Chapter IV

INTRODUCTION

The chemistry of thiadiazoles and pyrimidines is well documented. The pyrimidine ring is present in several pharmaceutical agents and thiadiazoles are an important class of chemically and biologically significant compounds. In addition, these nuclei form the active cores of various bioactive molecules.\textsuperscript{1-2}

Pyrimidine derivatives, including those where the pyrimidine structure constitutes a part of the condensed ring system, are well-known to be involved in various metabolic processes and consequently are biolabile. Thus, besides other useful biological activities, pyrimidine derivatives have been reported to possess antioxidant, immunotrophic, anti-inflammatory, membrane stabilizing properties,\textsuperscript{3-5} bactericidal\textsuperscript{6}, fungicidal\textsuperscript{7} and herbicidal\textsuperscript{8} activities. Similarly, 1,3,4-thiadiazoles condensed with other heterocycles have been reported as potential antifungal and antibacterial agents.\textsuperscript{9-11}

It is well known that these heterocycles are valuable building blocks. Many methods for preparation of these heterocyclic ring systems and their fused analogues have been described in the literature.\textsuperscript{12-13} 2-Amino-1,3,4-thiadiazoles as amidine moiety provided a useful method for the synthesis of thiadiazolopyrimidine.\textsuperscript{14}

Although research on 1,3,4-thiadiazolo[3,2-a]pyrimidines is not a new one, the first article devoted to this problem was published 50 years ago\textsuperscript{15}, new articles devoted to the chemistry and biological activity of these compounds have been recently published.\textsuperscript{16-28} In 2004, a monograph on chemistry and biological activity of 1,3,4 thiaidazolo[3,2-a]pyrimidines was published in Russian.\textsuperscript{29}

In view of the above facts and in continuation of our desire to develop new agents of high potency, we fused biolabile pyrimidine and 1,3,4-thiadiazole rings to probe how far this combination could be successful.

Structure, reactivity and biological significance of 1,3,4-thiadiazolo[3,2-a]pyrimidines

da Silva LE \textit{et al.}, have synthesized 2-ethyl-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one (179) with potential antiviral and antiparasitic activities. Also they investigated the crystal structure of this compound.\textsuperscript{30}
Singh JS et al., synthesized a number of 3,10-diaryl-2-thiothiazolo[4,5-<i>d</i>]pyrido[2,1-<i>b</i>] pyrimidines and 3,6,9-triaryl-2-thiothiazolo[4,5-<i>d</i>][1,3,4]thiadiazolo [2,3-<i>b</i>]pyrimidines from the Michael adducts which in turn have been prepared by the reaction of arylidenorhodanines with 2-aminopyridine and 2-amino-5-aryl-1,3,4-thiadiazoles. The title compounds have been screened for antifungal activity and it was found that thiazolo-thiadiazolo-pyrimidines (180) showed greater activity than thiazolo-pyrido-pyrimidines whose activity is comparable with commercial fungicide Carbendazim.31

\[
\begin{align*}
\text{thiazolo-thiadiazolo-pyrimidines} \\
\text{R}_1 = \text{Br, Cl, H, C}_2\text{H}_5, \text{C}(\text{CH}_3), \text{C}_6\text{H}_5, \text{p-C}_6\text{H}_4
\end{align*}
\]

Muhamadsho A. Kukanieva and Cyril Parkanyi have studied the possibilities of the synthesis of various derivatives of 1,3,4-thiadiazolo[3,2-<i>a</i>]pyrimidine (181) containing the fluorine group in 6<sup>th</sup> position.32

\[
\begin{align*}
\text{R} = \text{Br, Cl, H, C}_2\text{H}_5, \text{C}(\text{CH}_3), \text{C}_6\text{H}_5, \text{p-C}_6\text{H}_4
\end{align*}
\]

Kukaniev MA and Parkanyi C have studied the possibility of the synthesis of various derivatives of 5H-1,3,4-thiadiazolo[3,2-<i>a</i>]pyrimidin-5-one (182) containing the hydrazine fragment in 2<sup>nd</sup> position and fluorine in 6<sup>th</sup> position.33

\[
\begin{align*}
\text{R} = \text{Br, Cl, H, C}_2\text{H}_5, \text{C}(\text{CH}_3), \text{C}_6\text{H}_5, \text{p-C}_6\text{H}_4
\end{align*}
\]
Saifidin S et al., have made a substantial amount of synthetic efforts for the preparation of 7H-1,3,4-thiadiazolo[3,2-a]pyrimidin-7-ones (183, 184). Further they have reported that this class of compounds can be obtained by condensation and subsequent cyclization reactions of 2-amino-1,3,4-thiadiazoles with propiolates or acetylene dicarboxylates.34

Saifidin S et al., have prepared 7H-1,3,4-Thiadiazolo[3,2-a]pyrimidin-7-ones (185) by the acylation of 5-amino-1,3,4-thiadiazoles with diketene and subsequent ring closure (dehydration).35

Suiko and Nakatsu have reported the crystallographic study of 2-ethylsulfonyl-7-methyl-5H-1,3,4-thiadiazolo[3,2-a]pyrimidin-5-one (186).36

Robert AC et al., have reported a series of alkyl- and aryl-substituted mesoionic 1,3,4-thiadiazolo[3,2-a]pyrimidine-5,7-diones (187), mesoionic xanthine analogs, were prepared and examined for antibacterial activity in order to develop structure-activity relationships leading to more active derivatives.37
Alan RK et al., have reported the synthesis of sulfonamide derivatives of 1,3,4-thiadiazolo[3,2-a]pyrimidines (188).  

\[ \text{R}^1 = \text{H, Me}; \text{R}^2 = \text{H, Me, Et, PhCH}_2; \text{R}^3 = \text{Me, Et, Ph, PhCH}_2 \]

Sathisha KR et al., synthesized 7-methyl-2-(phenoxyethyl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one (189) derivatives and reported the xanthine oxidase inhibitory activity of these compounds.  

\[ \text{R} = \text{CH}_3, \text{C}_2\text{H}_5, \text{ClC}_2\text{H}_4 \]

Duan LP et al., have reported Novel 2H-[1,2,4]thiadiazolo[2,3-a]pyrimidine (190) derivatives with herbicidal activity.  

\[ \text{X} = \text{CH}_3, \text{Cl, OCH}_3, \text{OH}; \text{Y} = \text{CH}_3, \text{OCH}_3, \text{Cl} \]

Hamama WS et al., have synthesized 5,7-diphenyl-6-[1,3-diphenylpropan-1-on-3-yl][1,3,4]thiadiazolo[3,2-a]pyrimidine (191) via Michael addition reaction of the 2-amino-1,3,4-thiadiazole to chalcone as biselectrophile.
El-Sayed NS et al. have reported synthesis and antitumor activity of new sulfonamide derivatives of thiaiazolo[3,2-a]pyrimidines (192, 193).42

R = H; 4- NH₂; 3- CH₃; R₁ = H; 4-Br; 4-Cl; 4-NO₂; 4-OCH₃; 3,4-di-OCH₃; 2,6-di-Cl; 2-Cl-5- NO₂

R = H, Br, Cl, CH₃, OCH₃, NO₂
PRESENT WORK

A general approach to synthesize the designed compounds is outlined in Scheme IV. The required key intermediate necessary for this study, 2-amino-5-(4-fluorobenzyl)-1,3,4-thiadiazole (XXI), was prepared by phosphorous oxychloride cyclisation of 4-fluorophenyl acetic acid with thiosemicarbazide. Chalcones were prepared by an aldol condensation between a benzaldehyde and an acetophenone in the presence of sodium hydroxide as a catalyst.\textsuperscript{43} Compound (XXI) was reacted with the appropriate 1,3-di (substituted phenyl)-2-propen-1-one (XXII a-p) (chalcone analogues)\textsuperscript{44-57} in refluxing propylene glycol to afford the corresponding 2-(4-fluorobenzyl)-5,7-di (substituted phenyl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine (XXIII a-p).

Scheme IV

\[
\begin{align*}
\text{F} & \quad \text{O} \\
\text{O} & \quad \text{H} \\
\text{N} & \quad \text{S} \\
\text{N} & \quad \text{H}_2 \\
\text{POCl}_3 & \quad \text{reflux} \\
\text{XXI} & \quad \text{XXII a-p}
\end{align*}
\]

\[
\begin{align*}
\text{F} & \quad \text{S} \\
\text{N} & \quad \text{N} \\
\text{NH}_2 & \quad \text{XXI} \\
\text{XXII a-p} & \quad \text{XXIII a-p}
\end{align*}
\]

\[
\begin{align*}
a, R = H; R_1 = (o) \text{NO}_2 \\
b, R = H; R_1 = (m) \text{NO}_2 \\
c, R = H; R_1 = (p) \text{Cl} \\
d, R = H; R_1 = (p) \text{OCH}_3 \\
e, R = 3,4-di- \text{OCH}_3; R_1 = (o) \text{NO}_2 \\
f, R = 3,4-di- \text{OCH}_3; R_1 = (m) \text{NO}_2 \\
g, R = 3,4-di- \text{OCH}_3; R_1 = (p) \text{Cl} \\
h, R = 3,4-di- \text{OCH}_3; R_1 = (p) \text{OCH}_3 \\
i, R = (p) \text{OCH}_3; R_1 = (o) \text{NO}_2 \\
j, R = (p) \text{OCH}_3; R_1 = (m) \text{NO}_2 \\
k, R = (p) \text{OCH}_3; R_1 = (p) \text{Cl} \\
l, R = (p) \text{OCH}_3; R_1 = (p) \text{OCH}_3 \\
m, R = (p) \text{NO}_2; R_1 = (o) \text{NO}_2 \\
n, R = (p) \text{NO}_2; R_1 = (m) \text{NO}_2 \\
o, R = (p) \text{NO}_2; R_1 = (p) \text{Cl} \\
p, R = (p) \text{NO}_2; R_1 = (p) \text{OCH}_3
\end{align*}
\]
RESULTS AND DISCUSSION

A general approach to synthesize the designed compounds is outlined in Schemes IV. The required key intermediate necessary for this study, 2-amino-5-(4-fluorobenzyl)-1,3,4-thiadiazole (XXI), was prepared by phosphorous oxychloride cyclisation of 4-fluorophenyl acetic acid with thiosemicarbazide in excellent yield. Various chalcones were prepared by an aldol condensation between a benzaldehyde and an acetophenone in the presence of sodium hydroxide as a catalyst. The target compounds have been synthesized by condensation of (XXI) with the appropriate 1,3-di (substituted phenyl)-2-propen-1-one (XXII a-p) (chalcone analogues) in refluxing propylene glycol to afford the corresponding 2-(4-fluorobenzyl)-5,7-di (substituted phenyl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine (XXIII a-p). The structures of the synthesized compounds were established on the basis of physicochemical, elemental and spectral (IR, NMR and Mass) analysis.

From the IR spectra of the synthesized compounds (XXIII a-p) it was noticed that the presence of bands at around 3032-3079 cm\(^{-1}\), 2916-2950 cm\(^{-1}\), 1576-1601 cm\(^{-1}\) and 1120-1173 cm\(^{-1}\) attribute the presence of \(v_{\text{C-H (aromatic)}}\), \(v_{\text{C-H (aliphatic)}}\), \(v_{\text{C-N}}\) and \(v_{\text{C-F}}\) respectively. This is further substantiated by \(^1\)H NMR spectra, in which it was observed that the appearance of signal as singlet around \(\delta 1.30-1.40\) ppm indicating the presence of methylene protons at 2\(^{\text{nd}}\) position of the 1,3,4-thiadiazolo[3,2-a]pyrimidine nucleus.

Further the most characteristic peaks appeared at around \(\delta 3.82-3.89\) ppm and \(\delta 6.92-8.37\) ppm evidence methoxyl and aromatic protons respectively.
EXPERIMENTAL

Synthesis of 2-Amino-5-(4-fluorobenzyl)-1,3,4-thiadiazole (XXI)

A mixture of 4-Fluoro phenyl acetic acid (15.4g, 0.1 mol) and thiosemicarbazide (9.3g, 0.1 mol) in phosphorous oxychloride (30mL) was refluxed gently for 45 minutes. The reaction mixture was cooled and quenched (highly exothermic) with cold water (90 mL). The resulting solution was refluxed for additional 4 hrs and filtered hot. The filtrate was cooled and basified with aqueous potassium hydroxide solution. The solid that separated was filtered, washed with water, dried and recrystallized from ethanol. Yield: 73%, m.p 212-213°C (lit.58 210°C).

Synthesis of 1,3-di (substituted phenyl)-2-propen-1-one (chalcone analogues) (XXII a-p)

A solution of 0.42g of sodium hydroxide in 3.85 mL of water and 2.36 mL of rectified spirit was placed in a 50 mL bolt-head flask provided with a mechanical stirrer. Immerse the flask in a bath of crushed ice, pour in freshly distilled acetophenone (8.32 mmol), then add pure benzaldehyde (8.32 mmol). Keep the temperature of the mixture at about 25 °C (the limits are 15-30 °C) and stir vigorously until the mixture is so thick that stirring is no longer effective (2-3 h). Remove the stirrer and leave the reaction mixture in an ice chest or refrigerator overnight. Filter the product with suction on a buchner funnel or on a sintered glass funnel, wash with cold water until the washings are neutral to litmus, and then with ice cold rectified spirit (10 mL). The crude chalcone was recrystallized from rectified spirit warmed to 50 °C. XXII a; Yield 65%, m.p. 118-120°C (lit.44 119°C). XXII b; Yield 68%, m.p. 142-144°C (lit.44 142°C). XXII c; Yield 72%, m.p. 108-110°C (lit.45 109°C). XXII d; Yield 73%, m.p. 76-78°C (lit.46 76°C). XXII e; Yield 69%, m.p. 108-110°C (lit.47 109°C). XXII f; Yield 75%, m.p. 105-107°C (lit.48 106°C). XXII g; Yield 78%, m.p. 112-114°C (lit.49 112°C). XXII h; Yield 79%, m.p. 116-118°C (lit.50 118°C). XXII i; Yield 77%, m.p. 107-109°C (lit.51 108°C). XXII j; Yield 69%, m.p. 110-112°C (lit.52 112°C). XXII k; Yield 82%, m.p. 114-116°C (lit.53 116°C). XXII l; Yield 78%, m.p. 100-102°C (lit.54 101°C). XXII m; Yield 79%, m.p. 110-112°C (lit.55 112°C). XXII n; Yield 84%, m.p. 100-102°C (lit.56 102°C). XXII o; Yield 67%, m.p. 105-107°C (lit.57 106°C). XXII p; Yield 74%, m.p. 108-110°C (lit.57 110°C).
Synthesis of 5,7-Di (substituted phenyl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine (XXIII a-p)

A mixture of 2-amino-5-(4-fluorobenzyl)-1,3,4-thiadiazole (XXI) (2.5 mmol) and the appropriate chalcone analogue (XXII a-p) (2.5 mmol) in propylene glycol (10 mL) was heated for 3-5 h at 200-220 °C. The mixture was cooled and diluted with water (50 mL) with vigorous stirring. The separated solid was collected by filtration, washed with water, dried and recrystallized from ethanol to afford target compounds (XXIII a-p).

2-(4-fluorobenzyl)-5-(2-nitrophenyl)-7-phenyl-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine (XXIII a)

Yield: 73%; mp: 122-124 °C; IR (KBr) cm⁻¹: 3033 (vC-H, aromatic), 2918 (vC-H, aliphatic), 1589 (vC=N), 1125 (vC-F). ¹H NMR (300MHz, DMSO-d₆) δ: 6.98-8.20 (m, 15H, Ar-H), 1.35 (s, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 159.2, 158.3, 145.2, 141.2, 140.3, 136.6, 135.3, 133.6, 132.1, 130.5, 130.2, 127.9, 127.6, 127.2, 126.4, 126.1, 125.7, 125.3, 120.5, 115.6, 115.2, 113.0, 48.5, 36.7. Mass m/z: 444.15 (m⁺). Anal. Calcd. for C₂⁴H₁₇FN₄O₂S: C, 64.85; H, 3.86; N, 12.60. Found: C, 64.75; H, 3.63; N, 12.54 (Vide Spectrum No. 51, 52 & 53).

2-(4-fluorobenzyl)-5-(3-nitrophenyl)-7-phenyl-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine (XXIII b)

Yield: 75%; mp: 148-150 °C; IR (KBr) cm⁻¹: 3032 (vC-H, aromatic), 2926 (vC-H, aliphatic), 1592 (vC=N), 1172 (vC-F). ¹H NMR (300MHz, DMSO-d₆) δ: 6.94-8.24 (m, 15H, Ar-H), 1.36 (s, 2H, CH₂); Mass m/z: 444.23 (m⁺). Anal. Calcd. for C₂⁴H₁₇FN₄O₂S: C, 64.85; H, 3.86; N, 12.60. Found: C, 64.72; H, 3.59; N, 12.51 (Vide Spectrum No. 54).
2-(4-fluorobenzyl)-5-(4-chlorophenyl)-7-phenyl-5H-[1,3,4]thiadiazolo[3,2-a]-pyrimidine (XXIII c)

Yield: 69%; mp: 118-120 °C; IR (KBr) cm⁻¹: 3050 (v_C-H, aromatic), 2930 (v_C-H, aliphatic), 1588 (v_C=N), 1170 (v_C-N), 1135 (v_C-F), 1088 (v_C-Cl).¹HNMR (300 MHz, CDCl₃) δ: 7.04-8.35 (m, 15H, Ar-H), 1.35 (s, 2H, CH₂).¹³CNMR (75 MHz, CDCl₃) δ: 159.3, 158.4, 144.5, 143.7, 140.2, 135.8, 132.3, 131.1, 129.7, 129.5, 127.9, 127.6, 127.5, 127.4, 127.3, 127.2, 127.0, 125.5, 125.2, 115.7, 115.4, 114.6, 50.5, 37.3. Mass m/z: 433.12 (m⁺). Anal. Calcd. for C₂₄H₁₇CIFN₃S; C, 66.43; H, 3.95; N, 9.68. Found: C, 66.33; H, 3.83; N, 9.71 (Vide Spectrum No. 55).

2-(4-fluorobenzyl)-5-(4-methoxyphenyl)-7-phenyl-5H-[1,3,4]thiadiazolo[3,2-a]-pyrimidine (XXIII d)

Yield: 72%; mp: 88-90 °C; IR (KBr) cm⁻¹: 3050 (v_C-H, aromatic), 2920 (v_C-H, aliphatic), 1595 (v_C=N), 1512 (v_C-0), 1180 (v_C-N), 1130 (v_C-F).¹HNMR (300 MHz, CDCl₃) δ: 7.04-8.32 (m, 15H, Ar-H), 3.85 (s, 3H, OCH₃), 1.36 (s, 2H, CH₂).¹³CNMR (75 MHz, CDCl₃) δ: 159.6, 158.4, 157.3, 144.6, 140.3, 135.7, 135.4, 132.4, 130.4, 130.1, 127.9, 127.5, 127.4, 127.2, 127.0, 125.7, 125.2, 115.6, 115.2, 112.6, 112.4, 112.1, 54.1, 50.5, 37.1. Mass m/z: 429.23 (m⁺). Anal. Calcd. for C₂₅H₂₀FN₂S; C, 69.91; H, 4.69; N, 9.78. Found: C, 69.82; H, 4.72; N, 9.83 (Vide Spectrum No. 56).

2-(4-fluorobenzyl)-7-(3,4-dimethoxyphenyl)-5-(2-nitrophenyl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine (XXIII e)

Yield: 68%; mp: 120-122 °C; IR (KBr) cm⁻¹: 3030 (v_C-H, aromatic), 2916 (v_C-H, aliphatic), 1590 (v_C=N), 1306 (v_C-O), 1174 (v_C-N), 1125 (v_C-F).¹HNMR (300 MHz, DMSO-d₆) δ: 7.02-8.30 (m, 13H, Ar-H), 3.88 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 1.32 (s, 2H, CH₂); Mass m/z: 504.25 (m⁺). Anal. Calcd. for C₂₆H₂₁FN₄O₄S; C, 61.89; H, 4.20; N, 11.10. Found: C, 61.92; H, 4.22; N, 11.15 (Vide Spectrum No. 57).
2-(4-fluorobenzyl)-7-(3,4-dimethoxyphenyl)-5-(3-nitrophenyl)-5H-[1,3,4]-thiadiazolo[3,2-a]pyrimidine (XXIII f)

Yield: 71%; mp: 120-122 °C; IR (KBr) cm\(^{-1}\): 3079 (\(\nu_{\text{C-H, aromatic}}\)), 2935 (\(\nu_{\text{C-H, aliphatic}}\)), 1591 (\(\nu_{\text{C=N}}\)), 1157 (\(\nu_{\text{C-N}}\)), 1023 (\(\nu_{\text{C-F}}\)). \(^1\)H NMR (300MHz, DMSO-d\(_6\)) \(\delta\): 7.04-8.37 (\(m\), 13H, Ar-H), 3.89 (s, 3H, OCH\(_3\)), 3.87 (5, 3H, OCH\(_3\)), 1.30 (5, 2H, CH\(_2\)); Mass \(m/z\): 504.19 (m\(^+\)). Anal. Calcd. for C\(_{26}\)H\(_{21}\)FN\(_4\)O\(_4\)S; C, 61.89; H, 4.20; N, 11.10. Found: C, 61.88; H, 4.19; N, 11.20 (Vide Spectrum No. 58 & 59).

2-(4-fluorobenzyl)-5-(4-chlorophenyl)-7-(3,4-dimethoxyphenyl)-5H-[1,3,4]-thiadiazolo[3,2-a]pyrimidine (XXIII g)

Yield: 65%; mp: 130-132 °C; IR (KBr) cm\(^{-1}\): 3076 (\(\nu_{\text{C-H, aromatic}}\)), 2926 (\(\nu_{\text{C-H, aliphatic}}\)), 1591 (\(\nu_{\text{C=N}}\)), 1265 (\(\nu_{\text{C-O}}\)), 1151 (\(\nu_{\text{C-F}}\)), 1086 (\(\nu_{\text{C-Cl}}\)). \(^1\)H NMR (300MHz, DMSO-d\(_6\)) \(\delta\): 6.97-8.02 (\(m\), 13H, Ar-H), 3.88 (s, 3H, OCH\(_3\)), 3.86 (5, 3H, OCH\(_3\)), 1.35 (s, 2H, CH\(_2\)); Mass \(m/z\): 493.26 (m\(^+\)). Anal. Calcd. for C\(_{26}\)H\(_{21}\)ClFN\(_3\)O\(_2\)S; C, 63.22; H, 4.28; N, 8.51. Found: C, 63.27; H, 4.19; N, 8.45 (Vide Spectrum No. 60 & 61).

2-(4-fluorobenzyl)-7-(3,4-dimethoxyphenyl)-5-(4-methoxyphenyl)-5H-[1,3,4]-thiadiazolo[3,2-a]pyrimidine (XXIII h)

Yield: 72%; mp: 136-138 °C; IR (KBr) cm\(^{-1}\): 3033 (\(\nu_{\text{C-H, aromatic}}\)), 2925 (\(\nu_{\text{C-H, aliphatic}}\)), 1592 (\(\nu_{\text{C=N}}\)), 1302 (\(\nu_{\text{C-O}}\)), 1117 (\(\nu_{\text{C-N}}\)), 1120 (\(\nu_{\text{C-F}}\)). \(^1\)H NMR (300MHz, DMSO-d\(_6\)) \(\delta\): 7.02-8.12 (\(m\), 13H, Ar-H), 3.86 (s, 3H, OCH\(_3\)), 3.84 (s, 3H, OCH\(_3\)), 3.82 (s, 3H, OCH\(_3\)), 1.32 (s, 2H, CH\(_2\)); Mass \(m/z\): 489.11 (m\(^+\)). Anal. Calcd. for C\(_{27}\)H\(_{24}\)FN\(_3\)O\(_3\)S; C, 66.24; H, 4.94; N, 8.58. Found: C, 66.31; H, 4.89; N, 8.45.
2-(4-fluorobenzyl)-7-(4-methoxyphenyl)-5-(2-nitrophenyl)-5H-[1,3,4]-thiadiazolo[3,2-a]pyrimidine (XXIII i)

Yield: 68%; mp: 116-118 °C; IR (KBr) cm⁻¹: 3060 (ν_C-H, aromatic), 2930 (ν_C-H, aliphatic), 1594 (ν_C=N), 1270 (ν_C-O), 1160 (ν_C-N), 1025 (ν_C-F). ¹H NMR (300 MHz, DMSO-d₆) δ: 6.94-8.04 (m, 14H, Ar-H), 3.84 (s, 3H, OCH₃), 1.34 (s, 2H, CH₂); Mass m/z: 474.11 (m⁺). Anal. Calcd. for C₂₅H₁₉FN₄O₃S; C, 63.28; H, 4.04; N, 11.81. Found: C, 63.31; H, 4.12; N, 11.74.

2-(4-fluorobenzyl)-7-(4-methoxyphenyl)-5-(3-nitrophenyl)-5H-[1,3,4]-thiadiazolo[3,2-a]pyrimidine (XXIII j)

Yield: 65%; mp: 122-124 °C; IR (KBr) cm⁻¹: 3055 (ν_C-H, aromatic), 2935 (ν_C-H, aliphatic), 1590 (ν_C=N), 1265 (ν_C-O), 1165 (ν_C-N), 1130 (ν_C-F). ¹H NMR (300 MHz, DMSO-d₆) δ: 6.92-8.02 (m, 14H, Ar-H), 3.86 (s, 3H, OCH₃), 1.35 (s, 2H, CH₂); Mass m/z: 474.23 (m⁺). Anal. Calcd. for C₂₅H₁₉FN₄O₃S; C, 63.28; H, 4.04; N, 11.81. Found: C, 63.23; H, 4.15; N, 11.69.

2-(4-fluorobenzyl)-5-(4-chlorophenyl)-7-(4-methoxyphenyl)-5H-[1,3,4]-thiadiazolo[3,2-a]pyrimidine (XXIII k)

Yield: 74%; mp: 130-132 °C; IR (KBr) cm⁻¹: 3030 (ν_C-H, aromatic), 2921 (ν_C-H, aliphatic), 1601 (ν_C=N), 254 (ν_C-O), 1224 (ν_C-N), 1172 (ν_C-F), 1089 (ν_C-Cl). ¹H NMR (300 MHz, DMSO-d₆) δ: 7.01-8.19 (m, 14H, Ar-H), 3.87 (s, 3H, OCH₃), 1.40 (s, 2H, CH₂); Mass m/z: 463.12 (m⁺). Anal. Calcd. for C₂₅H₁₉ClFN₃O₃S; C, 64.72; H, 4.13; N, 9.06. Found: C, 64.69; H, 4.18; N, 9.12 (Vide Spectrum No. 62 & 63).
2-(4-fluorobenzyl)-5,7-bis(4-methoxyphenyl)-5H-[1,3,4]thiadiazolo[3,2-a]-pyrimidine (XXIII l)

Yield: 66%; mp: 112-114 °C; IR (KBr) cm⁻¹: 3030 (vC-H, aromatic), 2950 (vC-H, aliphatic), 1596 (vC=N), 1254 (vC=O), 1217 (vC=S), 1170 (vC-F). ¹H NMR (300MHz, DMSO-d6) δ: 7.00-8.17 (m, 14H, Ar-H), 3.86 (s, 3H, OCH₃), 3.84 (s, 3H, OCH₃), 1.40 (s, 2H, CH₂); Mass m/z: 459.12 (m⁺). Anal. Calcd. for C₂₆H₂₂FN₃O₂S: C, 67.96; H, 4.83; N, 9.14. Found: C, 67.85; H, 4.76; N, 9.19 (Vide Spectrum No. 64 & 65).

2-(4-fluorobenzyl)-5-(2-nitrophenyl)-7-(4-nitrophenyl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine (XXIII m)

Yield: 69%; mp: 124-126 °C; IR (KBr) cm⁻¹: 3055 (vC-H, aromatic), 2935 (vC-H, aliphatic), 1590 (vC=N), 1165 (vC=S), 1130 (vC-F). ¹H NMR (300MHz, DMSO-d6) δ: 6.92-8.10 (m, 14H, Ar-H), 1.34 (s, 2H, CH₂); Mass m/z: 489.12 (m⁺). Anal. Calcd. for C₂₄H₁₆FN₅O₄S: C, 58.89; H, 3.29; N, 14.31. Found: C, 58.85; H, 3.31; N, 14.25.

2-(4-fluorobenzyl)-5-(3-nitrophenyl)-7-(4-nitrophenyl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine (XXIII n)

Yield: 72%; mp: 110-112 °C; IR (KBr) cm⁻¹: 3033 (vC-H, aromatic), 2942 (vC-H, aliphatic), 1595 (vC=N), 1227 (vC=S), 1171 (vC-F). ¹H NMR (300MHz, DMSO-d6) δ: 6.98-8.22 (m, 14H, Ar-H), 1.35 (s, 2H, CH₂); Mass m/z: 489.15 (m⁺). Anal. Calcd. for C₂₄H₁₆FN₅O₄S: C, 58.89; H, 3.29; N, 14.31. Found: C, 58.72; H, 3.35; N, 14.19 (Vide Spectrum No. 66).

2-(4-fluorobenzyl)-5-(4-chlorophenyl)-7-(4-nitrophenyl)-5H-[1,3,4]thiadiazolo-[3,2-a]pyrimidine (XXIII o)

Yield: 76%; mp: 118-120 °C; IR (KBr) cm⁻¹: 3033 (vC-H, aromatic), 2935 (vC-H, aliphatic), 1590 (vC=N), 1165 (vC=S), 1132 (vC-F), 1090 (vC-Cl). ¹H NMR (300MHz, DMSO-d6) δ: 6.96-8.12 (m, 14H, Ar-H), 1.33 (s, 2H, CH₂); Mass m/z: 478.23 (m⁺). Anal. Calcd. for C₂₄H₁₆ClFN₄O₂S: C, 60.19; H, 3.37; N, 11.70. Found: C, 60.23; H, 3.33; N, 11.63.
2-(4-fluorobenzyl)-5-(4-methoxyphenyl)-7-(4-nitrophenyl)-5H-[1,3,4]thiadiazolo-
[3,2-a]pyrimidine (XXIII) p

Yield 73%, m.p: 126-128 °C; IR (KBr) cm⁻¹: 3029 (νC-H, aromatic), 2928 (νC-H, aliphatic), 1576 (νC=N), 1298 (νC-O), 1254 (νC=N), 1173 (νC-F). ¹H NMR (300 MHz, DMSO-d6) δ: 6.95-8.07 (m, 13H, Ar-H), 3.83 (s, 3H, OCH₃), 1.30 (s, 2H, CH₂); Mass m/z: 474.15 (m⁺). Anal. Calcd. for C₂₅H₁₉FN₄O₃S; C, 63.28; H, 4.04; N, 11.81. Found: C, 63.18; H, 4.11; N, 11.72 (Vide Spectrum No. 67 & 68).
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Spectrum 51: IR (KBr) Spectrum of compound XXIII a

Spectrum 52: $^1$H NMR (300 MHz) Spectrum of compound XXIII a in DMSO
Spectrum 53: $^{13}$C NMR (300 MHz) Spectrum of compound XXIII a in CDCl$_3$

Spectrum 54: IR (KBr) Spectrum of compound XXIII b
Spectrum 55: $^{13}$C NMR (300 MHz) Spectrum of compound XXIII c in CDCl$_3$

Spectrum 56: $^{13}$C NMR (300 MHz) Spectrum of compound XXIII d in CDCl$_3$
Chapter 4

Spectrum 57: IR (KBr) Spectrum of compound XXIII e

Spectrum 58: IR (KBr) Spectrum of compound XXIII f
Chapter 4

Spectrum 59: $^1$H NMR (300 MHz) Spectrum of compound XXIII f in DMSO

Spectrum 60: IR (KBr) Spectrum of compound XXIII g
Spectrum 61: $^1$H NMR (300 MHz) Spectrum of compound XXIII g in DMSO

Spectrum 62: IR (KBr) Spectrum of compound XXIII k
Chapter 4

Spectrum 63: $^1$H NMR (300 MHz) Spectrum of compound XXIII k in DMSO

Spectrum 64: IR (KBr) Spectrum of compound XXIII l
Spectrum 65: $^1$H NMR (300 MHz) Spectrum of compound XXIII I in DMSO

Spectrum 66: IR (KBr) Spectrum of compound XXIII n
Chapter 4

Spectrum 67: IR (KBr) Spectrum of compound XXIII p

Spectrum 68: $^1$H NMR (300 MHz) Spectrum of compound XXIII p in DMSO
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