxothiazolidin-4-one (8j): Isolated as a orange solid, mp 145.1-146.3 °C. IR (KBr): 3400, 1717, 1618 cm⁻¹. ¹H NMR (CDCl₃): 8.20 (s, 1H, vinyl-H), 7.72 (d, $J = 7.8$ Hz, 2H, Ar-CH), 6.69 (d, $J = 7.8$ Hz, 2H, Ar-CH), 3.82-3.81 (m, 2H, CH₂), 3.57-3.56 (m, 2H, CH₂), 3.07 (s, 3H, CH₃), 2.64-2.60 (m, 4H, CH₂), 2.44 (s, 3H, CH₃), 1.82-1.81 (m, 4H, CH₂). ¹³C NMR (CDCl₃): 196.8 (C=S), 166.8 (C=O), 166.2 (C), 159.0 (C), 152.6 (C), 144.1 (CH), 134.5 (C), 131.6 (CH), 130.2 (CH), 127.2 (C), 123.1 (C), 116.1 (C), 115.3 (C), 113.2 (C), 111.7 (CH), 60.1 (CH₂), 54.5 (CH₂) 39.2 (CH₃), 25.2 (CH₂), 24.4 (CH₃), 23.2 (CH₂), 22.1 (CH₂), 22.0 (CH₂). HRMS: m/z calculated for C₂₄H₂₄N₄O₂S₃, 496.1061. Found: 497.1069 [M⁺+1].

(5Z)-[(5-Furan-2-yl)methylene]-3-(2-methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4-yl)-2-thioxothiazolidin-4-one (8k): Isolated as a yellow fine solid powder, mp 153.3-154.9 °C; IR (KBr): 1716, 1616 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 8.36 (s, 1H, vinyl-H), 8.02 (d, $J = 3.5$ Hz, 1H, Ar-CH), 7.29 (d, $J = 3.5$ Hz, 1H, Ar-CH), 6.74 (d, $J = 3.5$ Hz, 1H Ar-CH), 2.64-2.63 (m, 4H, CH₂), 2.47 (s, 3H, CH₃), 1.75-1.76 (m, 4H, CH₂). ¹³C NMR (DMSO-*d*₆): δ 193.5 (C=S), 166.9 (C=O), 166.3 (C), 156.1 (C), 151.1 (C), 148.9 (C), 148.1 (CH), 146.1 (CH), 135.0 (C), 132.9 (C), 122.5 (C), 121.6 (CH), 113.9 (CH), 25.1 (CH₂), 24.2 (CH₃), 23.0 (CH₂), 22.0 (CH₂), 21.9 (CH₂). HRMS: m/z calculated for C₁₉H₁₅N₃O₂S₃: 413.0326. Found: 414.0326 [M⁺+1].

(5E)-3-(2-Methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4-yl)-5-[(1*H*-pyrrol-2-yl)methylene]-2-thioxothiazolidin-4-one (8l): Isolated as a dark brown solid, mp 192.1-193.0 °C; IR (KBr): 3215, 1718, 1620 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 11.18 (brs, 1H, NH), 8.23 (s, 1H, Ar-CH), 7.15 (s, 1H, vinyl-H), 6.87 (s, 1H, Ar-CH), 6.25 (d, $J = 3.5$ Hz, 1H, Ar-CH), 2.59 (brs, 4H, CH₂), 2.48 (s, 3H, CH₃), 1.73-1.72 (m, 4H, CH₂). ¹³C NMR (DMSO-*d*₆): δ 195.6 (C=S), 166.3 (C=O), 162.5 (C), 150.8 (C), 145.3 (C), 137.3 (C), 134.5 (CH), 129.8 (C), 127.5 (C), 122.8 (C), 120.2 (CH), 111.6 (CH), 102.7 (CH), 24.9 (CH₂), 24.3 (CH₂), 24.1 (CH₃), 23.1 (CH₂), 22.1 (CH₂). HRMS: m/z calculated for C₁₉H₁₆N₄O₃S₃: 412.0486. Found: 413.0582 [M⁺+1].

(5E)-5-[(1*H*-Imidazol-2-yl)methylene]-3-(2-methyl-5,6,7,8-tetrahydro[4,5]thieno[2,3-*d*]pyrimidin-4-yl)-2-thioxothiazolidin-4-one (8m): Isolated as a bright yellow colored solid powder, mp 248.4-249.0 °C; IR (KBr): 3216, 1721, 1638 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 12.44 (brs, 1H, NH), 8.30 (s, 1H, Ar-CH), 7.42 (s, 1H, Ar-CH), 7.26 (s, 1H, vinyl-H), 2.63-2.62 (brs, 4H, CH₂), 2.52 (s, 3H, CH₃), 1.74-1.73 (m, 4H, CH₂). ¹³C NMR (DMSO-*d*₆): δ 192.8 (C=S), 166.3 (C=O), 166.2 (C), 160.0 (C), 150.3 (C), 143.9 (CH),

135.4 (C), 135.1 (CH), 135.0 (CH), 127.8 (C), 122.0 (C), 25.0 (CH₂), 24.3 (CH₃), 23.0 (CH₂), 22.1 (CH₂), 21.9 (CH₂). HRMS: m/z calculated for C₁₈H₁₅N₅OS₃: 413.0439. Found: 427.0428) [M⁺+1].

(5E)-5-[(4-Methyl-1H-imidazol-5-yl)methylene]-3-(2-methyl-5,6,7,8-tetrahydro[4,5]thieno[2,3-d]pyrimidin-4-yl)-2-thioxothiazolidin-4-one (8n): Isolated as a dark yellow solid, mp 268.1-269.9 °C. IR (KBr): 3318, 1715, 1617 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 12.98 (brs, 1H, NH), 8.37 (s, 1H, Ar-CH), 7.73 (s, 1H, vinyl-H), 2.61-2.50 (m, 4H, CH₂), 2.47 (s, 3H, CH₃), 2.44 (s, 3H, CH₃), 1.74-1.64 (m, 4H, CH₂). ¹³C NMR (DMSO-*d*₆): δ 198.3 (C=S), 166.9 (C=O), 166.3 (C), 156.3 (C), 145.3 (C), 144.3 (C), 137.3 (C), 136.1 (CH), 131.0 (CH), 127.2 (C), 122.1 (C), 115.3 (C), 113.3 (C), 25.0 (CH₂), 24.3 (CH₃), 23.1 (CH₂), 22.0 (CH₂), 21.0 (CH₂), 16.3 (CH₃). HRMS: m/z : calculated for C₁₉H₁₇N₅OS₃: 427.0595. Found: 428.0605.

(5E)-3-(2-Methyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidin-4-yl)-5-(2-thienylmethylene)-2-thioxothiazolidin-4-one (8o): Isolated as a yellow powder, mp 121.9-123.0 °C; IR (KBr) 1700, 1592 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 8.59 (s, 1H, Ar-CH), 8.30 (d, $J = 5.5$ Hz, 1H, Ar-CH), 7.67 (dd, $J = 2.5, 5.5$ Hz, 1H, Ar-CH), 7.55 (s, 1H, vinyl-H), 2.64-2.52 (m, 2H, CH₂), 2.53-2.47 (m, 2H, CH₂), 2.41 (s, 3H, CH₃), 1.75-1.74 (m, 2H, CH₂). ¹³C NMR (DMSO-*d*₆): δ 196.1 (C=S), 166.2 (C=O), 161.0 (C), 156.1 (C), 143.9 (C), 143.0 (CH), 139.7 (C), 135.2 (C), 130.1 (CH), 128.9 (CH), 128.3 (CH), 122.1 (C), 25.0 (CH₂), 24.2 (CH₃), 23.0 (CH₂), 22.0 (CH₂), 21.5 (CH₂). HRMS: m/z calculated for C₁₉H₁₅N₃OS₄: 429.0098. Found: 430.0102. [M⁺+1].

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