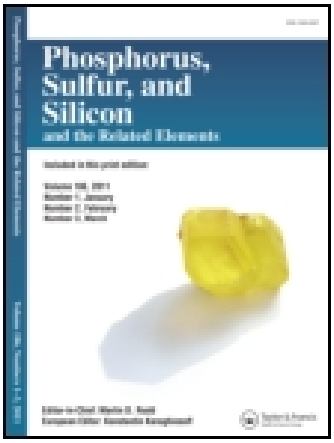

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One-Pot Synthesis of Pyrimidinothiazolidinones and Their Anti-Inflammatory and Antimicrobial Studies

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ONE-POT SYNTHESIS OF PYRIMIDINOTHIAZOLIDINONES AND THEIR ANTI-INFLAMMATORY AND ANTIMICROBIAL STUDIES

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In the present investigation, we report a one-pot synthesis of the title compounds, 2-arylidene-5-(2,3,6-trimethyl-4-methoxyphenyl)-7-substituted-5H-pyrimidino-[2,3-b]thiazolidine-3-ones 6a–j and 2-(5-nitro-2-thienylidine)-5-(2,3,6-trimethyl-4-methoxyphenyl)-7-substituted-5H-pyrimidino-[2,3-b]thiazolidine-3-ones 7a–e. Thus, 6a–j and 7a–e were prepared in good yields by refluxing 4-(2,3,6-trimethyl-4-methoxyphenyl)-6-methyl/aryl-3,4-dihydropyrimidin-2-(1H)-thiones 5, monochloro acetic acid, and anhydrous sodium acetate with the appropriate aromatic aldehyde/5-nitro-2-thiophenediacetate in acetic acid/acetic anhydride medium. The structures of these new compounds were established on the basis of their analytical and spectral data. Some of the newly synthesized compounds were screened for their anti-inflammatory and antimicrobial activity. They show moderate anti-inflammatory activity, and some of them were found to be promising antibacterial and antifungal agents.

Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.

Keywords Anti-inflammatory and antimicrobial activity; multicomponent reaction; 5-nitro-2-thiophenaldiacetate; pyrimidinones

INTRODUCTION

Multicomponent reactions (MCR) are special types of theoretically useful organic reactions in which three or more starting materials react to give a product.[1] Convergent synthetic pathways generally show advantages over linear or divergent approaches with

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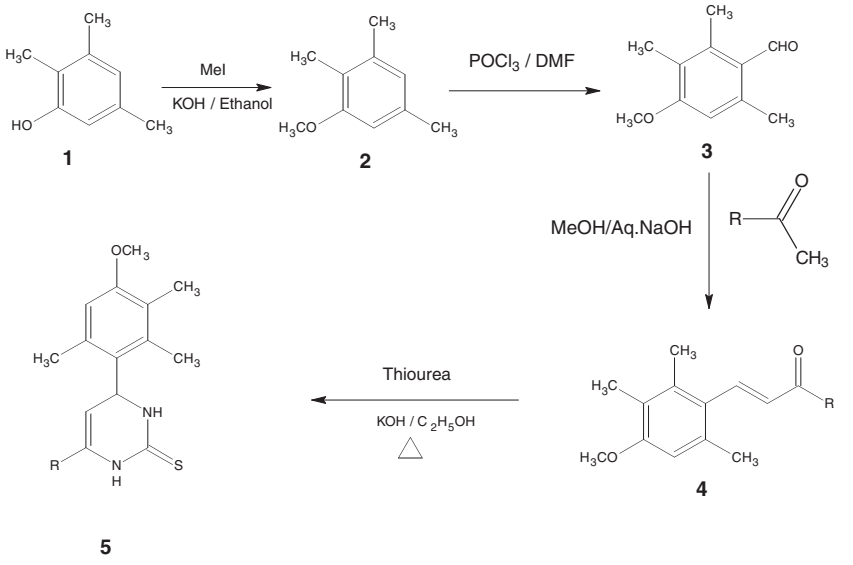
respect to time, speed, yield, and reproducibility. Among organic reactions, MCR with more than two starting materials are assembled to afford a complex product. Therefore, they constitute a superior tool for diversity-oriented and complexity-generating synthesis for drug discovery.[2,3] Well known examples for the synthesis of heterocycles through MCR are the Biginelli reaction[4] and the Hantzsch dihydropyridine synthesis.[5] Pyrimidine derivatives are known for their varied biological properties.[6–8] Thiazoles and their derivatives are found to be associated with various biological activities such as antibacterial, antifungal, and anti-inflammatory activities.[9–11] Prompted by the biological and pharmacological applications of thiazolidinone derivatives and in view of the diversity of MCRs, we planned to synthesize a series of thiazolidinone derivatives containing a pyrimidine nucleus. The results of such experiments including the synthesis, characterization, and biological studies of these newly synthesized thiazolidinone derivatives are reported in this article.

RESULTS AND DISCUSSION

The synthetic route followed for obtaining the title compound is outlined in Scheme 1. Vilsmeier–Haack reaction of 1-methoxy-2,3,5-trimethylbenzene **2** with phosphorous oxychloride and dimethyl formamide produced 2,3,6-trimethyl-4-methoxybenzaldehyde **3**, whereas 1-methoxy-2,3,5-trimethylbenzene **2** was in turn obtained by the methylation of 2,3,5-trimethylphenol **1** using methyl iodide in ethanol medium in the presence of potassium hydroxide as a catalyst. Chalcones **4** were prepared by condensing 2,3,6-trimethyl-4- methoxybenzaldehyde **3** with the appropriate ketone in the presence of sodium hydroxide under the Clasein–Schmidt reaction conditions. However 4-(2,3,6-trimethyl-4-methoxyphenyl)-3-butene-2-one **4a** was prepared by the condensation of 2,3,6-trimethyl-4-methoxybenzaldehyde **3** with acetone as described in the literature.[12] The characterization data of these chalcones are given in Table I. When these chalcones **4** were treated with thiourea in the presence of potassium hydroxide as a catalyst in ethanol



Scheme 1

Table I Characterization data of 3-(2,3,6-trimethyl-4-methoxyphenyl)-1-methyl/aryl-2-propen-1-ones **4a–e** and 4-(2,3,6-trimethyl-4-methoxyphenyl)-6-methyl/aryl-3,4-dihydropyrimidin-2-(1H)-thiones (**5a–e**)

Compd. No.	R	Molecular Formulae (Mol. Wt.)	Mp (°C) (Yield %)	Analysis (%) Found (Calculated)		
				C	H	N
4a	CH_3	$C_{14}H_{18}O_2$ (218)	64–66 (44)	77.17 (77.06)	8.21 (8.25)	—
4b	Phenyl	$C_{19}H_{20}O_2$ (280)	98–100 (70)	81.59 (81.42)	7.51 (7.14)	—
4c	4-Chloro phenyl	$C_{19}H_{19}ClO_2$ (314)	126–128 (65)	72.41 (72.61)	7.22 (7.32)	—
4d	4-Tolyl	$C_{20}H_{22}O_2$ (294)	102–104 (67)	81.82 (81.63)	7.73 (7.48)	—
4e	4-Nitro phenyl	$C_{19}H_{19}NO_4$ (325)	114–116 (64)	70.33 (70.15)	6.98 (5.84)	4.33 (4.30)
5a	CH_3	$C_{15}H_{20}N_2OS$ (276)	180–182 (72)	65.28 (65.21)	7.20 (7.24)	10.17 (10.14)
5b	Phenyl	$C_{20}H_{22}N_2OS$ (338)	196–198 (71)	71.19 (71.00)	6.44 (6.50)	8.26 (8.28)
5c	4-Chloro phenyl	$C_{20}H_{21}ClN_2OS$ (372)	202–204 (62)	64.36 (64.42)	5.61 (5.63)	7.55 (7.51)
5d	4-Tolyl	$C_{21}H_{24}N_2OS$ (352)	128–130 (66)	71.68 (71.59)	6.83 (6.81)	7.91 (7.95)
5e	4-Nitro phenyl	$C_{20}H_{21}N_3O_3S$ (383)	144–148 (67)	62.59 (62.66)	5.50 (5.48)	10.93 (10.96)

medium gave 4-(2,3,6-trimethyl-4-methoxyphenyl)-6-methyl/aryl-3,4-dihydropyrimidin-2-(1H)-thiones **5**. These pyrimidin-2-thiones **5** were further used for the synthesis of *N*-bridged heterocycles. From the previous study,[13] it is clear that the preparation of pyrimidinothiazolinones starting from pyrimidine-2-thiones involves two steps. In the first step, pyrimidine-2-thione was condensed with monochloroacetic acid in the presence of anhydrous sodium acetate, and then in the next step it was converted into arylidene derivatives by condensing with aromatic aldehydes in the presence of piperidine. However in the present investigation, it was contemplated to carry out the synthesis of the title compounds 2-substituted-5-(2,3,6-trimethyl-4-methoxyphenyl)-7-methyl/aryl-5H-pyrimidino-[2,3-b]thiazolidine-3-ones **6** and **7** by one-pot synthesis in good yields by refluxing 4-(2,3,6-trimethyl-4-methoxyphenyl)-6-methyl/aryl-3,4-dihydropyrimidin-2-(1H)-thiones **5**, monochloro acetic acid, and anhydrous sodium acetate with the corresponding aldehyde/5-nitro-2-thiophenaldiacetate in acetic acid/acetic anhydride medium (Table II and Scheme 2). The structures of these compounds were established on the basis of elemental analysis, IR, ^{1}H NMR, and mass spectral studies.

Condensation of 2,3,6-trimethyl-4-methoxybenzaldehyde **3** with methyl ketones gave 3-(2,3,6-Trimethyl-4-methoxyphenyl)-1-methyl/aryl-2-propen-1-ones **4** (Table I). In a typical example of the ^{1}H NMR spectrum of **4c**, the three methyl protons came into resonance as singlets at δ 2.16, 2.31, and 2.40 integrating for nine protons. The signal due to the methoxy proton appeared as a singlet at δ 3.83. The olefinic protons appeared as two doublets at δ 6.99 and 8.03 integrating for one proton each. The ortho- and meta-protons of the 4-chlorophenyl group appeared as two doublets centered at δ 7.43 and 7.90 each integrating for two protons. The other aromatic proton came into resonance as a singlet at δ 6.62 integrating for one proton. Similarly the mass spectrum of **4c** showed the molecular ion peak at m/z 315 (M^++1 peak)/317.

Reaction of chalcone **4** with thiourea in the presence of alcoholic potassium hydroxide gave 4,6-disubstituted-3,4-dihydropyrimidin-2(1H)thiones **5**. Characterization data of these compounds **5** are given in Table I. In a typical example of the IR spectrum of **5a,** the N—H stretching absorption was observed at 3200cm^{-1} and the C—H stretching band was observed at 2956 cm^{-1}. The C=S stretching absorption was seen at around 1174 cm^{-1}. In the ^{1}H NMR spectrum of **5a**, the four methyl groups came into resonance as four singlets at δ 1.77, 2.17, 2.33, and 2.40 integrating to 12 protons. The methoxy proton appeared as a singlet

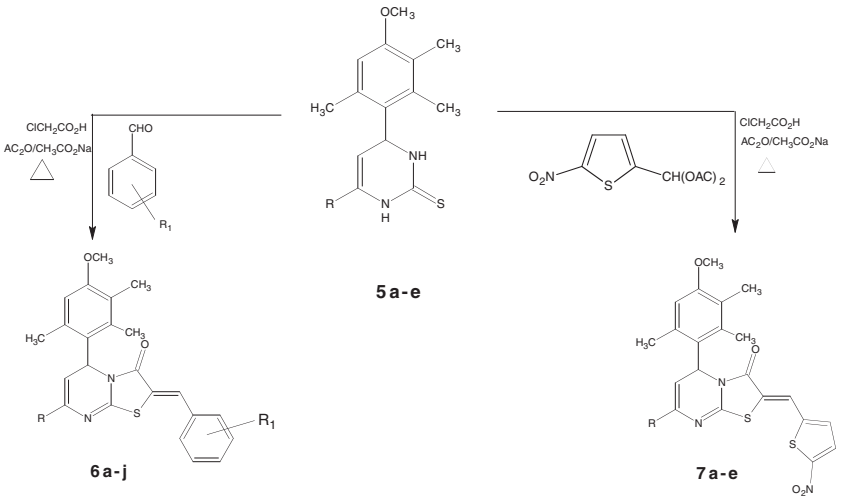
Table II Characterization data of 2-arylidine-5-(2,3,6-trimethyl-4-methoxyphenyl)-7-methyl/aryl-5H-pyrimidino-[2,3-b]thiazolidine-3-ones **6a–j** and 2-(5-nitro-2-thienylidine)-5-(2,3,6-trimethyl-4-methoxyphenyl)-7-methyl/aryl-5H-pyrimidino-[2,3-b]thiazolidine-3-ones (**7a–e**)

Comp. No.	R	R_1	Molecular Formulae (Mol. Wt.)	Mp (°C) (Yield%)	Analysis (%) Found (Calculated)		
					C	H	N
6	CH_3	4-Chloro	$C_{24}H_{23}N_2\ ClO_2S$ (438)	195–198 (71)	65.68 (65.75)	5.21 (5.25)	6.43 (6.39)
6b	CH_3	4-Methyl	$C_{25}H_{26}N_2O_2S$ (418)	179–181 (69)	71.81 (71.77)	6.25 (6.22)	6.65 (6.69)
6c	CH_3	4-Nitro	$C_{24}H_{23}N_3O_4S$ (449)	156–158 (69)	64.21 (64.14)	5.15 (5.12)	9.32 (9.35)
6d	CH_3	2-Bromo-6-Nitro	$C_{24}H_{22}BrN_3O_4S$ (527)	212–214 (62)	54.49 (54.54)	4.18 (4.16)	7.97 (7.95)
6e	CH_3	4-Phenyl	$C_{30}H_{28}N_2O_2S$ (480)	198–200 (64)	75.11 (75)	5.85 (5.83)	5.81 (5.83)
6f	4-Cl Phenyl	4-Chloro	$C_{29}H_{24}N_2Cl_2O_2S$ (535)	163–165 (73)	64.95 (65.04)	4.50 (4.48)	5.25 (5.23)
6g	4-Cl Phenyl	4-Methyl	$C_{30}H_{27}N_2ClO_2S$ (514)	180–182 (71)	70.14 (70.03)	5.22 (5.25)	5.48 (5.44)
6h	4-Cl Phenyl	4-Nitro	$C_{29}H_{24}N_3ClO_4S$ (545)	175–177 (63)	63.75 (63.85)	4.43 (4.40)	7.75 (7.70)
6i	4-Cl Phenyl	2-Bromo-6-Nitro	$C_{29}H_{23}N_3ClBrO_4S$ (623)	202–204 (62)	55.91 (55.85)	3.82 (3.85)	6.71 (6.74)
6j	4-Cl Phenyl	4-Phenyl	$C_{35}H_{29}N_2ClO_2S$ (576)	128–130 (64)	72.85 (72.91)	5.05 (5.03)	4.88 (4.86)
7a	CH_3	—	$C_{22}H_{21}N_3O_4S_2$ (455)	120–124 (71)	58.11 (58.02)	4.59 (4.61)	9.26 (9.23)
7b	Phenyl	—	$C_{27}H_{23}N_3O_4S_2$ (517)	161–163 (63)	62.72 (62.66)	4.51 (4.48)	8.14 (8.12)
7c	4-Cl phenyl	—	$C_{27}H_{22}ClN_3O_4S_2$ (551)	196–198 (62)	58.91 (58.80)	3.97 (3.99)	7.64 (7.61)
7d	4-Tolyl	—	$C_{28}H_{25}N_3O_4S_2$ (531)	215–217 (65)	64.29 (64.34)	5.61 (5.63)	7.55 (7.50)
7e	4-Nitro phenyl	—	$C_{27}H_{22}N_4O_6S_2$ (562)	221–224 (61)	59.68 (59.79)	3.94 (3.91)	10.01 (9.96)

at δ 3.83 integrating to three protons. The methine proton appeared as a doublet at δ 4.56, the pyrimidine-5H proton appeared as a doublet at δ 5.57, and the lone aromatic proton appeared as a singlet at δ 6.55. Further evidence in support of the proposed structure was obtained from the mass spectrum. It showed the molecular ion peak at m/z 276 in agreement with the proposed molecular formula $C_{15}H_{20}N_2OS$.

The one-pot three-component reaction of 4-(2,3,6-trimethyl-4-methoxyphenyl)-6-methyl/aryl-3,4-dihydropyrimidin-2-(1H)-thiones **5**, with the appropriate aldehyde and monochloroacetic acid in acetic anhydride medium in the presence of sodium acetate as a catalyst, gave a novel series of 2-arylidene-5-(2,3,6-trimethyl-4-methoxyphenyl)-7-methyl/aryl-5H-pyrimidino-[2,3-b]thiazolidine-3-ones **6**.

In the IR spectrum of **6a**, the carbonyl absorption band of the thiazolidinone was observed at 1653 cm^{-1} and the C—N absorption band was seen at 1581 cm^{-1}. In the ^1H NMR spectrum of **6a**, the pyrimidinyl methyl group appeared as a singlet at δ 1.96 integrating to three protons. The methyl groups appeared as three singlets at δ 2.09, 2.19,



Scheme 2

and 2.56 integrating to nine protons. The methoxy protons came into resonance as a singlet at δ 3.81 integrating to three protons. The signal due to the methine proton appeared as a doublet at δ 5.06 integrating to one proton, while the pyrimidine C_5-H proton came into resonance at δ 6.22 as a doublet integrating to one proton. The exo-cyclic vinylic protons appeared as a singlet at δ 6.60 integrating to one proton. The signal due to other aromatic protons merged together and appeared as multiplets in the region of δ 7.38–7.56 integrating to five protons. Further the mass spectra of compound **6a** showed the molecular ion peak at m/z 439 (M^++1 peak)/441.

A summary of the biological testing is provided in the Supplemental Materials (available online).

CONCLUSION

This article reports the successful synthesis and pharmacological studies of the title compounds via multicomponent reactions (MCR) in good yields. The anti-inflammatory activity study revealed that the tested compounds showed moderate to good activity. The antimicrobial activity study revealed that the compounds **6a**, **6b**, **6d**, and **6j** showed good antibacterial and antifungal activity comparable with that of the standard drug.

EXPERIMENTAL

The melting points of the newly synthesized compounds were determined in open capillary tubes and are uncorrected. IR spectra (cm^{-1}) were recorded on a Perkin Elmer 577 spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded on a Perkin Elmer (Model RB-12) spectrometer (300 MHz) using $CDCl_3$ or DMSO-d_6 as solvent and TMS as an internal standard. All chemical shift values are reported in δ scale downfield from TMS, and proton signals are indicated as s = singlet, d = doublet, t = triplet, m = multiplet. Mass spectrum was recorded on LC/MS (API 3000, Applied Biosystems) operating at 70 eV. C,

H, N analysis was carried out on a Vairo-EL (Elementa) model. Purity of the compounds was checked by TLC.

1-Methoxy-2,3,5-trimethylbenzene **2**, 2,3,6-trimethyl-4-methoxybenzaldehyde **3**, and 4-(2,3,6-trimethyl-4-methoxyphenyl)-3-butene-2-one **4a** were prepared as described in the literature.[12]

Procedure for the Preparation of 1-Aryl-3-(2,3,6-trimethyl-4-methoxyphenyl)-2-propene-1-ones 4b–e

A mixture of 2,3,6-trimethyl-p-methoxybenzaldehyde **3** (13.0 g, 0.07 mol) and substituted acetophenones (0.07 mol) in methanol (100 mL) were taken in a 250 mL RB flask. The reaction mixture was cooled to 0–5°C. Then 20% aqueous sodium hydroxide (35 mL) was added with stirring by maintaining the temperature at 0–5°C for about 30 min. The mixture was stirred overnight at room temperature. The solid formed was filtered, washed with water, and dried. It was further purified by recrystallization from ethyl acetate to give 1-aryl-3-(2,3,6-trimethyl-4-methoxyphenyl)-2-propen-1-ones **4b–e**.

Procedure for the Preparation of 4-(2,3,6-Trimethyl-4-methoxyphenyl)-6-methyl/aryl-3,4-dihydropyrimidin-2-(1H)-thiones 5a–e

A mixture of chalcone **4** (0.10 mol), thiourea (7.6 g, 0.10 mol), and potassium hydroxide 11.2 g (0.2 mol) in ethanol (200 mL) was heated under reflux for 6–7 h. The reaction was monitored by TLC. After the completion, the reaction volume was concentrated to half and then poured into ice cold water and acidified with acetic acid. The solid that separated was filtered, washed with water, and dried. It was further purified by recrystallization from ethyl acetate. The characterization data of these compounds are given in Table I.

4-(2,3,6-Trimethyl-4-methoxyphenyl)-6-(4-chorophenyl)-3,4-dihydropyrimidin-2-(1H)-thione 5c

^{1}H NMR ($CDCl_3$): δ 2.15 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.82 (S, 3H, OCH_3), 5.06 (d, 1H, $J = 4.6$ Hz, methine-H), 5.94 (d, 1H, $J = 4.6$ Hz, pyrimidine C_5—H), 6.57 (s, 1H, C_5—H of 2,3,6-trimethyl-4-methoxyphenyl), 6.75 (d, 2H, $J = 8.65$ Hz, ortho protons of 4-chlorophenyl), 7.79 (d, 2H, $J = 8.65$ Hz, meta-protons of 4-chlorophenyl), 7.81 (bs, 1H, N–H) and 7.92 (bs, 1H, NH); ^{13}C NMR; 175.45 (C=S), 157.14 (C-Cl), 135.32, 133.02, 131.84, 129.26, 128.40, 126.33 (aryl carbons), 100.91 (OCH_3), 55.49 and 53.06 (C—N), 20.98, 16.21 and 11.83 (CH_3); Mass: (M^++1) peak at m/z 373 (56%) (M. F. $C_{20}H_{21}N_2ClOS$). The chlorine isotope peak was observed at m/z 375 (18%).

General Procedure for the Preparation of 2-Substituted-5-(2,3,6-trimethyl-4-methoxyphenyl)-7-methyl/aryl-5H pyrimidino-[2,3-b] thiazolidine-3-ones 6a–j and 7a–e

A mixture of pyrimidino-2-(1H)-thione **5** (0.01 mol), monochloroacetic acid (1.41 g, 0.015 mol), anhydrous sodium acetate (2.0 g), glacial acetic acid (20 mL), acetic anhydride (15 mL), and arylaldehyde/5-nitro-2-thiophenaldiacetate (0.01 mol) was heated under reflux for 4 h. The reaction mixture was cooled and poured into crushed ice with vigorous stirring.

The contents were kept aside overnight. The separated solid was filtered, washed with water, and recrystallized from a mixture of ethyl acetate and hexane to give compounds **6a–j** and **7a–e**. The characterization data of these compounds are given in Table II.

2-(4-Nitrobenzylidine)-5-(2,3,6-trimethyl-4-methoxyphenyl)-7-methyl-5H-pyrimidino-[2,3-b]thiazolidine-3-one 6c. ^{1}H NMR ($CDCl_3$): δ 2.08 (s, 3H, pyrimidinyl CH_3) δ 2.11 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 5.69 (d, 1H, $J = 4.4$ Hz, methine- H), 6.44 (d, 1H, $J = 4.4$ Hz, pyrimidine C_5—H), 6.51 (s, 1H, C_5—H of 2,3,6-trimethyl-4-methoxyphenyl), 6.55 (s, 1H, exocyclic vinylic and 7.64 (d, 2H, $J = 8.80$ Hz, ortho protons of 4-nitrophenyl) and 7.84 (d, 2H, $J = 8.80$ Hz, meta protons 4-nitrophenyl); Mass: (M.F: $C_{24}H_{23}N_3O_4S$). m/z 449 (48%)(M^+); ^{13}C NMR; 163.45 (C=O), 146.53 (C—NO_2), 140.15–12.78 (aryl carbons), 101.02 (OCH_3), 55.49 and 53.06 (C—N), 19.76, 17.32 and 14.27 (CH_3).

2-(2-Bromo-6-nitrobenzylidine)-5-(2,3,6-trimethyl-4-methoxyphenyl)-7-methyl-5H-pyrimidino-[2,3-b]thiazolidine-3-one 6d. ^{1}H NMR ($CDCl_3$): δ 2.07 (s, 3H, pyrimidinyl CH_3) δ 2.13 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 5.71 (d, 1H, $J = 4.8$ Hz, methine H), 6.49 (d, 1H, $J = 4.8$ Hz, pyrimidine C_5—H), 6.58 (s, 1H, C_5—H of 2,3,6-trimethyl-4-methoxyphenyl), 6.65 (s, 1H, exocyclic vinylic) and 7.64–8.34 (m, 3H, Ar-H); Mass: (M.F: $C_{24}H_{22}N_3O_4BrS$). m/z 528 (46%)(M^++1). The bromine isotope peak was observed at m/z, 530 (42%).

2-(4-Phenylbenzylidine)-5-(2,3,6-trimethyl-4-methoxyphenyl)-7-methyl-5H-pyrimidino-[2,3-b]thiazolidine-3-one 6e. ^{1}H NMR ($CDCl_3$): δ 1.96 (s, 3H, pyrimidinyl CH_3), δ 2.10 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 5.05 (d, 1H, $J = 4.4$ Hz, methine H), 6.31 (d, 1H, $J = 4.4$ Hz, pyrimidine C_5—H), 6.56 (s, 1H, C_5—H of 2,3,6-trimethyl-4-methoxyphenyl), 6.61 (s, 1H, exocyclic vinylic) and 7.40–7.99 (m, 9H, Ar-H); Mass: (M.F: $C_{30}H_{28}N_2O_2S$). m/z 481 (38%)(M^++1).

2-(2-Bromo-6-nitrobenzylidine)-5-(2,3,6-trimethyl-4-methoxyphenyl)-7(4-chlorophenyl)-5H-thiozolo-[2,3-b]pyrimidin-3-one 6i. ^{1}H NMR ($CDCl_3$): δ, 2.16 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 5.76 (d, 1H, $J = 4.8$ Hz, methine H), 6.40 (d, 1H, $J = 4.8$ Hz, pyrimidine C_5—H), 6.52 (s, 1H,exocyclic vinylic), 6.63 (s, 1H, C_5—H of 2,3,6-trimethyl-4-methoxyphenyl), and 7.34–7.98 (m, 7H, Aryl-H); Mass: (M.F: $C_{29}H_{23}N_3O_4BrClS$). m/z 624 (48%)(M^++1) and the cluster of isotope peaks were observed at 625 (M^++3), 627 (M^++5) due to the presence of isotopes of chlorine and bromine.

2-(5-Nitro-2-thienylidine)-5-(2,3,6-trimethyl-4-methoxyphenyl)-7-methyl-5H-pyrimidino-[2,3-b]thiazolidine-3-one (7a). ^{1}H NMR ($CDCl_3$): δ 1.97 (s, 3H, CH_3 pyrimidinyl), δ 2.18 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 5.11 (d, 1H, $J = 4.7$ Hz, methine H), 6.28 (d, 1H, $J = 4.7$ Hz, pyrimidine C_5—H), 6.63 (s, 1H, C_5—H of 2,3,6-trimethyl-4-methoxyphenyl), 7.19 (d, 1H, $J = 8.36$ Hz, thiophene-3H), 7.76 (s, 1H, exocyclic vinylic) and 7.93 (d, 1H, $J = 8.36$ Hz, thiophene-4H); Mass: (M.F: $C_{22}H_{21}N_3O_4S_2$). m/z 456 (36%)(M^++1).

2-(5-Nitro-2-thienylidine)-5-(2,3,6-trimethyl-4-methoxyphenyl)-7-(p-chlorophenyl)-5H-pyrimidino-[2,3-b]thiazolidine-3-one (7c). ^{1}H NMR (DMSO-d_6): δ 2.21 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 5.23 (d, 1H, $J = 4.8$ Hz, methine H), 6.31 (d, 1H, $J = 4.8$ Hz, pyrimidine C_5—H), 6.72 (s, 1H, C_5—H of 2,3,6-trimethyl-4-methoxyphenyl), 6.91 (d, 2H, $J = 8.68$ Hz, ortho protons of p-chlorophenyl), 7.24 (d, 1H, $J = 8.36$ Hz, thiophene-3H), 7.79 (s, 1H, exocyclic vinylic) and 7.89 (d, 2H, $J = 8.68$ Hz, meta protons of 4-chlorophenyl), 8.10 (d, 1H, $J = 8.36$ Hz, thiophene-4H); Mass: (M.F: $C_{27}H_{22}ClN_3O_4S_2$). m/z 552 (41%)(M^++1)

and 554 (14%)(M^++3). ^{13}C NMR: 165.94 (C=O), 150.53 (C-Cl), 138.34–128.64 (aryl carbons), 101.22 (OCH_3), 59.11 and 56.86 (C−N), 20.98, 16.21 and 11.83 (CH_3).

2-(5-Nitro-2-thienylidine)-5-(2,3,6-trimethyl-4-methoxyphenyl)-7-(p-tolyl)-5H-pyrimidino-[2,3-b]thiazolidine-3-one (7d). ^{1}H NMR ($CDCl_3$): δ 2.13 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 5.08 (d, 1H, $J = 4.6$ Hz, methine H), 6.31 (d, 1H, $J = 4.6$ Hz, pyrimidine C_5−H), 6.58 (s, 1H, C_5−H of 2,3,6-trimethyl-4-methoxyphenyl), 6.93 (d, 2H, $J = 8.64$ Hz, ortho protons of 4-tolyl), 7.11 (d, 1H, $J = 8.36$ Hz, thiophene-3H), 7.41 (d, 2H, $J = 8.64$ Hz, meta protons of 4-tolyl), 7.79 (s, 1H, exocyclic vinylic) and 7.91 (d, 1H, $J = 8.36$ Hz, thiophene-4H); Mass: (M.F: $C_{28}H_{25}N_3O_4S_2$). m/z 532 (38%)(M^++1).

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