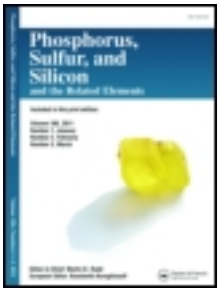

Phosphorus, Sulfur, and Silicon and the Related Elements

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# Synthesis and Reactions of Some New Spiropyranthiazoline Derivatives

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# Synthesis and Reactions of Some New Spiropyranthiazoline Derivatives

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*Pyrano[2,3-d]thiazoline-7-spiro-3′-(1′-substitutedindoline-2′-ones)* ***5a,b*** *has been synthesized and reacted with some nucleophile reagents to afford new spirothiazolino[4,5:2′,3′]pyrano[6′,5′-d]pyrimidine derivatives* ***6a,b–13a,b,*** *which are analogues of some reported biologically active spiroheterocyclic compounds.*

**Keywords** Indoline; Pyranothiazolidine; Spiro; Spiroheterocyclic; Thiazolinopyranopyrimidine



## INTRODUCTION

Spiro derivatives have anticonvulsants, antibacterial and anticancer activities.[1,2] Spiro heterocycles were used as nitric oxide synthesis inhibitors,[3] photoisomerization,[4,5] and potential topical agents for vaginal infection.[6] Photochromism of indolinospirochromenes containing condensed fragments in the indoline part of the molecule were achieved.[7] Nitrils were used as starting materials to prepare a verity of condensed pyrans[8–12] for their medicinal importance.[13,14] Pyrano derivatives have well-known biological effects, such as analgesic and anti-inflammatory activities,[15] and pyrimidine derivatives have been used as adenosine kinase inhibitors.[16] Further, spiropolycycles were important for the synthesis of ptilomycalin A and fredricmycine A models, which was used as an antitumor agent. Our continuing interest in this area[18–25] encouraged us to suggest the synthesis of some new spiropolycycles of pyranothiazoline.

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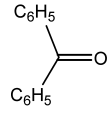
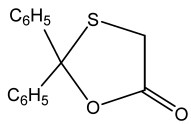
## RESULTS AND DISSCUSION

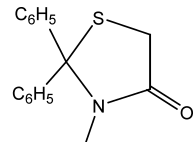
Our syntheses started with the reaction of benzophenone **1** with mercaptoacetic acid in dry toluene[18] and catalytic amount of p-toluenesulphonic acid to yield 2,2-diphenyloxathiolidine-4-one **2**, which then reacted with benzyl amine in absolute ethanol to afford 3-benzyl-2,2-diphenylthiazolidine-4-one **3** in good yield.




**1**




**2**



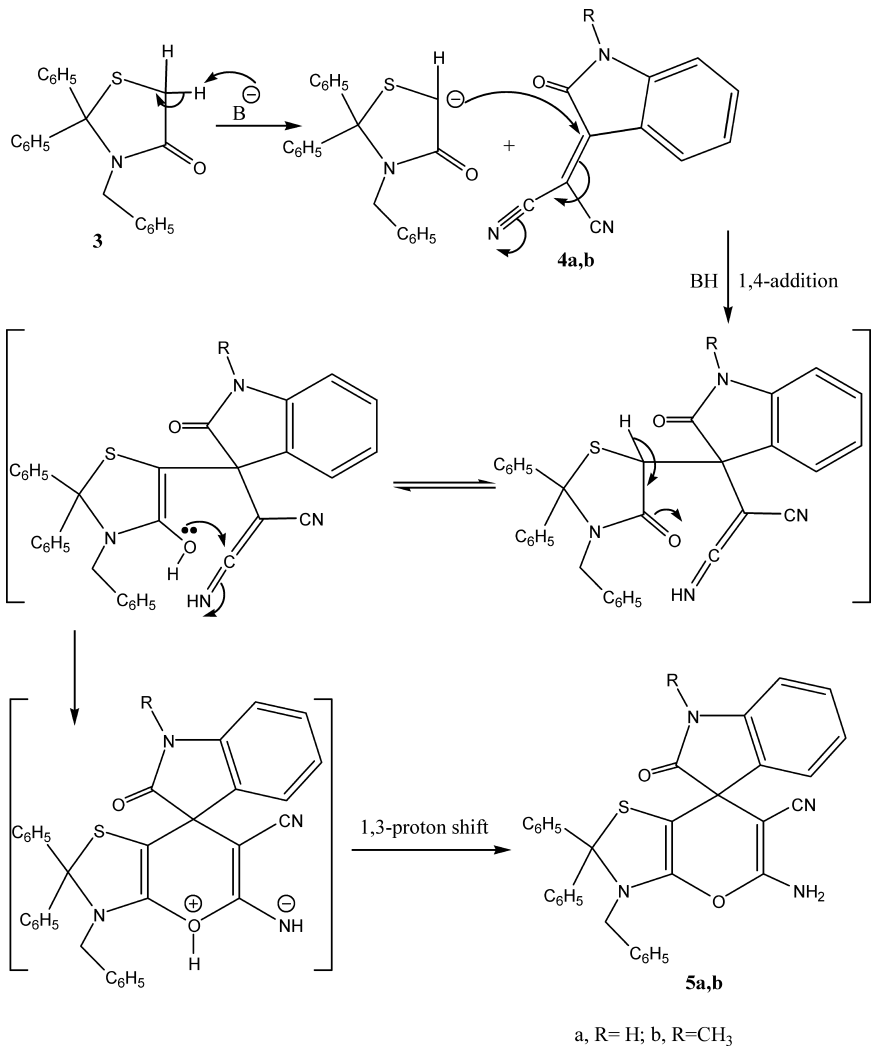

**3**

Compound **3** reacted with 3-dicyanomethylidine-2-oxoindolines **4a,b** in refluxed ethanol and catalytic amount of triethyl amine to afford pyrano[2,3-*d*]thiazoline-7-spiro-3′-(1′-substitutedindoline-2′-ones) **5a,b**, via a type of Michael addition shown in (Scheme 1).

The structures of the prepared compounds **2**, **3**, and **5a,b** were established from their elemental analyses and spectral data. The IR spectrum of compound **2** showed absorption bands at $\acute{\upsilon}$ 1700 and 690 $cm^{-1}$ for the carbonyl group of the oxathiolidine ring and C—S bond respectively. The $^1H$ NMR spectrum of compound **2** revealed the presence of a singlet signal of two protons at $\delta$ 3.90 assignable to the methylene protons and multiplet signal of ten protons at 7.85–6.90 for the aromatic protons. The $^1H$ NMR spectrum of compound **3** revealed showed a singlet signal of two protons at $\delta$ 3.95 assignable to the methylene protons in the thiazolidine ring and a singlet signal of two protons at $\delta$ 2.96 for the methylene protons in the benzyl group.

The IR spectrum of compound **5a** showed characteristic absorption bands at $\acute{\upsilon}$ 3320, 3260, 2200, and 1710 $cm^{-1}$ corresponding to $NH_2$, NH, CN, and C=O groups respectively. Its $^1H$ NMR spectrum showed multiplet signal at $\delta$ 7.71–6.61 for aromatic protons and three singlet signals at 10.35, 5.00, and 3.51 for NH, $NH_2$, and $CH_2$ protons, respectively. However, the IR spectrum of compound **5b** showed absorption bands at $\acute{\upsilon}$ 3340–3200, 2200, and 1705 $cm^{-1}$ corresponding to $NH_2$, CN, and C=O groups, respectively. Its $^1H$ NMR spectrum showed multiplet signal at $\delta$ 7.89–6.75 for aromatic protons and three singlet signals at 5.02, 3.24, and 2.51 for $NH_2$, $CH_3$, and $CH_2$ protons, respectively.

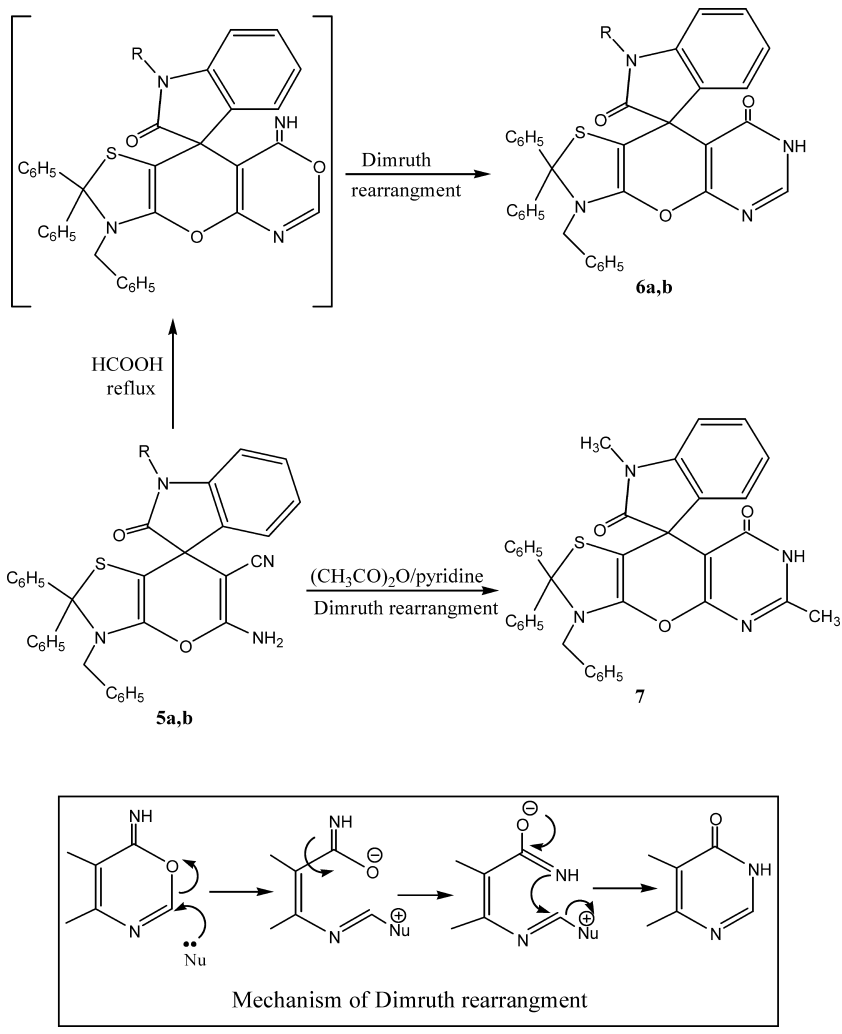
However, compounds **5a,b** represents a good synthon for pyrimidines synthesis, which found considerable interest in field of medicine and biology.[26–28] Compounds 5a,b refluxed with formic acid to afford




**SCHEME 1**

3-benzyl-2,2-diphenyl-7(H)-8-oxothiazolino[4,5:2′,3′]pyrano[6′,5′-*d*] pyrimidine-9-spiro-3′(2′-oxoindoline) derivatives **6a,b**.

Reaction of **5b** with acetic anhydride/pyridine mixture gave 3-benzyl-2,2-diphenyl-7(H)-8-oxo-6-methylthiazolino[4,5:2′,3′]pyrano[6′,5′-*d*]pyrimidine-9-spiro-3′(1′-methyl indolin-2′-one) **7** (Scheme 2). Compounds **6a,b** and 7 were formed via Dimruth rearrangement illustrated in (Scheme 2).




**SCHEME 2**

The IR spectrum of compounds **6a**, **6b**, and **7** revealed absorption bands at $\upsilon$ 3250, 3300, and 3500, respectively, which corresponded to the NH group with disappearance of the absorption bands corresponding to the cyano and amino groups. The $^1$H NMR spectrum of compounds **6a** and **6b** revealed a singlet signal for one proton at $\delta$ 5.49–5.40 exchanged with $D_2O$ indicated to NH proton with absence of the signal corresponding to $NH_2$ protons. However, the $^1$H NMR spectrum of compound 7 revealed a singlet signal at $\delta$ 5.40 exchanged with $D_2O$

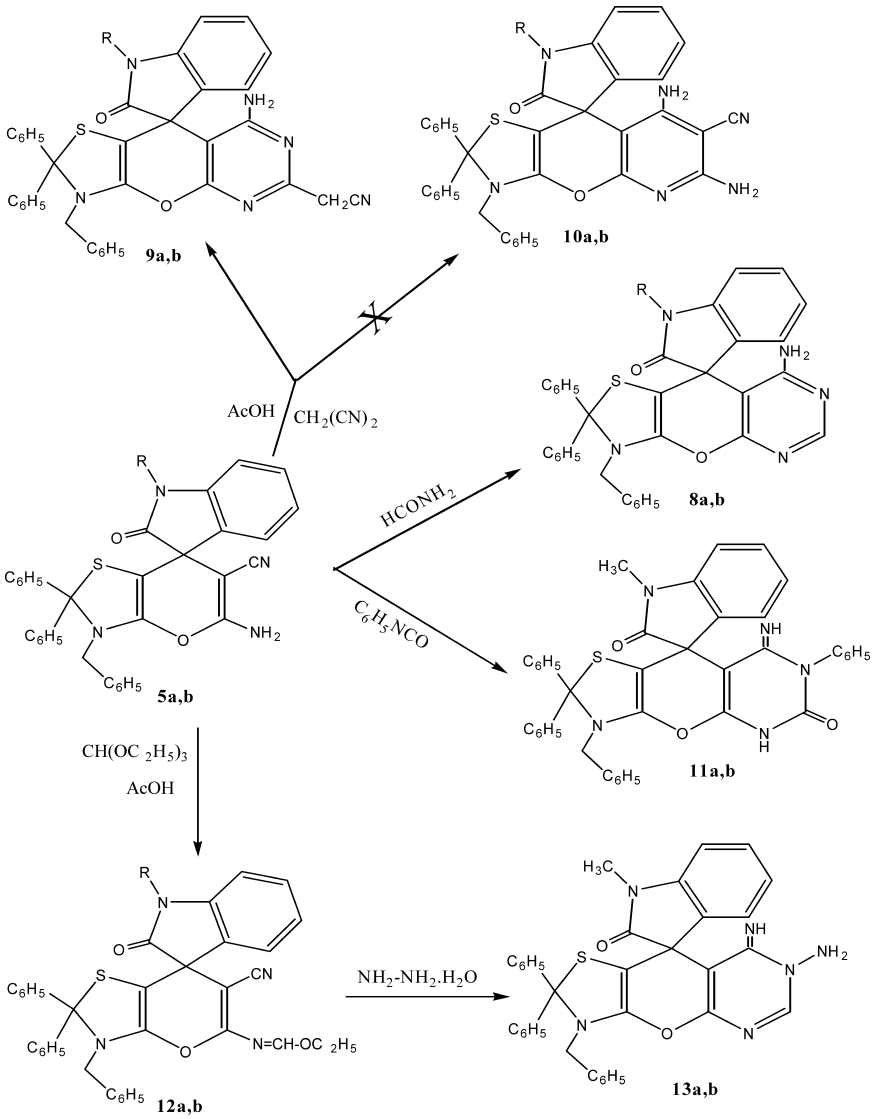
for NH proton, and two singlet signals at 3.39 and 2.10 for two methyl protons.

Interaction of **5a,b** with formamide afforded 8-amino-3-benzyl-2,2-diphenylthiazolino[4,5:2′,3′]pyrano[6′,5′-*d*]pyrimidine-9-spiro-3′(1′-substitutedindolin-2′-one) **8a,b**. Reaction of **5a,b** with malononitrile in glacial acetic acid under reflux gave the corresponding spirothiazolino[4,5:2′,3′]pyrano[6′,5′-*d*]pyrimidine derivatives **9a,b** rather than spirothiazolino[4,5:2′,3′]pyrano[6′,5′-*b*]pyridine derivatives **10a,b**. Reaction of **5a,b** with phenylisocyanate in refluxed pyridine afforded 5(H)-3-benzyl-8-imino-6-oxo-2,2,7-triphenylthiazolino[4,5:2′,3′] pyrano[6′,5′-*d*]pyrimidine-9-spiro-3′(1′-substitu-tedindolin-2′-one) **11a, b**. The reaction of **5a,b** with triethyl orthoformate in the presence of few drops of glacial acetic acid gave the corresponding 3-benzyl-6-cyano-2,2-diphenyl-5-ethoxymethiniminopyrano[2,3-*d*]thiazolino-7-spiro-3′-(1′-substitutedindoline-2′-ones) **12a,b**. Finally, compounds **12a,b** reacted with hydrazine hydrate to afford 7-amino-3-benzyl-2,2-diphenyl-8-iminothiazolino[4,5:2′,3′]pyrano[6′,5′-*d*]pyrimidine-9-spiro-3′(1′-substitutedindolin-2′-one) **13a,b**. (Scheme 3).

The chemical structures of all compounds **8a,b–13a,b** were established based on their elemental and spectral analyses. The IR spectrum of compounds **8a** and **8b** revealed absorption band at $\upsilon$ 3360–3210 corresponding to $NH_2$ group with disappearance of the absorption band corresponding to the cyano group. The structures of 8-amino-3-benzyl-6-cyanomethyl-2,2-diphenylthiazolino[4,5:2′,3′]pyrano[6′,5′–*d*]pyrmidine-9-spiro-3′-(N′-substitutedindolin-2′-ones) **9a,b** were tentatively preferred for these products based on its $^1$H NMR spectrum of compound **9b** for example, shown the following signals: four singlet signals at $\delta$ 8.39, 3.99, 3.50, and 2.52 for NH, cyanomethyl, methyl, and methylene protons, respectively.

The IR spectrum of compounds **11a,b** shown the absorption bands at $\upsilon$ 3320, and 3290–3280 for two NH groups with absence of the absorption band corresponding to cyano group. The IR spectrum of compounds **12a,b** shown the disappearance of the band for $NH_2$ group, and the $^1$H NMR spectrum of compound **12b** shown the following signals: multiplet signals at $\delta$ 7.85-6.76 for aromatic protons, quartet and triplet signals at 4.00 and 1.05 for ethyl protons, and two singlet signals at 3.25 and 2.56 for methyl and benzylic protons, respectively.

The IR spectrum of compounds **13a,b** revealed the absorption bands $\upsilon$ 3310–3200 for NH2 group with absence of the band for cyano group and its $^1$H NMR spectrum shown the absence of signals corresponding to ethyl protons.




**SCHEME 3**

## CONCLUSION

The previously discussed reactions described a simple synthetic procedure to prepare new spiroheterocyclic derivatives of pyranothiazolines and thiazolino- pyranopyrimidines, which might have important biological applications.

## EXPERIMENTAL

The time required for completion of each reaction was monitored by TLC. Melting points are uncorrected and were measured on a Gallen Kamp apparatus.

The IR spectra were recorded on a Chimadz 470 IR spectrometer (KBr) $\acute{\upsilon}$ $cm^{-1}$. The $^1H$ NMR spectra were measured on Varian EM-200 MHz spectrometer with TMS as internal standard. Mass spectra were determined on a Jeol-600 spectrometer. Elemental analyses were performed on an elemental analyses system GmbH varioel $V_{2.3}$.

### Synthesis of 2,2-diphenyloxathiolidine-4-one (2)

A mixture of benzophenone **1** (18.2 g, 100 mmol), mercaptoacetic acid (6.95 mL, 100 mmol), and p-toluenesulphonic acid (0.5 g) in dry toluene (200 mL) was refluxed for 5 h, whereby the liberated water was removed by water separator. After cooling, the solvent was removed under vacuum, and the oily residue was left at room temperature for three days to give a solid. The product was treated with $Et_2O$ to form a crystalline product, dried and recrystallized from toluene to give colorless crystals; yield (60%); m.p. 161–163°C; IR: $\acute{\upsilon}$ $cm^{-1}$ 1700 (C=O), 690 (C–S); $^1H$ NMR (DMSO-$d_6$): $\delta$ 7.81–6.90 (m, 10H, Ar–H), 3.90 (s, 2H, $CH_2$); Anal. calcd. for $C_{15}H_{12}O_2S$ (256.13): C, 70.33; H, 4.68; S, 12.49. Found: C, 69.98; H, 4.67; S, 12.62.

### Synthesis of 3-Benzyl-2,2-diphenylthiazolidin-4-one (3)

A mixture of **2** (5.12 g, 20 mmol) and benzyl amine (2.18 mL, 20 mmol) in absolute ethanol (20 mL) was stirred at room temperature for 4h. The product was precipitated, collected by filtration, dried and recrystallized from ethanol to give colorless needles; yield (55%); m.p. 158–160°C; IR: $\acute{\upsilon}$ $cm^{-1}$ 1710 (C=O), 695 (C–S); $^1H$ NMR (DMSO-$d_6$): $\delta$ 7.89–6.75 (m, 15H, Ar–H), 3.95 (s, 2H, $CH_2$ in thiazolidine ring), 2.96 (s, 2H, $CH_2$ benzylic); Anal. calcd. for $C_{22}H_{19}NOS$ (345.21): C, 76.53; H, 5.50; N, 4.05; S, 9.26. Found: C, 76.45; H, 5.46; N, 4.06; S, 9.01.

### Synthesis of Compounds 5a,b—General Procedure[25]

A mixture of 3 (3.45 g, 10 mmol) and 3-dicyanomethylidine-2-oxoindolines **4a,b** (10 mmol) in absolute ethanol (20 mL) in the presence of TEA (1 mL) was heated under reflux for 6 h. The reaction mixture

was cooled to room temperature, and the solvent was removed under reduced pressure. The formed product was collected by filtration, dried, and recrystallized from a mixture of ethanol/water (2:1).

### *5-Amino-3-benzyl-6-cyano-2,2-diphenylpyrano[2,3-d]thiazolidine-7-spiro-3′-(indolin-2′-one) (5a)*

Pale brown crystals; yield (60%); m.p. 136–138°C; IR: $\upsilon$ $cm^{-1}$ 3320, 3260 (NH, $NH_2$), 2200 (CN), 1710 (C=O); $^1H$ NMR (DMSO-$d_6$): $\delta$ 10.35 (s, 1H, NH), 7.70–6.61 (m, 19H, Ar—H), 5.00 (s, 2H, $NH_2$), 3.51 (s, 2H, $CH_2$); Anal. calcd. for $C_{33}H_{24}N_4O_2S$ (540.31): C, 73.35; H, 4.44; N, 10.36; S, 5.92. Found: C, 73.25; H, 4.36; N, 10.28; S, 6.00.

### *5-Amino-3-benzyl-6-cyano-2,2-diphenylpyrano[2,3-d]thiazolidine-7-spiro-3′-(1′-methylindolin-2′-one) (5b)*

Pale brown crystals; yield (60%); m.p. 120–122°C; IR: $\upsilon$ $cm^{-1}$ 3340–3200 ($NH_2$), 2200 (CN), 1705 (C=O); $^1H$ NMR (DMSO-$d_6$): $\delta$ 7.89–6.75 (m, 19H, Ar—H), 5.02 (s, 2H, $NH_2$), 3.24 (s, 3H, $CH_3$), 2.51 (s, 2H, $CH_2$); Anal. calcd. for $C_{34}H_{26}N_4O_2S$ (554.32): C, 73.66; H, 4.69; N, 10.10; S, 5.77. Found: C, 73.47; H, 4.39; N, 9.98; S, 5.79.

## Synthesis of Compounds 6a,b—General Procedure

A mixture of **5a** or **5b** (5 mmol) and formic acid (5 mL, 85%) was heated under reflux for 3 h, the reaction mixture was cooled and poured into an ice/water mixture; the formed solid product was filtered off, dried, and recrystallized from ethanol.

### *3-Benzyl-2,2-diphenyl-7(H)-8-oxothiazolino[4,5:2′,3′]pyrano[6′,5′-d]pyrimidine-9-spiro-3′-(indolin-2′-one) (6a)*

Brown crystals; yield (56%); m.p. 120–123°C; IR: $\upsilon$ $cm^{-1}$ 3250 (NH), 1705 (C=O), 1650 (C=N); $^1H$ NMR (DMSO-$d_6$): $\delta$ 10.31 (s, 1H, NH indoline), 8.13–6.83 (m, 20H, Ar—H and CH pyrimidine), 5.49 (s, 1H, NH pyrimidine), 2.51 (s, 2H, $CH_2$); Anal. calcd. for $C_{34}H_{24}N_4O_3S$ (568.31): C, 71.85; H, 4.22; N, 9.85; S, 5.63. Found: C, 71.69; H, 4.20; N, 9.81; S, 5.70.

### *3-Benzyl-2,2-diphenyl-7(H)-8-oxothiazolino[4,5:2′,3′]pyrano[6′,5′-d]pyrimidine-9-spiro-3′-(1′-methylindolin-2′-one) (6b)*

Yellowish brown crystals; yield (50%); m.p. 115–118°C; IR: $\upsilon$ $cm^{-1}$ 3300 (NH), 1705 (C=O), 1655 (C=N); $^1H$ NMR (DMSO-$d_6$): $\delta$ 8.13–6.84 (m, 20H, Ar—H and CH pyrimidine), 5.40 (s, 1H, NH pyrimidine), 3.39 (s, 3H, $CH_3$), 2.51 (s, 2H, $CH_2$); Anal. calcd. for $C_{35}H_{26}N_4O_3S$ (582.32): C, 72.18; H, 4.46; N, 9.61; S, 5.49. Found: C, 72.04; H, 4.31; N, 9.56; S, 5.45.

## Synthesis of 3-Benzyl-2,2-diphenyl-7(H)-6-methyl-8-oxothiazolino[4,5:2′,3′]pyrano [6′,5′-*d*]pyrimidine-9-spiro-3′-(1′-methylindolin-2′-one) (7)

A solution of **5b** (5.54 g, 10 mmol) in $Ac_2O$/pyridine mixture (15 mL, 2/1 v/v) was heated in water bath for 4 h, then cooled to room temperature, poured into an ice/water mixture, the formed solid product was collected by filtration, washed several times with cold water, dried and recrystallized from ethanol to give dark brown crystals; yield (66%); m.p. 151–154°C; IR: $\upsilon$ $cm^{-1}$ 3500 (NH), 1710 (C=O), 1660 (C=N); $^1H$ NMR (DMSO-$d_6$): $\delta$ 8.21–6.85 (m, 19H, Ar—H), 5.40 (s, 1H, NH), 3.39 (s, 3H, $CH_3$), 2.52 (s, 2H, $CH_2$), 2.10 (s, 3H, $CH_3$); Anal. calcd. for $C_{36}H_{28}N_4O_3S$ (596.33): C, 72.50; H, 4.69; N, 9.39; S, 5.36. Found: C, 72.30; H, 4.48; N, 9.25; S, 5.30.

## Synthesis of Compounds 8a,b—General Procedure

A mixture of **5a** or **5b** (5 mmol) and formamide (10 mL) was heated under reflux for 3 h. The reaction mixture was cooled, then poured into an ice/water mixture, and the formed product filtered off, washed several times by cold water, dried, and recrystallized from ethanol.

### *8-Amino-3-benzyl-2,2-diphenylthiazolino[4,5:2′,3′]pyrano [6′,5′-d]pyrimidine-9-spiro-3′-(indolin-2′-ones) (8a)*

Yellowish green crystals; yield (45%); m.p. 144–147°C; IR: $\upsilon$ $cm^{-1}$ 3360–3210 ($NH_2$), 3190 (NH), 1705 (C=O), 1665 (C=N); $^1H$ NMR (DMSO-$d_6$): $\delta$ 10.21 (s, 1H, NH), 8.31-6.91 (m, 20H, Ar—H and CH pyrimidine), 5.43 (s, 2H, $NH_2$), 2.52 (s, 2H, $CH_2$); Anal. calcd. for $C_{34}H_{25}N_5O_2S$ (567.32): C, 71.97; H, 4.40; N, 12.33; S, 5.64. Found: C, 71.86; H, 4.35; N, 12.29; S, 5.52.

### *8-Amino-3-benzyl-2,2-diphenylthiazolino[4,5:2′,3′]pyrano [6′,5′-d]pyrimidine-9-spiro-3′-(1′-methylindolin-2′-one) (8b)*

Green crystals; yield (43%); m.p. 151–154°C; IR: $\upsilon$ $cm^{-1}$ 3360-3210 ($NH_2$), 1705 (C=O), 1660 (C=N); $^1H$ NMR (DMSO-$d_6$): $\delta$ 8.40–6.85 (m, 20H, Ar—H and CH pyrimidine), 5.02 (s, 2H, $NH_2$), 3.51 (s, 3H, $CH_3$), 2.51 (s, 2H, $CH_2$); Anal. calcd. for $C_{35}H_{27}N_5O_2S$ (581.33): C, 72.30; H, 4.64; N, 12.04; S, 5.50. Found: C, 72.23; H, 4.62; N, 11.91; S, 5.41.

## Synthesis of Compounds 9a,b—General Procedure

A mixture of **5a** or **5b** (5 mmol) and malononitrile (0.33 g, 5 mmol) in glacial acetic acid (10 mL) was heated under reflux for 4 h. The reaction mixture was cooled to room temperature, and the formed solid product

was filtered off, washed by cold water, dried, and recrystallized from acetic acid.

### *8-Amino-3-benzyl-6-cyanomethyl-2,2-diphenylthiazolino[4,5:2′,3′]pyrano[6′,5′-d] pyrimidine-9-spiro-3′-( indolin-2′-one) (9a)*

Bright brown crystals; yield (71%); m.p. 168–170°C; IR: $\upsilon$ $cm^{-1}$ 3330–3210 ($NH_2$), 3200 (NH), 2200 (CN), 1715 (C=O); $^1H$ NMR (DMSO-$d_6$): $\delta$ 9.92 (s, 1H, NH), 8.40 (s, 2H, $NH_2$), 7.77–6.50 (m, 19H, Ar—H), 3.99 (s, 2H, $CH_2$), 2.51 (s, 2H, $CH_2$); Anal. calcd. for $C_{36}H_{26}N_6O_2S$ (606.34): C, 71.30; H, 4.28; N, 13.85; S, 5.27. Found: C, 71.18; H, 4.27; N, 13.69; S, 5.19.

### *8-Amino-3-benzyl-6-cyanomethyl-2,2-diphenylthiazolino[4,5:2′,3′]pyrano[6′,5′-d] pyrimidine-9-spiro-3′-(1′-methyl indolin-2′-one) (9b)*

Red crystals; yield (70%); m.p. 160–163°C; IR: $\upsilon$ $cm^{-1}$ 3320–3220 ($NH_2$), 2200 (CN), 1710 (C=O); $^1H$ NMR (DMSO-$d_6$): $\delta$ 8.39 (s, 2H, $NH_2$), 7.71–6.50 (m, 19H, Ar—H), 3.99 (s, 2H, $CH_2$), 3.50 (s, 3H, $CH_3$), 2.52 (s, 2H, $CH_2$); Anal. calcd. for $C_{37}H_{28}N_6O_2S$ (620.35): C, 71.63; H, 4.51; N, 13.54; S, 5.27. Found: C, 71.52; H, 4.42; N, 13.43; S, 5.06.

## Synthesis of Compounds 11a,b—General Procedure

A solution of **5a** or **5b** (5 mmol) in pyridine (15 mL) and phenylisocyanate (0.54 mL, 5 mmol) was heated under reflux for 5 h. After cooling, the reaction mixture was poured into an ice/water mixture, the formed product was collected by filtration, washed by cold water, dried, and recrystallized from ethanol.

### *5(H)-3-benzyl-8-imino-6-oxo-2,2,7-triphenylthiazolino[4,5:2′,3′]pyrano[6′,5′-d] pyrimidine-9-spiro-3′-(indolin-2′-one) (11a)*

Green crystals; yield (70%); m.p. 158–160°C; IR: $\upsilon$ $cm^{-1}$ 3320 (NH), 3290 (NH), 1715 (C=O); $^1H$ NMR (DMSO-$d_6$): $\delta$ 10.32 (s, 1H, NH), 9.75 (s, 1H, NH), 8.61 (s, 1H, NH), 7.85–6.42 (m, 24H, Ar—H), 2.51 (s, 2H, $CH_2$); Anal. calcd. for $C_{40}H_{29}N_5O_3S$ (659.37): C, 72.85; H, 4.39; N, 10.61; S, 4.85. Found: C, 72.63; H, 4.38; N, 10.49; S, 4.71.

### *5(H)-3-Benzyl-8-imino-6-oxo-2,2,7-triphenylthiazolino[4,5:2′,3′]pyrano[6′,5′-d] pyrimidine-9-spiro-3′-(1′-methyl indolin-2′-one) (11b)*

Green crystals; yield (60%); m.p. 170–171°C; IR: $\upsilon$ $cm^{-1}$ 3320 (NH), 3285 (NH), 1710 (C=O); $^1H$ NMR (DMSO-$d_6$): $\delta$ 9.81 (s, 1H, NH), 8.62

(s, 1H, NH), 7.85–6.43 (m, 24H, Ar—H), 3.43 (s, 3H, $CH_3$), 2.56 (s, 2H, $CH_2$); Anal. calcd. for $C_{41}H_{31}N_5O_3S$ (673.38): C, 73.12; H, 4.60; N, 10.39; S, 4.75. Found: C, 73.05; H, 4.50; N, 10.28; S, 4.71.

## Synthesis of Compounds 12a,b—General Procedure

A mixture of **5a** or **5b** (10 mmol), triethyl orthoformate (10 mL), and glacial acetic acid (2 mL) was heated under reflux for 5 h. The reaction mixture was cooled then poured into an ice/water mixture with vigorous stirring, the oily product thus formed was extracted by chloroform, dried using anhydrous $MgSO_4$ overnight, and filtered off. Then the solvent was removed under reduced pressure, and the formed solid product was collected by filtration and recrystallized from benzene.

### *3-Benzyl-6-cyano-2,2-diphenyl-5-ethoxymethiniminopyrano [2,3-d]thiazoline-7-spiro-3′-(indolin-2′-ones) (12a)*

Brown crystals; yield (60%); m.p. 125–127°C; IR: $\upsilon$ $cm^{-1}$ 3200 (NH), 2200 (CN), 1705 (C=O); $^1$H NMR ($CDCl_3$): $\delta$ 10.35 (s, 1H, NH), 7.80–6.80 (m, 19H, Ar—H), 5.10 (s, 1H, CH), 3.95 (q, 2H, $CH_2$), 2.52 (s, 2H, $CH_2$ benzylic), 1.52 (t, 3H, $CH_3$); Anal. calcd. for $C_{36}H_{28}N_4O_3S$ (596.33): C, 72.50; H, 4.69; N, 9.39; S, 5.36. Found: C, 72.39; H, 4.85; N, 9.28; S, 5.29.

### *3-Benzyl-6-cyano-2,2-diphenyl-5-ethoxymethiniminopyrano [2,3-d]thiazoline-7-spiro-3′-(1′-methylindolin-2′-ones) (12b)*

Reddish brown crystals; yield (65%); m.p. 112–114°C; IR: $\upsilon$ $cm^{-1}$ 2200 (CN), 1705 (C=O); $^1$H NMR ($CDCl_3$): $\delta$ 7.85–6.76 (m, 19H, Ar—H), 5.15 (s, 1H, CH), 4.00 (q, 2H, $CH_2$), 3.25 (s, 3H, $CH_3$), 2.56 (s, 2H, $CH_2$ benzylic), 1.05 (t, 3H, $CH_3$); Anal. calcd. for $C_{37}H_{30}N_4O_3S$ (610.34): C, 72.80; H, 4.91; N, 9.17; S, 5.24. Found: C, 72.62; H, 4.85; N, 9.16; S, 5.20.

## Synthesis of Compounds 13a,b: General Procedure

A mixture of **5a** or **5b** (10 mmol) and hydrazine (5 mL, 80% ) in benzene (15 mL) was heated in water bath for 2 h, cooled, the solvent was removed under reduced pressure. The formed solid product was collected by filtration washed by petroleum ether, dried and recrystallized from ethanol.

### *7-Amino-3-benzyl-6-cyano-2,2-diphenyl-8-iminothiazolino [4,5:2′,3′]pyrano[5′,6′-d]pyrimidine-9-spiro-3′-(indolin-2′-ones) (13a)*

Gray crystals; yield (50%); m.p. 140–143°C; IR: $\upsilon$ $cm^{-1}$ 3310–3210 ($NH_2$), 3190 (NH), 1705 (C=O); $^1$H NMR (DMSO-$d_6$): $\delta$ 10.40 (s, 1H,

NH), 10.05 (s, 2H, $NH_2$), 9.05 (s, 1H, NH), 7.94–6.40 (m, 20H, Ar—H and CH pyrimidine), 2.48 (s, 2H, $CH_2$); Anal. calcd. for $C_{34}H_{26}N_6O_2S$ (582.32): C, 70.12; H, 4.46; N, 14.42; S, 5.49. Found: C, 70.01; H, 4.45; N, 14.31; S, 5.40.

### *7-Amino-3-benzyl-6-cyano-2,2-diphenyl-8-imino-thiazolidino[4,5:2′,3′]pyrano[5′,6′-d]pyrimidine -9-spiro-3′-(1′-methylindolin-2′-ones) (13b)*

Green crystals; yield (45%); m.p. 134–136°C; IR: $\upsilon$ $cm^{-1}$ 3310–3200 ($NH_2$), 3190 (NH), 1705 (C=O); $^1H$ NMR (DMSO-$d_6$): $\delta$ 9.95 (s, 2H, $NH_2$), 9.00 (s, 1H, NH), 7.89–6.41 (m, 20H, Ar—H and CH pyrimidine), 3.34 (s, 3H, $CH_3$), 2.51 (s, 2H, $CH_2$); Anal. calcd. for $C_{35}H_{28}N_6O_2S$ (596.33): C, 70.48; H, 4.69; N, 14.08; S, 5.36. Found: C, 70.38; H, 4.60; N, 14.00; S, 5.27.

## REFERENCES


[1] G. S. Singh, T. Singh, and R. Lakhan, *Indian J. Chem. Sect. B*: *Org. Chem. Incl. Med. Chem.*, **36** (B), 95 (1997).
[2] K. H. Chikhalia and K. R. Desia, *J. Inst. Chem.* (*India*), **70,** 121 (1998).
[3] P. Hamley, T. McInally, and A. Tinker, PCT Int. Appl. WO 98 46, 611, (Cl. CO7D491 10), 22 Oct. 1998, SE Appl. 97/1, 396, 15 Apr. 1997; 32 PP.; *Chem. Abstr.*, **129,** 316237f (1998).
[4] L. A. Paquette, T. Lowinger, D. G. Bolin, and B. M. Branan, *J. Org. Chem.*, **61,** 7489 (1996).
[5] A. Miyashita and J. Hama, Jpn. Kokai Tokkyo Koho Jp 08, 245, 627 [96, 245, 62] (Cl. CO7D491/107), 24 Sep. 1996, Appl.95/51, 082, 10 Mar. 1995; 7 PP.; *Chem. Abstr.*, **126,** 18798w (1997).
[6] A. Trani, C. Dallanoce, G. Panzone, F. Ripamonti, B. P. Goldstein, and R. Ciabatti, *J. Med. Chem.*, **40** (6), 967 (1997).
[7] I. V. Manakova, M. A. Gal'bershtam, G. K. Bobyleva, N. M. Prizhiyalgovskaya, and L. N. Kurkovskaya, *Khim. Geterotsikl., Soedin*, **1,** 104 (1988); *Chem. Abstr.*, **110,** 23707q (1989).
[8] P. Czerney and H. Hartmann, *J. Prakt. Chem.*, **324,** 21 (1982).
[9] O. H. Hartwing and S. Herbert, *Montsh. Chem.*, **110,** 279 (1979).
[10] M. Quinteiro, C. Seoane, and J. L. Soto, *J. Heterocycl. Chem.* **15,** 57 (1978).
[11] S. E. Abdou, S. M. Fahmy, K. U. Sadek, and M. H. Elnagdi, *Heterocycles*, **16,** 57 (1981).
[12] H. A. F. Daboun, S. E. Abdou, M. M. Husien, and M. H. Elnagdi, *Synthesis*, **6,** 502 (1982).
[13] G. P. Ellis and G. P. West, *Prog. Med. Chem.*, **10,** 109 (1974).
[14] P. F. Schada, *Top. Curr. Chem.*, **91,** 75 (1980).
[15] S. C. Kuo, L. J. Huang, and H. Nakamura, *J. Med. Chem.*, **27,** 539 (1984).
[16] S. S. Bhagwat, C. Lee, M. D. Cowart, J. McKie and A. L. Grillot, PCT Int. Appl. WO 98 46, 605 (Cl. CO7D471/04) 22 Oct. 1998, U.S. Appl. 838, 216, 16 Apr. 1997; 172 PP.; *Chem. Abstr.*, **129**: 316240b (1998).
[17] T. R. Kelly, Q. Li and V. B. Lohray, U.S. U.S. 5, 166, 208 (Cl. 514-278; CO7D 22/20), 24 Nov. 1992, Appl. 774, 780, 09 Oct. 1991; 22 PP.; *Chem. Abstr.*, **118,** 191434g (1993).
[18] M. S. Al-Thebeiti and M. F. El-Zohry, *Phosphorus, Sulfur, and Silicon*, **88,** 251 (1994).

[19] M. S. Al-Thebeiti and M. F. El-Zohry, *Heterocycles*, **41** (11), 2475 (1995).
[20] M. F. El-Zohry, I. M. A. Awad, Z. A. Hozien, and A. A. Abdel-Hafez, *Indian J. of Chem.*, **32 (**B), 1109 (1993).
[21] A. A. Al-Ahmadi and M. F. El-Zohry, *Phosphorus, Sulfur, and Silicon*, **97,** 35 (1994).
[22] M. S. Al-Thebeiti and M. F. El-Zohry, *Indian J. Chem*., **37 (**B), 804 (1998).
[23] A. A. Abdel-Hafez and M. F. El-Zohry, *Heterocyclic Communications*, **7** (6), 583 (2001).
[24] M. F. El-Zohry, A. A. Al-Ahmadi, and F. A. Aquily, *Heterocyclic Communications*, **8** (2), 187 (2002).
[25] M. F. El-Zohry, Y. A. Elossaily, Th. A. Mohamed, and E. M. Hussein, *Heterocyclic Communications*, 2008, in press.
[26] T. C. Maria, C. Cenzo, L. Valentina, and O. Valentina, *Bioorg. Med. Chem*., **14,** 366 (2006).
[27] P. L. Michael, M. B. Thomas, D. L. Miles, and F. B. Michael, *J. Exper. Marina Biology and Ecology.*, **328,** 10 (2006).
[28] A. Anu, G. Neena, M. S. C. Prem, and G. Suman, *Bioorg. Med. Chem*., **13,** 6678 (2005).