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Full Length Research

Synthesis of some new pyridines, thienopyridines and pyridothienopyrimidines bearing 1,3-diphenyl-1*H*-pyrazole moiety

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Abstract: ***1-phenyl/(2-thienyl)-3-(1,3-Diphenyl-1H-pyrazol-4-yl)-2-propen-1-ones (3a,b) were prepared. Reaction of 3b with hydroxyl amine, phenyl hydrazine or ethyl cyanoacetate gave the corresponding heterocyclic compounds 4, 5 and 6 respectively. Treatment compounds 3a,b with cyanothioacetaimde furnished 3-cyano-4-(1,3-diphenyl-1H-pyrazol-4-yl)-6-phenyl/(2-thienyl)pyridine-2(1H)-thiones (7a,b). Reaction of 7a,b with chloroacetamide, p-methylphenacyl chloride, ethyl chloroacetate, chloro-N-(aryl)acetamides gave S-substituted methylthiopyridines 8a-g. Upon treatment of compounds 8a-g with sodium ethoxide in boiling ethanol, they underwent intramolecular Thorpe-Zeigler cyclization giving 2-functionalized 3-amino-4-(1,3-diphenyl-1H-pyrazol-4-yl)-6-phenyl/(2-thienyl)thieno[2,3-b]pyridines (9a-g). Compounds 9a,c were subjected to some sequence reactions to produce new pyrazolylpyridothienopyrimidines 10a-c, 11a,b and 13-16.***

Key words*: 1,3-diphenylpyrazole, 3-cyanopyridine-2(1H)-thiones, pyrazolylthienopyridines, pyrazolylpyridothienopyrimidines*

INTRODUCTION

Pyrazole derivatives are the subject of many research studies due to their widespread potential biological activities such as antimicrobial (Pimerova and Voronina, 2001), antiviral (Janus *et al.*, 1999), antitumor (Bouabdallah *et al.*, 2006; Park *et al.*, 2005), antihistaminic (Yildirim, 2005), antidepressant (Bailey *et al.*, 1985), insecticides and fungicides (Chu and Cutler, 1986). On the other hand, many pyridines (Ahmed *et al.*, 2009; Amr *et al.*, 2006; Galya *et al.*, 2008; Onnis *et al.*, 2009; Shi *et al.*, 2009; Thapa *et al.*, 2010) and thienopyridines (Bakhite, 2003; Bompart *et al.*, 1988; El-Abadelah *et al.*, 1998; Miki *et al.*, 1999; Furuya *et al.*, 1998; Vieweg *et al.*, 1992; Litvinov *et al.*, 2005) are reported to possess versatile applications as biologically active compounds. In view of the above facts and as a continuation of our previous work on pyridine-containing compounds (Abdel-Rahman *et al.*, 2015; El-Emary and Bakhite, 1999; Mohamed *et al.*, 2007), the present project was planned to synthesize other new heterocyclic compounds containing mainly 4-(1,3-diphenyl-1*H*-pyrazol-4-yl)-6-phenyl/(2-thienyl)pyridine skeleton hoping to get novel compounds with anticipated biological activities.

RESULTS AND DISCUSSION

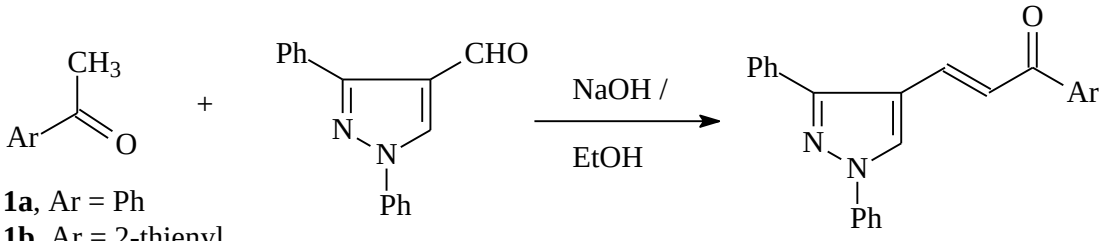
The starting compounds, 1-phenyl or (2-thienyl)-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-2-propen-1-ones **3a,b** were prepared by condensation of acetophenone (**1a**) or 2-acetylthiophene (**1b**) with 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde (**2**) in an ethanolic sodium hydroxide solution (Figure 1).

Compound **3b** underwent a cyclocondensation reaction upon treatment with hydroxylamine hydrochloride in the presence of sodium acetate to give the isooxazoline derivative **4**. By the same manner, the reaction of **3b** with phenyl hydrazine in ethanol produced the pyrazoline compound **5** (Figure 2).

Heating compound **3b** with ethyl cyanoacetate in glacial acetic acid containing an excess amount of ammonium acetate led to the formation of 3-cyanopyridine-2(1*H*)-one **6** in a good yield. The thione analogues **7a,b** were prepared by refluxing

compounds **3a,b** with cyanothioacetamide in ethanol containing catalytic amount of triethylamine (Figure 3).

Reaction of 3-cyanopyridine-2(1*H*)-thiones **7a,b** with some halocompounds namely: chloroacetamide, chloro-*N*-phenylacetamide, chloroacetonitrile, phenacyl bromide, ethyl chloroacetate or chloro-*N*-(*p*-tolyl)acetamide, in the presence of sodium acetate as a basic catalyst produced the corresponding substituted methylthio-pyridines **8a-g**. On treatment of the latter compounds (**8a-g**) with sodium ethoxide in boiling ethanol, they underwent intramolecular *Thorpe-Zeigler*

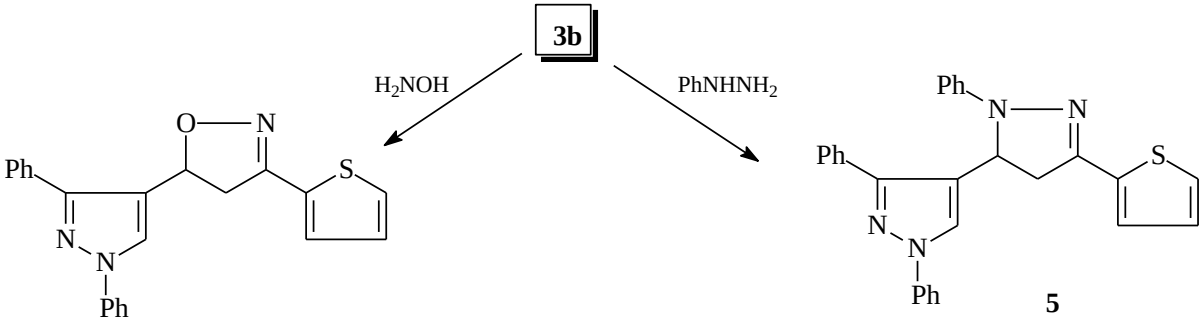


1a, Ar = Ph
1b, Ar = 2-thienyl

2

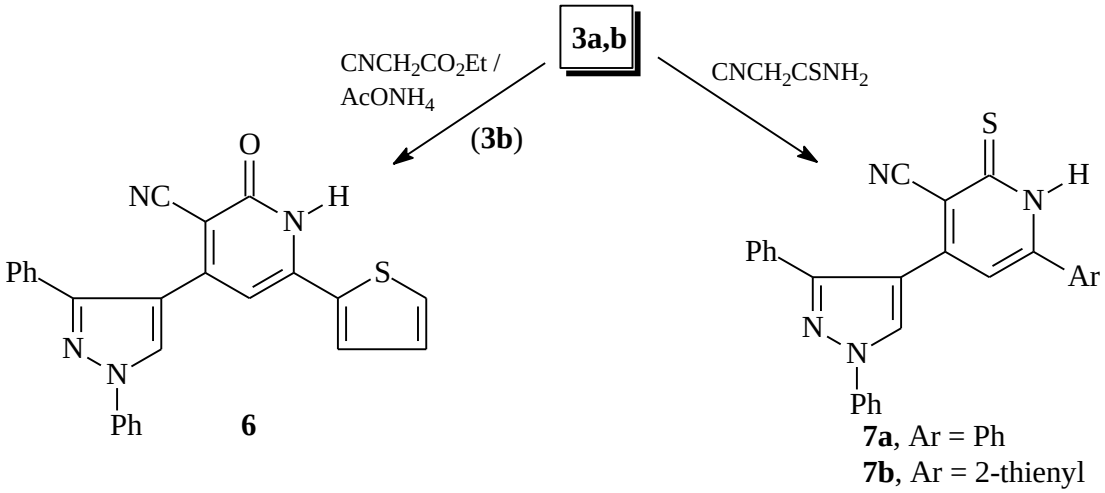
3a, Ar = Ph
3b, Ar = 2-thienyl

Figure 1



4 **5**

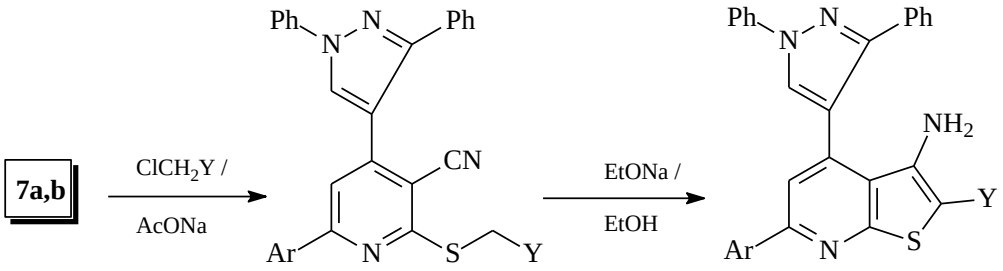
Figure 2



6

7a, Ar = Ph
7b, Ar = 2-thienyl

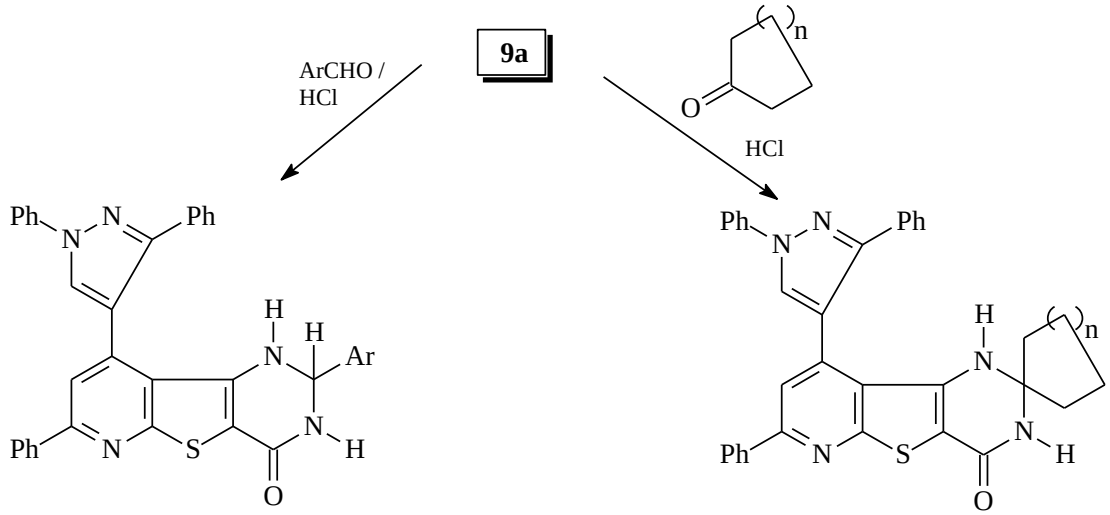
Figure 3



8a, Ar = Ph, Y = $CONH_2$
8b, Ar = Ph, Y = CONHPh
8c, Ar = Ph, Y = CN
8d, Ar = 2-thienyl, Y = CO_2Et
8e, Ar = 2-thienyl, Y = $COC_6H_4Me(p)$
8f, Ar = 2-thienyl, Y = CONHPh
8g, Ar = 2-thienyl, Y = $CONHC_6H_4Me(p)$

9a, Ar = Ph, Y = $CONH_2$
9b, Ar = Ph, Y = CONHPh
9c, Ar = Ph, Y = CN
9d, Ar = 2-thienyl, Y = CO_2Et
9e, Ar = 2-thienyl, Y = $COC_6H_4Me(p)$
9f, Ar = 2-thienyl, Y = CONHPh
9g, Ar = 2-thienyl, Y = $CONHC_6H_4Me(p)$

Figure 4



10 a, Ar = Ph
10 b, Ar = $C_6H_4OMe(p)$
10 c, Ar = $C_6H_4Cl(p)$

11 a, n = 1
11 b, n = 2

Figure 5

cyclization giving 2-functionalized 3-amino-4-(1,3-diphenyl-1*H*-pyrazol-4-yl)-6-phenyl/(2-thienyl)thieno [2,3-*b*]pyridines (**9a-g**) in nearly quantitative yields (Figure 4).

Compound **9a** was reacted with some aromatic aldehydes namely; benzaldehyde, *p*-methoxybenzaldehyde or *p*-chlorobenzaldehyde in ethanol containing few drops of conc. HCl at reflux temperature to give 2-aryl-9-(1,3-diphenyl-1*H*-pyrazol-4-yl)-4-oxo-7-phenyl-1,2,3,4-tetrahydropyrido[3',2':4,5]thieno[3,2-*d*]pyrimidines (**10a-c**). In the same manner, reaction of compound **9a** with cyclopentanone or cyclohexanone furnished the corresponding spiro compounds **11a,b** in excellent yields (Figure 5).

Condensation of *o*-aminocarbonitrile **9c** with triethyl orthoformate, in the presence of acetic anhydride, led to the formation of ethyl *N*-(2-cyano-4-(1,3-diphenyl-1*H*-pyrazol-4-yl)-6-phenylthieno[2,3-*b*]pyridine-3-yl)methanimidate(**12**). Treatment compound **12** with hydrazine hydrate in dioxane at room temperature furnished 3-amino-3,4-dihydro-9-(1,3-

diphenyl-1*H*-pyrazol-4-yl)-4-imino-7-phenylpyrido[3',2': 4,5]thieno[3,2-*d*]pyrimidine(**13**).Heating compound **13** with an excess amount of triethyl orthoformate in the presence of few crystals of *p*-toluene sulphonic acid led to the formation of pyrazolyltriazolopyridothienopyrimidine derivative **14**. Compound **15** was synthesized by reacting **13** with acetic anhydride at reflux temperature. Reaction of compound **13** with neat diethyl malonate gave the expected ethyl7-(1,3-diphenyl-1*H*-pyrazol-4-yl)-9-phenyl[1,2,4]triazolo[2",3"-*c*]pyrido [3',2':4,5]thieno[2,3-*e*]pyrimidine-2-acetate (**16**) (Figure 6).

The structures of all newly synthesized compounds were elucidated and confirmed by elemental analyses, IR and ^{1}H NMR spectral data (*cf*. Experimental part).

Experimental

Melting points were measured with Gallan-Kamp melting-point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 470 IR-spectrophotometer (KBr; ν_{max} in cm^{-1}). ^{1}H-NMR spectra were taken on a Varian EM-390, 90 MHz spectrometer using TMS as internal standard. Chemical shifts are given in δ, ppm. Elemental analyses (C, H, N and S) were performed on an Elemental Analyses system GmbH VARIO EL $V_{2.3}$ 1998 CHNS Mode.

3-(1,3-Diphenyl-1H-pyrazol-4-yl)-1-phenyl-2-propen-1-one (3a)

This compound was prepared according to the reported method (El-Emary and Bakhite, 1999).

*3-(1,3-Diphenyl-1H-pyrazol-4-yl)-1-(2-thienyl)-2-propen-1-one (***3b)**

To a mixture of 1,3-Diphenyl-1*H*-pyrazole-4-carboxaldehyde (**2**) (2.48 g, 10 mmol) and 2-acetylthiophene (**2b**) (1.1 ml, 10 mmol) in ethanol (20 mL), 0.5 mL of aqueous NaOH 10 % was added. The reaction mixture was stirred at room temperature for 3 h whereby a precipitate formed. It was collected and recrystallized from aqueous ethanol as pale yellow crystals of **3b.** Yield: 87 %, m. p.: 182-184°C. IR: 1650 (C=O) cm.$^{-1}$ Elemental Anal. Calculated for $C_{22}H_{16}N_2OS$ (356.44): C, 74.13; H, 4.52; N, 7.86; S, 8.99 %. Found: C, 74.44; H, 4.48; N, 7.61; S, 8.77 %.

5-(1,3-diphenyl-1H-pyrazol-4-yl)-3-(2-thienyl)-Δ^2*-isooxazoline* (**4**)

To a suspension of chalcone **3** (1.78 g, 5 mmol) and hydroxylamine hydrochloride (0.4 g) in ethanol (20 ml), anhydrous sodium acetate (1.0 g) was added. The resulting mixture heated under reflux for 4 h. The solid that formed after cooling and dilution with water (15 ml) was collected and recrystallized from methanol to give white needles of compound **4**.Yield: 68 %; m.p. 150-152°C. IR: 1600 (C=N) cm^{-1}.^{1}H NMR (DMSO-d_6): δ 8.7 (s, 1H, CH pyrazole), 7.2-8.2(m, 13H, aryl and thienyl protons), 4.5-4.7 (t, 1H, CH isooxazole), 3.1-3.3 (d, 2H, CH_2). Elemental Anal. Calculated for $C_{22}H_{17}N_3OS$ (371.46): C, 71.14; H, 4.61; N, 11.31; S, 8.63 %. Found: C, 71.00; H, 4.53; N, 11.25; S, 8.49 %.

5-(1,3-diphenyl-1H-pyrazol-4-yl)-1-phenyl-3-(2-thienyl)-Δ^2*-pyrazoline* (**5**)

A mixture of chalcone **3b** (1.78 g, 5 mmol) and phenyl hydrazine (0.5 ml, 5 mmol) in ethanol (20 ml) was heated under reflux for 4 h. The solid that formed after cooling and dilution with water (15 ml) was collected and recrystallized from methanol to give yellow needles of compound **5**. Yield: 78 %; m.p. 220-222° C. IR: 1600 (C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.8 (s, 1H, CH pyrazole), 7.0-8.2 (m, 18H, aryl and thienyl protons), 4.3-4.6 (t, 1H, CH pyrazoline), 3.0-3.3 (d, 2H, CH_2). Elemental Anal. Calculated for $C_{28}H_{22}N_4S$ (446.57): C, 75.31; H, 4.97; N, 12.55; S, 7.18 %. Found: C, 75.11; H, 4.80; N, 12.64; S, 7.00 %.

3-Cyano-4-(1,3-diphenyl-1H-pyrazol-4-yl)-6-(2-thienyl)pyridine-2(1H)-one (**6**)

A mixture of chalcone **3b** (1.78 g, 10 mmol), ethyl cyanoacetate (2.26 g, 20 mmol) and ammonium acetate (7.7 g, 100 mmol) was heated at 150° C in an oil bath for 3 h. The solid that formed after cooling was collected and recrystallized from acetic acid to give pale yellow crystals of compound **6**. Yield: 62 %; m.p. 260-261°C. IR: 3428 (NH), 2209 (C≡N), 1639 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 9.8 (s, 1H, NH), 9.2 (s, 1H, CH pyrazole), 7.0-8.2 (m, 14H, aryl, pyridyl and thienyl protons). Elemental Anal. Calculated for $C_{25}H_{16}N_4OS$ (420.49): C, 71.41; H, 3.84; N, 13.32; S, 7.62 %. Found: C, 71.47; H, 3.83; N, 13.12; S, 7.55 %.

3-Cyano-4-(1,3-diphenyl-1H-pyrazol-4-yl)-6-phenylpyridine-2(1H)-thione (**7a**)

This compound was prepared by reacting chalcone **3a** with cyanothioacetamide according to the reported method (El-Emary and Bakhite, 1999).

3-Cyano-4-(1,3-diphenyl-1H-pyrazol-4-yl)-6-(2-thienyl)pyridine-2(1H)-thione (**7b**)

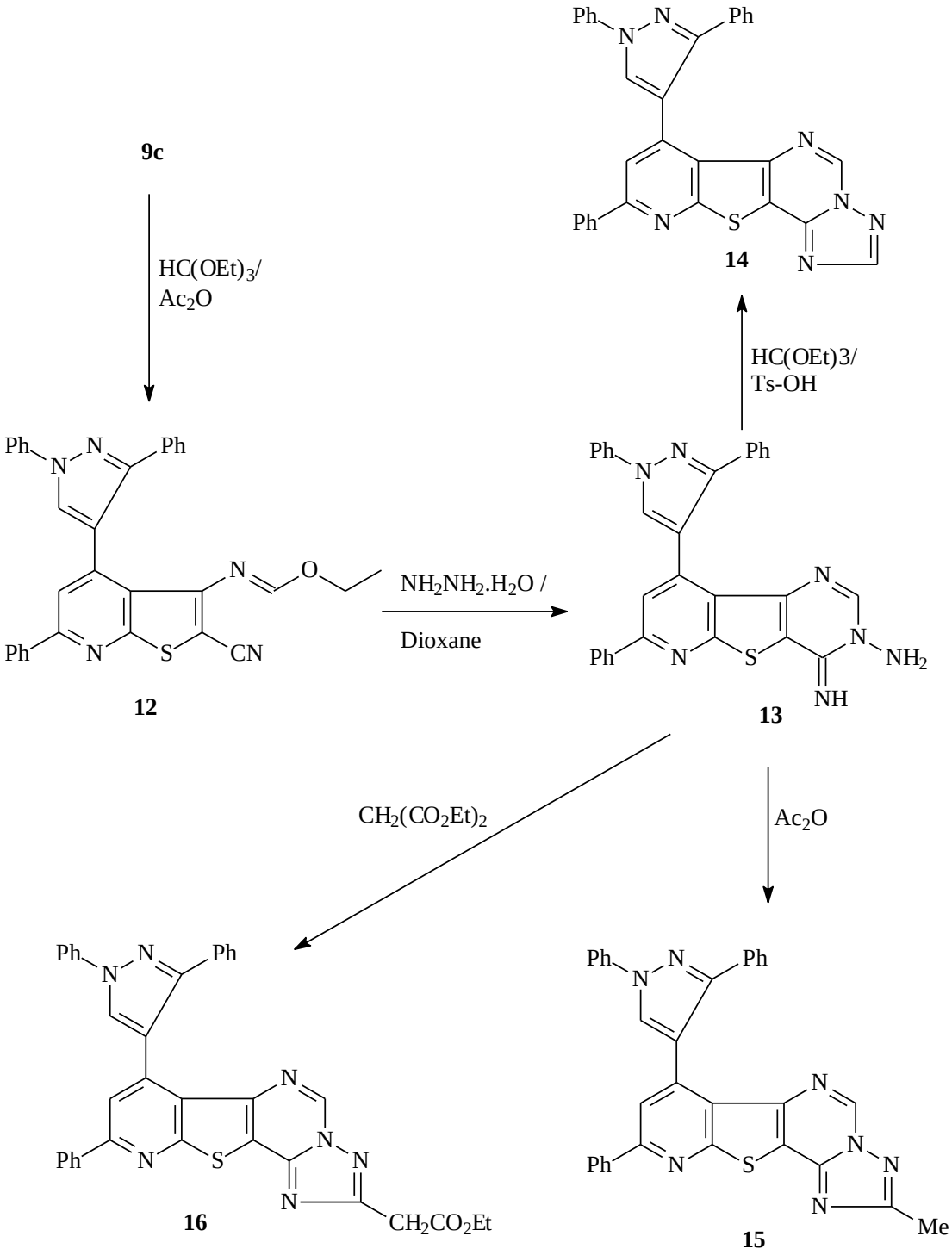


Figure 6

To a solution of chalcone **3b** (3.56 g, 10 mmol) and cyanothioacetamide (1.0 g, 10 mmol) in ethanol (25 ml), few drops of triethylamine were added**.** The resulting mixture was heated under reflux for 3 h. The precipitate that formed while hot was collected and recrystallized from acetic acid to give compound **7b** in the form of orange crystals. Yield: 88 %; m.p.

290-292° C. IR: 3432 (NH), 2214 (CN) cm^{-1}. ^1H NMR (DMSO-d6): δ 12.4 (s, 1H, NH), 9.1 (s, 1H, CH pyrazole), 6.7-8.1 (m, 14H, aryl, pyridyl and thienyl protons). Elemental Anal. Calculated for $C_{25}H_{16}N_4S_2$ (436.55): C, 68.78; H, 3.69; N, 12.83; S, 14.69 %. Found: C, 68.51; H, 3.68; N, 12.63; S, 14.54%.

Reaction of 3-cyanopyridine-2(1H)-thione* 7a,b *with halo compounds; Formation of compounds* 8a-g*; General procedure.

To a suspension of compounds **7a,b** (5 mmol) and sodium acetate trihydrate (1.5 g, 11 mmol) in ethanol (25 ml), the appropriate halo compound (5 mmol) was added. The resulting mixture was heated under reflux for one hour. The precipitate that formed on cooling was collected and recrystallized from ethanol to give compounds **8a-g** in the form of pale yellow needles.

***3-Cyano-4-(1,3-diphenyl-1H-pyrazol-4-yl)-6-phenylpyridin-2-ylthioacetamide* (8a)**

It was prepared according to the reported method (El-Emary and Bakhite, 1999).

***3-Cyano-4-(1,3-diphenyl-1H-pyrazol-4-yl)-6-phenyl-2-(N-phenyl)carbamoyl methylthiopyridine* (8b)**

It was prepared by reaction of **7a** with chloro-*N*-phenylacetamide. Yield: 82 %; m.p.: 255-256° C. IR: 3310 (NH), 2200 (C≡N), 1660 (C=O) $cm.^{-1}$ ^1H NMR (DMSO-d_6): δ 10.5 (s, 1H, NH), 9.3 (s, 1H, CH pyrazole), 7.0-8.1 (m, 21H, aryl and pyridyl protons), 4.3 (s, 2H, SCH_2). Elemental analysis calculated for $C_{35}H_{25}N_5OS$ (563.68): C, 74.58; H, 4.47; N, 12.42; S, 5.69 %. Found: C, 74.88; H, 4.44; N, 12.23; S, 5.60 %.

***3-Cyano-2-cyanomethylthio-4-(1,3-diphenyl-1H-pyrazol-4-yl)-6-phenyl* pyridine (8c)**

It was prepared by reaction of **7a** with chloroacetonitrile. Yield: 80 %; m.p.: 210-211°C . IR: 2230 (C≡N, non conjugated), 2200 (C≡N, conjugated) $cm.^{-1}$ ^1H NMR (DMSO-d_6): 9.2 (s, 1H, CH pyrazole), 7.0-8.0 (m, 16H, aryl and pyridyl protons), 4.4 (s, 2H, SCH_2). Elemental Anal. Calculated for $C_{29}H_{19}N_5S$ (469.56): C, 74.18; H, 4.08; N, 14.91; S, 6.83 %. Found: C, 73.83; H, 3.94; N, 14.98; S, 6.49 %.

3-*Cyano-4-(1,3-diphenyl-1H-pyrazol-4-yl)-2-(p-methylphenacylthio)-6-(2- thienyl)pyridine* (8d)

It was prepared by reaction of **7b** with *p*-methylphenacyl chloride. Yield: 79 %; m.p.: 228-230° C. IR: 2220 (C≡N), 1680 (C=O) $cm.^{-1}$ ^1H NMR (DMSO-d_6): 9.2 (s, 1H, CH pyrazole), 7.0-8.2 (m, 20H, aryl and pydidy protons), 5.1 (s, 2H, SCH_2), 2.0 (s, 3H, CH_3). Elemental analysis calculated for $C_{33}H_{22}N_4OS_2$ (554.68): C, 71.46; H, 4.00; N, 10.10; S, 11.56 %. Found: C, 71.66; H, 4.12; N, 10.00; S, 11.39 %.

***Ethyl (3-cyano-4-(1,3-diphenyl-1H-pyrazol-4-yl)-6-(2-thienyl)pyridin-2-ylthio)acetate* (8e)**

It was prepared by reaction of **7b** with ethyl chloroacetate. Yield: 80 %; m.p.: 175-176 °C. IR: 2210 (C≡N), 1731 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 9.0 (s, 1H, CH pyrazole), 7.1-8.0 (m, 14H, aryl, pyridyl and thienyl protons), 4.0-4.3 (m, 4H: OCH_2 and SCH_2), 1.2-1.4 (t, 3H, CH_3). Elemental Anal. Calculated for $C_{29}H_{22}N_4O_2S_2$ (522.64): C, 66.65; H, 4.24; N, 10.72; S, 12.27%. Found: C, 66.44; H, 4.20; N, 10.51; S, 12.37%.

***3-Cyano-4-(1,3-diphenyl-1H-pyrazol-4-yl)-2-(N-(phenyl))carbamoymethyl-thio)-6-(2-thienyl)pyridine* (8f)**

It was prepared by reaction of **7b** with chloro-*N*-(phenyl)acetamide. Yield: 79 %; m.p. 241-243° C. IR: 3300 (NH), 2220 (C≡N), 1670 (C=O) $cm.^{-1}$ ^1H NMR (DMSO-d_6): δ 10.6 (s, 1H, NH), 9.0 (s, 1H, CH pyrazole), 6.9-8.0 (m, 19H, aryl, pyridyl and thienyl protons), 4.2 (s, 2H, SCH_2). Elemental Anal. Calculated for $C_{33}H_{23}N_5OS_2$ (569.70): C, 69.57; H, 4.07; N, 12.29; S, 11.26%. Found: C, 69.67; H, 4.00; N, 12.11; S, 11.00%.

***3-Cyano-4-(1,3-diphenyl-1H-pyrazol-4-yl)-2-(N-(p-tolyl))carbamoymethyl-thio-6-(2-thienyl)-pyridine* (8g)**

It was prepared by reaction of **7b** with chloro-*N*-(*p*-tolyl)acetamide. Yield: 88 %; m.p. 249-251° C. IR: 3310 (NH), 2200 (C≡N), 1670 (C=O) $cm.^{-1}$ ^1H NMR (DMSO-d6): δ 10.5 (s, 1H, NH), 8.8 (s, 1H, CH pyrazole), 6.9-8.0 (m, 18H, aryl, pyridyl and thienyl protons), 4.2 (s, 2H, SCH_2), 2.1 (s, 3H, CH_3). Elemental Anal. Calculated for $C_{34}H_{25}N_5OS_2$ (583.73): C, 69.96; H, 4.32; N, 12.00; S, 10.98 %. Found: C, 69.89; H, 4.19; N, 12.10; S, 10.82 %.

Cyclization of compounds* 8a-g*; Formation of pyrazolylthienopyridines* 9a-f*; General procedure.

Compound **8a-g** (10 mmol) was suspended in sodium ethoxide solution (0.12 g of sodium in 30 ml of abs. ethanol) and heated under reflux for 5 mins. The yellow precipitate that formed on cooling was collected and recrystallized from an ethanol-chloroform mixture to give **9a-g**.

***3-Amino-4-(1,3-diphenyl-1H-pyrazol-4-yl)-6-phenylthieno[2,3-b]pyridine-2 carboxamide* (9a)**

It was prepared by cyclization of compound **8a** according to the reported method (El-Emary and Bakhite, 1999).

***3-Amino-4-(1,3-diphenyl-1H-pyrazol-4-yl)-6-phenyl-2-(N-phenyl)carbamoyl thieno[2,3-b]pyridine* (9b)**

It was prepared by cyclization of compound **8b**. Yield: 92 %; m.p.: 278-290° C. IR: 3490, 3300, 3150 (NH_2, NH), 1640 (C=O) $cm.^{-1}$ ^1H NMR (DMSO-d_6): 9.9 (s, 1H, NH), 9.2 (s, 1H, CH pyrazole), 7.0-8.1 (m, 21H, aryl and pyridyl protons), 6.1 (s, 2H, NH_2). Elemental analysis calculated for $C_{35}H_{25}N_5OS$ (563.68): C, 74.58; H, 4.47; N, 12.42; S, 5.69 %. Found: C, 74.46; H, 4.46; N, 12.27; S, 5.82 %.

***3-Amino-4-(1,3-diphenyl-1H-pyrazol-4-yl)-6-phenylthieno[2,3-b]pyridine-2 carbonitrile* (9c)**

It was prepared by cyclization of compound **8c.** Yield: 94 %; m.p.: 247-248° C. IR: 3460, 3350 (NH_2), 2200 (C≡N) $cm.^{-1}$ ^1H NMR (DMSO-d_6): 9.3 (s, 1H, CH pyrazole), 7.1-8.2 (m, 16H, aryl and pyridyl protons), 5.8 (s, 2H, NH_2). Elemental Anal. Calculated for $C_{29}H_{19}N_5S$ (469.56): C, 74.18; H, 4.08; N, 14.91; S, 6.83 %. Found: C, 73.83; H, 3.94; N, 14.90; S, 6.49 %.

***3-Amino-2-(p-methylbenzoyl)-4-(1,3-diphenyl-1H-pyrazol-4-yl)-6-(2-thienyl) thieno[2,3-b]pyridine* (9d)**

It was prepared by cyclization of compound **8d**. Yield: 89 %; m.p.: 252-253°C. IR: 3500, 3300 (NH_2), 1630 (C=O) $cm.^{-1}$ ^1H NMR (DMSO-d_6): 9.3 (s, 1H, CH pyrazole), 7.1-8.2 (m, 20H, aryl and pydidy protons), 6.3 (s, 2H, NH_2), 1.9 (s, 3H, CH_3). Elemental analysis calculated for $C_{33}H_{22}N_4OS_2$ (554.68): C, 71.46; H, 4.00; N, 10.10; S, 11.56 %. Found: C, 71.15; H, 4.22; N, 10.04; S, 11.40 %.

***Ethyl 3-amino-4-(1,3-diphenyl-1H-pyrazol-4-yl)-6-(2-thienyl)thieno[2,3-b] pyridine-2-carboxylate* (9e)**

It was prepared by cyclization of compound **8e**. Yield: 91 %; m.p.: 204-205°C. IR: 3500, 3300 (NH_2), 1660 (C=O) $cm.^{-1}$ ^1H NMR (DMSO-d_6): δ 8.9 (s, 1H, CH pyrazole), 7.0-8.0 (m, 14H, aryl, pyridyl and thienyl protons), 5.7 (s, 2H, NH_2), 4.0-4.3 (q, 2H, OCH_2), 1.2-1.4 (t, 3H, CH_3). Elemental Anal. Calculated for $C_{29}H_{22}N_4O_2S_2$ (522.64): C, 66.65; H, 4.24; N, 10.72; S, 12.27%. Found: C, 66.42; H, 4.28; N, 10.65; S, 12.18%.

***3-Amino-4-(1,3-diphenyl-1H-pyrazol-4-yl)-2-(N-(phenyl))carbamoy-6-(2 thienyl)thieno[2,3-b]pyridine* (9f)**

It was prepared by cyclization of compound **8f**. Yield: 98 %; m.p. 259-260° C. IR: 3500, 3300, 3180 (NH_2, NH), 1630 (C=O) $cm.^{-1}$ ^1H NMR (DMSO-d6): δ 9.6 (s, 1H, NH), 9.2 (s, 1H, CH pyrazole), 6.9-8.0 (m, 19H, aryl, pyridyl and thienyl protons), 6.2 (s, 2H, NH_2). Elemental Anal. Calculated for $C_{33}H_{23}N_5OS_2$ (569.70): C, 69.57; H, 4.07; N, 12.29; S, 11.26%. Found: C, 69.33; H, 4.09; N, 12.18; S, 11.06 %.

3-Amino-4-(1,3-diphenyl-1H-pyrazol-4-yl)-2-(N-(p-tolyl))

***carbamoy-6-(2-thienyl)thieno[2,3-b]pyridine* (9g)**

It was prepared by cyclization of compound **8g**. Yield: 95 %; m.p. 281-282° C. IR: 3480, 3310, 3160 (NH_2, NH), 1630 (C=O) $cm.^{-1}$ ^1H NMR (DMSO-d_6): δ 10.0 (s, 1H, NH), 8.9 (s, 1H, CH pyrazole), 7.1-8.2 (m, 18H, aryl, pyridyl and thienyl protons), 5.9 (s, 2H, NH_2), 2.0 (s, 3H, CH_3),. Elemental Anal. Calculated for $C_{34}H_{25}N_5OS_2$ (583.73): C, 69.96; H, 4.32; N, 12.00; S, 10.98%. Found: C, 69.88; H, 4.48; N, 12.26; S, 11.06 %.

Reaction of compound* 9a *with aromatic aldehydes or cycloalkanones; Formation of compounds* 10a-c *and* 11a,b*; General procedure.

To a mixture of **9a** (0.97 g, 2 mmol) and the respective aldehyde or cycloalkanone (2 mmol) in absolute ethanol (15 ml), few drops of conc. HCl were added. The reaction mixture was heated under reflux for 3 h. The product that formed on cooling was collected and recrystallized from dioxane as yellow needles of **10a-c** or **11a,b**.

***2,7-Diphenyl-9-(1,3-diphenyl-1H-pyrazol-4-yl)-4-oxo-1,2,3,4-tetrahydro-pyrido[3',2':4,5]thieno[3,2-d]pyrimidine* (10a).**

It was prepared by using benzaldehyde. Yield: 97 %; m. p.: 304-306° C. IR: 3410 (NH), 3171 (NH), 1645 (C=O) cm^{-1}. ^1H NMR (CD_3CO_2D): δ 9.3 (s, 1H, CH pyrazole), 7.4-8.4 (m, , 21H, aryl and pyridyl protons), 6.1 (s, 1H, CH at C-2). Elemental Anal. Calculated for $C_{36}H_{25}N_5OS$ (575.69): C 75.11; H, 4.38; N, 12.17; S, 5.57 %. Found: C, 75.01; H, 4.33; N, 12.00; S, 5.77 %.

9-(1,3-Diphenyl-1H-pyrazol-4-yl)-2-(4-methoxyphenyl)-4-oxo-7-phenyl-1,2,3,4-tetrahydropyrido[3',2':4,5]thieno[3,2d]pyrimidine (10b).

It was prepared by using 4-methoxybenzaldehyde. Yield: 98 %; m. p.: 308-309°C. IR: 3406 (NH), 3188 (NH), 1643 (C=O) cm^{-1}. ^1H NMR (CD_3CO_2D): δ 9.2 (s, 1H, CH pyrazole), 7.2-8.3 (m, 20H, aryl and pyridyl protons), 6.0 (s, 1H, C-2), 4.1 (s, 3H, OCH_3). Elemental Anal. Calculated for $C_{37}H_{27}N_5O_2S$ (605.71): C, 73.37; H, 4.49; N, 11.56; S, 5.29 %. Found: C, 73.41; H, 4.51; N, 11.35; S, 5.09 %.

***2-(4-Chlorophenyl)-9-(1,3-diphenyl-1H-pyrazol-4-yl)-4-oxo-7-phenyl-1,2,3,4-tetrahydropyrido[3',2':4,5]thieno[3,2-d]pyrimidine* (10c).**

It was prepared by using 4-chlorobenzaldehyde. Yield: 95 %; m. p.: 309-310°C. IR: 3413 (NH), 3169 (NH), 1645 (C=O) cm^{-1}. ^1H NMR (CD_3CO_2D): δ 9.2 (s, 1H, CH pyrazole), 7.4-8.4 (m, 20H, aryl and pyridyl protons), 6.2 (s, 1H, CH at C-2). Elemental Anal. Calculated for $C_{36}H_{24}ClN_5OS$ (610.13): C, 70.87; H, 3.96; N, 11.48; S, 5.25 %. Found: C, 70.67; H, 3.97; N, 11.84; S, 5.20 %.

***9-(1,3-Diphenyl-1H-pyrazol-4-yl)-4-oxo-7-phenyl--2,2-tetramethylene-1,2,3,4-tetrahydropyrido[3',2':4,5]thieno[3,2-d]pyrimidine* (11a).**

It was prepared by using cyclopentanone. Yield: 98 %; m. p.: 302-304°C. IR: IR: 3411 (NH), 3160 (NH), 1640 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 9.1 (s, 1H, CH pyrazole), 7.0-8.1 (m, 16H, aryl and pyridyl protons), 6.7 (s, 1H, CONH), 3.7 (s, 1H, NH), 1.6-2.0 (m, 6H, $(CH_2)_3$ of cyclopentylidene ring), 1.2-1.4 (m, 2H, CH_2 of cyclopentylidene ring). Elemental Anal. Calculated for $C_{34}H_{27}N_5OS$ (553.68): C,73.76; H, 4.92; N, 12.65; S, 5.79 %. Found: C, 73.51; H, 4.87; N, 12.95; S, 5.62 %.

***9-(1,3-Diphenyl-1H-pyrazol-4-yl)-4-oxo-2,2-pentamethylene-7-phenyl-1,2,3,4-tetrahydropyrido[3',2':4,5]thieno[3,2-d]pyrimidine* (11b).**

It was prepared by using cyclohexanone. Yield: 94 %; m. p.: 311-312°C. IR: 3418 (NH), 3169 (NH), 1639 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 9.2 (s, 1H, CH pyrazole), 7.2-8.3 (m, 16H, aryl and pyridyl protons), 6.6 (s, 1H, CONH), 3.5 (s, 1H, NH), 1.8-2.3 (m, 4H, $(CH_2)_2$ of cyclohexylidene ring), 1.3-1.7 (m, 4H, $(CH_2)_2$ of cyclohexylidene ring), 0.7-0.9 (m, 2H, (CH_2) of cyclohexylidene ring). Elemental Anal. Calculated for $C_{35}H_{29}N_5OS$ (567.71): C, 74.05; H, 5.15; N, 12.34; S, 5.65 %. Found: C, 74.00; H, 5.12; N, 12.16; S, 5.71 %.

***Ethyl N-(2-cyano-4-(1,3-diphenyl-1H-pyrazol-4-yl)-6-phenylthieno[2,3-b] pyridin-3-yl)methanimidate* (12)**

A mixture of compound **9c** (2.35 g, 5 mmol), triethyl orthoformate (7 ml) and acetic anhydride (20 ml) was refluxed for 4 h. The precipitate that formed after cooling was collected and recrystallized from ethanol as pale yellow plates of **12**. Yield: 81 %; m. p.: 216-218°C. IR: 2225 (C≡N). Elemental Anal. Calculated for $C_{32}H_{23}N_5OS$ (525.63): C, 73.12; H, 4.41; N, 13.32; S, 6.10 %. Found: C, 73.03; H, 4.33; N, 13.02; S, 6.00 %.

***3-Amino-3,4-dihydro-9-(1,3-diphenyl-1H-pyrazol-4-yl)-4-imino-7-phenyl-pyrido[3',2':4,5]thieno[3,2-d]pyrimidine* (13)**

To a suspension of compound **12** (2.10 g, 4 mmol) in dioxane (15 ml), hydrazine hydrate 99 % (2 ml) was added. The resulting mixture was stirred at room temperature for 4 h. The product that formed was collected and recrystallized from ethanol to give fine white needles of **13**. Yield: 81 %; m. p.: 249-251° C. IR: 1731 (C=O). Elemental Anal. Calculated for $C_{30}H_{21}N_7S$ (511.60): C, 70.43; H, 4.14; N, 19.16; S, 6.27 %. Found: C, 70.18; H, 3.96; N, 18.95; S, 6.14 %.

***7-(1,3-Diphenyl-1H-pyrazol-4-yl)-9 phenyl[1,2,4]triazolo[2'',3''-c]pyrido[3',2':4,5]thieno[2,3e]pyrimidine* (14)**

To a solution of compound **13** (1.02 g, 2 mmol) in triethyl orthoformate (10 ml), few crystals of *p*-toluenesulphonic acid were added. The reaction mixture was heated under reflux for 4 h. The precipitate that formed while hot was collected and recrystallized from an ethanol-chloroform mixture to give white needles of **14**. Yield: 76 %; m. p.: 204-206° C. IR: 1731 (C=O). Elemental Anal. Calculated for $C_{31}H_{19}N_7S$ (521.60): C, 71.38; H, 3.67; N, 18.80; S, 6.15 %. Found: C, 71.17; H, 3.82; N, 18.60; S, 6.12 %.

***7-(1,3-Diphenyl-1H-pyrazol-4-yl)-2-methyl-9-phenyl[1,2,4]triazolo[2'',3''-c]pyrido[3',2':4,5]thieno[2,3-e]pyrimidine* (15)**

Compound **13** (1.02 g, 2 mmol) in acetic anhydride (10 ml) was heated under reflux for 3 h. The crystalline precipitate that formed on cooling was collected by filtration and recrystallized from ethanol as white crystals of **15**. Yield: 80 %; m. p.: 267-269° C. IR: 1731 (C=O). Elemental Anal. Calculated for $C_{32}H_{21}N_7S$ (535.63): C, 71.76; H, 3.95; N, 18. 31; S, 5.99 %. Found: C, 71.33; H, 3.87; N, 18. 20; S, 5.61 %.

***Ethyl 7-(1,3-diphenyl-1H-pyrazol-4-yl)-9-phenyl[1,2,4]triazolo[2'',3''-c]pyrido[3',2':4,5]thieno[2,3-e]pyrimidine-2-acetate* (16)**

A suspension of compound **13** (1.02 g, 2 mmol) in diethyl malonate (12 ml) was gently heated under reflux for 2 h. The reaction mixture was triturated with ethanol (15 ml) and then allowed to cool. The formed precipitate was collected and recrystallized from an ethanol-chloroform mixture as pale yellow needles of **16**. Yield: 73 %; m.p. 228-229 ° C. IR: 1731 (C=O). ^{1}H NMR ($CDCl_3$): δ 9.2 (s, 1H, CH pyrazole), 8.6 (s, 1H, CH pyrimidine), 7.2-8.2 (m, 16H, aryl and pyridyl protons), 4.2-4.5 (q, 2H, OCH_2), 4.0 (s, 2H, CH_2), 1.2-1.5 (t, 3H, CH_3). Elemental Anal. Calculated for $C_{35}H_{25}N_7O_2S$ (607.69): C, 69.18; H, 4.15; N, 16.13; S, 5.28 %. Found: C, 69.46; H, 4.31; N, 16.00; S, 5.32 %.

Conflict of interest

Authors have none to declare

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