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New Method for Efficient Synthesis of 4,8-dioxothienopyrimidine Derivatives: an Important Synthon for the Carbazol Derivatives

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Abstract: The synthesis of the title compounds was achieved using ethyl 2-amino-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**1**) as a starting material. The reaction of the amino ester **1** with phenylisothiocyanate in boiling ethanol or triethylformate afforded the thiourea derivative **2** and compound **1'**. Cyclisation of compound **2** and **1'** via appropriate methods and hydrazine hydrate allowed obtaining different compounds **3a** and **3b**. The amino anilino **3a** and amino **3b** were used as a useful synthon in the synthesis of several heterocycles derivatives such as Schiff bases **(5a,b-12a,b)** and carbazole derivatives **[19 ,20 (a,b)** and **16-18 (a,b)]**.

Key words: Pyrimidine · Thienopyrimidines · 4,8-dioxo thienopyrimidincarbazole

INTRODUCTION

Thienopyrimidine derivatives are considerable interest not only for their potential biological activity but also for their versatility as synthons in organic transformations. Pyrimidine and thienopyrimidine derivatives and heterocyclic annulated has acquired conspicuous popularity in recent years because of their wide spectrum of biological activity, including anticancer [1,2], antiviral [3], antitumo [4,5], antianaphylactic [6], anti-inflammatory[7] and antimicrobial activities [8]. Moreover, biological activities of some thienopyrimidines derivatives have been reviewed [9]. The carbazol derivatives were screened for antifungal and antibacterial activity, most of these compounds exhibited a moderate activity [10].

We describe herein the synthesis of new novel pentacyclic structure **[13-15(a,b)and19a,b]** by cyclisatione of the hydrazones intermediate compounds under Fischer indole synthesis conditions.

MATERIALS AND METHODS

All melting points were uncorrected and measured using a capillary melting point apparatus. The IR spectra were recorded on a Shimadzu 470 IR-Spectrophotometer using KBr wafer technique. ^{1}H-NMR spectra were measured in $CDCl_3$ and DMSO-d_6 and were determined on a Varian Mercury (300 and 90 MHz) spectrometer (Varian, UK) and chemical shifts were expressed in ppm relative to $SiMe_4$ as internal standard. Elemental analyses were carried out using a Perkin-Elmer 240C Microanalyzer, and the results were in an acceptable range.

Ethyl2-(Anilinocarbothioyl)amino-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate(2): To a solution of amino ester **1** (0.03 mol) in ethanol (25 ml), the phenylisothiocyanate (4.2 g, 0.03 mol) was added dropwise. After the addition was completed the mixture was refluxed for 2h. After cooling, the solvent was evaporated under reduced pressure to third volume and the resulting precipitate was filtered and recrystallized from ethanol to give a yellow needles (Yield%: 86), mp. 138 -140°C.

^{1}H-NMR (DMSO-d_6, δ ppm):1.35 (t, 3H, J=7.0Hz, $COOCH_2\underline{CH_3}$), 2.03 (t, 2H, CH_2), 2.60 (t, 2H, CH_2), 3.16 (t, 2H, CH_2), 4.25 (q, 2H, $COO\underline{CH_2}CH_3$), 7.23 (t, 2H, ArH), 7.37 (t, 2H, J=7.3Hz, ArH), 7.46 (m, 1H, ArH), 10.2 (brs, 2H,2NH). IR (KBr, υ cm^{-1}) :3180 (NH), 1720 (C=O).1620 (C=O), 1180 (C=S).

Anal. Calcd% for $C_{18}H_{18}N_2O_3S_2$(374.48) : C, 57.73;H, 4.84;N,7.48. Found%: C,57.63; H, 4.88; N, 7.37.

3-amino-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzo [4,5]thieno[2,3-*d*]pyrimidine (3a): A mixture of the amino ester compound 1 (0.06 mol) and triethyl orthoformate (5 ml) was maintained at reflux for 4 h. After cooling, the excess of triethyl orthoformate was removed, and the oil

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material obtained was used directly without purification in the next step. A mixture of the latter intermediate and excess of hydrazine hydrate (5 ml) in ethanol (10 ml) was refluxed for 1h. The solvent was then removed under reduced pressure. The solid product obtained was triturated with water, filtered and recrystallized from ethanol into pale buff crystals (Yield%: 78), mp. 215 - 216 °C.^{1}H-NMR (DMSO-d_6, δ ppm): 2.11 (m, 2H, CH_2), 2.55 (t, J = 6 Hz, 2H, CH_2), 2.18 (t, J = 5.6 Hz, 2H, CH_2), 4.23 (bs, 2H, NH_2), 8.55 (bs, 1H, N=CH). IR (KBr, υ cm^{-1}) :3300, 3350, (NH_2),1730 (C=O), 1660 (C=O) Anal. Calcd% for $C_{10}H_9N_3O_2S$ (235.26): C, 51.05; H, 3.86; N, 17.86. Found%: C, 51.16; H, 3.93; N, 17.81.

3-amino-2-anilino-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzo [4,5]thieno[2,3-*d*]pyrimidine (3b): A mixture of **2** (0.06 mol) and excess hydrazine hydrate (5 ml) was heated under reflux for 10 h. After cooling, the precipitate formed was filtered, dried and recrystalized from ethanol to give yellow crystals (Yield%: 78), mp. 273 - 275°C. ^{1}H-NMR ($CDCl_3$, δ ppm): 2.08 (m, 2H, CH_2), 2.64 (t, J = 6 Hz, 2H, CH_2), 3.08 (t, J = 5.6 Hz, 2H, CH_2), 4.19 (bs, 2H, NH_2), 6.06 (t, J = 7.1 Hz, 2H, Ar-H), 6.42 (t, 1H, J = 7.3 Hz, Ar-H), 7.61 (d, J = 7.6 Hz, 2H, Ar-H), 8.22 (bs, 1H,NH). IR (KBr, υ cm^{-1}) : 3350, 3390 (NH_2), 3200 (NH), 1720 (C=O), 1660 (C=O).

Anal. Calcd% for $C_{16}H_{14}N_4O_2S$ (326.37): C, 58.88; H, 4.32; N, 17.17. Found%: C, 58.81; H, 4.12; N, 17.03.

Compounds (4a,b)

General Procedure: A mixture of compounds **3a** or **3b** (0.07 mol), cyclohexanone (6.87 g, 0.07 mol) in ethanol (5 ml) was refluxed for 4 h. After cooling, the solid precipitate was filtered off and recrystallized from appropriate solvents

3-(Cyclohexylidenamino)-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine (4a): This compound was obtained as a white powder from ethanol/dioxane mixture, (Yield%: 79), mp. 174-176 °C.^{1}H-NMR (DMSO-d_6, δ ppm): 2.14 (m, 2H, CH_2), 2.18-2.67 (m, 10H, $5CH_2$), 2.69 (t, 2H, J = 6 Hz,CH_2), 3.08 (m, 2H, CH_2), 8.23 (s, 1H, CH=N). IR (KBr, υ cm^{-1}) :1710 (C=O), 1640 (C=O).

Anal. for $C_{16}H_{17}N_3O_2S$ (315.39) Calcd%: C, 60.93; H, 5.43; N, 13.32. Found%: C, 61.01; H, 5.56; N, 13.18.

2-anilino-3-(Cyclohexylidenamino)-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine (4b): This compound was obtained as a yellow powder from dioxane, (Yield%: 48), mp. 185-187 °C.^{1}H-NMR ($CDCl_3$, δ ppm): 2.19-2.57 (m, 10H, $5CH_2$), 2.09 (m, 2H, CH_2), 2.61 (t, 2H, J = 6 Hz, CH_2), 3.01 (m, 2H, CH_2), 6.63 -7.17 (m, 5H, Ar-H), 7.88 (s,1H, NH). IR (KBr, υ cm^{-1}) :3180 (NH), 1720 (C=O), 1660 (C=O).

Anal. for $C_{22}H_{22}N_4O_2S$ (406.50) Calcd%: C, 65.00; H, 5.46; N, 13.78. Found%: C, 64.88; H, 5.56; N, 13.91.

3-(Arylidene)amino-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzo [4,5]thieno[2,3-*d*] pyrimidine (5a-12a). And 2-anilino-3-(Arylidene)amino-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-d]pyrimidine(5b-12b): General Procedure: A mixture of equimolar amounts (0.01 mol) of compounds **(3a)** or **(3b)** and the appropriate aromatic aldehyde in ethanol (10 ml) was refluxed for 3 h. After cooling, the solid precipitate was collected by filtration and recrystallized from the appropriate solvent.

3-(Benzylidene)amino-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzo [4,5]thieno[2,3-*d*]pyrimidine (5a): This compound was obtained as a white powder from ethanol, (Yield%: 86), mp.132-133 °C.^{1}H-NMR ($CDCl_3$, δ ppm): 2.17 (dd, 2H, CH_2), 2.59 (t, 2H, CH_2), 3.02 (t, 2H, CH_2), 7.03-7.18 (m, 5H, Ar-H), 8.21 (s, 1H, N=CH), 8.38 (s, 1H, N=CH). IR (KBr, υ cm^{-1}) :3100 (CH arom), 1720 (C=O), 1660 (C=O), 1590 (C=C).

Anal. for $C_{17}H_{13}N_3O_2S$ (323.37) Calcd%: C, 63.14; H, 4.05; N, 12.99. Found%: C, 63.05; II, 4.25; N,13.08.

2-anilino-3-(Benzylidene)amino-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine (5b): This compound was obtained as a yellowish powder from ethanol, (Yield%: 66), mp.181 -182 °C.^{1}H-NMR ($CDCl_3$, δ ppm): 2.19 (m, 2H, CH_2), 2.56 (t, 2H, CH_2), 3.08 (t, 2H, CH_2), 6.03-7.48 (m, 10H, Ar-H), 8.21 (s, 1H, N=CH), 8.38 (brs, 1H, NH). IR (KBr, υ cm^{-1}) :3200 (NH), 3100 (CH arom.), 1650 (C=O), 1730 (C=O).

Anal. for $C_{23}H_{18}N_4O_2S$ (414.48) Calcd%: C, 66.65; H, 4.38; N, 13.52. Found%: C, 66.81; H, 4.58; N,13.62.

3-(4-chlorobenzylidene)amino-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine (6a): This compound was obtained as a buff powder from ethanol, (Yield%: 84), mp. 238 -239°C.^{1}H-NMR (DMSO-d_6, δ ppm): 2.30 (dd, 2H, CH_2), 2.66 (t, 2H, J=6,CH), 3.04 (t, 2H, J=6,CH_2), 7.35 (d, J = 8Hz, 2H, H, Ar-H),7.53 (m, 2H, Ar-H), 7.60 (m, H, Ar-H), 8.08 (s,1H, N=CH), 8.29 (s,1H, N=CH). IR (KBr, υ cm^{-1}) :3100 (CH arom.), 1720 (C=O), 1640 (C=O), 1590 (C=C).

Anal. for $C_{17}H_{12}ClN_3O_2S$ (357.81) Calcd%: C, 57.06; H, 3.38; N,11.74. Found%: C, 56.96; H, 3.18; N, 11.84.

2-anilino-3-(4-chlorobenzylidene)amino-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]Pyrimidine (6b): This compound was obtained from ethanol as yellow crystals, (Yield%: 59), mp. 113 -115°C. ^{1}H-NMR ($CDCl_3$, δ ppm): 2.21 (dd, 2H, CH_2), 2.69 (t, 2H, J=6, CH_2), 3.12 (t, 2H, J=6, CH_2), 7.23 -7.30 (m, 5H, Ar-H), 7.40-7.97 (m, 4H, H, Ar-H), 8.21 (s, 1H, CH=N), 8.29 (brs, 1H, NH). IR (KBr, υ cm^{-1}) :3200 (NH), 1660 (C=O), 1710 (C=O).

Anal. for $C_{23}H_{17}ClN_4O_2S$ (448.93) Calcd%: C, 61.54; H, 3.82; N, 12.48. Found%: C, 61.43; H, 3.93; N, 12.30.

3-(4-bromobenzylidene)amino-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine (7a): This compound was obtained from dioxane as yellow crystals, (Yield%: 93), mp.161 -162 °C. ^{1}H-NMR (DMSO-d_6, δ ppm): 2.19 (m, 2H, CH_2), 2.66 (t, 2H, J=6,CH_2), 3.10 (t, 2H, J=6, CH_2), 7.41-8.25 (m, 4H, Ar-H), 8.49 (s,1H, N=CH), 8.59 (s, 1H, N=CH). IR (KBr, υ cm^{-1}): 1720 (C=O),1660 (C=O).

Anal. for $C_{17}H_{12}BrN_3O_2S$ (402.27) Calcd%: C, 50.76; H, 3.01;N, 10.45. Found%: C, 50.78; H, 2.91; N, 10.63.

2-anilino-3-(4-bromobenzylidene)amino-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]Pyrimidine (7b): This compound was obtained from ethanol/water as a pale yellow crystals, (Yield%: 48), mp.197-199°C. ^{1}H-NMR ($CDCl_3$, δ ppm): 2.17 (dd, 2H, CH_2), 2.45 (t, 2H, J=6, CH_2), 3.14 (t, 2H, J=6, CH_2), 7.16 -7.25 (m,5H,Ar-H), 7.40 (d, *J* = 6 Hz, 2H, Ar-H), 7.56 (m, 2H, Ar-H), 8.30 (s,1H, CH=N), 8.52 (brs, 1H, NH). IR (KBr, υ cm^{-1}) :3250 (NH), 1710 (C=O), 1660 (C=O).

Anal. for $C_{23}H_{17}BrN_4O_2S$ (493.38) Calcd%: C, 55.99; H, 3.47; N, 11.36. Found%: C, 56.09; H, 3.44; N,11.23.

3-(4-methylbenzylidene)amino-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine (8a): This compound was obtained from ethanol as a colorless crystals, (Yield%: 88), mp.151-152°C. ^{1}H-NMR ($CDCl_3$, δ ppm): 2.14 (dd, 2H, CH_2), 2.46 (s, 3H, CH_3), 2.56 (t, 2H, J=6, CH_2); 3.11(t, 2H, J=6,CH_2),7.11 (m, 2H, Ar-H), 7.31 (m, 2H, Ar-H), 8.21 (s,1H,N=CH), 8.60 (s,1H, N=CH). IR(KBr, υ cm^{-1}) :1710 (C=O),1640 (C=O).

Anal. for $C_{18}H_{15}N_3O_2S$ (337.40) Calcd%: C, 64.08; H, 4.48; N, 12.45. Found%: C, 64.18; H, 4.32; N, 12.39.

2-anilino-3-(4-methylbenzylidene)amino-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]Pyrimidine (8b): This compound was obtained from ethanol/water as a yellow crystals, (61), mp.170-171°C. ^{1}H-NMR (DMSO-d_6, δ ppm): 2.18 (dd, 2H, CH_2), 2.37 (t, 2H, J=6,CH_2), 2.39 (s, 3H, CH_3), 3.14 (t, 2H, J=6,CH_2), 7.12-7.32 (m,5H,Ar-H), 7.40 -8.56 (m, 4H, Ar-H), 8.26 (s, 1H, CH=N), 8.51 (brs, 1H, NH). IR (KBr, υ cm^{-1}) :3250 (NH), 1710 (C=O), 1670 (C=O).

Anal. for $C_{24}H_{20}N_4O_2S$ (428.51) Calcd%: C, 67.27; H, 4.70; N, 13.07. Found%: C, 67.17; H, 4.74; N, 13.01.

3-(3-nitrobenzylidene)amino-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine (9a): This compound was obtained from ethanol as a yellowish crystals, (Yield%: 42), mp.185-186°C. ^{1}H-NMR ($CDCl_3$, δ ppm): 2.11 (m, 2H, CH_2), 2.69 (t, 2H, CH_2), 3.12 (t, 2H, CH_2), 7.23 (d, 2H, J=8, Ar-H), 7.83 (d, 2H, J=8.8, Ar-H), 8.19 (s, H, N-CH), 8.54 (s, 1H, N=CH). IR (KBr, υ cm^{-1}) : 1710 (C=O),1620 (C=O).

Anal. for $C_{17}H_{12}N_4O_4S$ (368.37) Calcd%: C, 55.43; H, 3.28; N, 15.21. Found%: C, 55.33; H, 3.34; N, 15.06.

2-anilino-3-(4-nitrobenzylidene)amino-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]Pyrimidine (9b): This compound was obtained from ethanol as a colorless crystals, (Yield%: 92), mp.108 -109°C,. ^{1}H-NMR (C,DC,l_3, δ ppm): 2.18 (dd, 2H, C,H_2), 2.37 (t, 2H, J=6, C,H_2), 3.14 (t, 2H, J=6,C,H_2), 7.32 (m, 5H, Ar-C,H), 7.36-7.56 (m, 4H, Ar-H), 7.67 (s, 1H, C,H=N), 8.52 (brs, 1H, NH). IR (KBr, υ C,m^{-1}) :3130 (NH), 1710 (C,=O), 1620 (C=O).

Anal. for $C_{23}H_{17}N_5O_4S$ (459.48) Calcd%: C, 60.12; H, 3.73; N, 15.24. Found%: C, 59.99; H, 3.83; N,15.12.

3-(2-hydroxybenzylidene)amino-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine(10a): This compound was obtained from ethanol as a yellowish crystals, (Yield%: 32), mp.118 -119°C. ^{1}H-NMR (DMSO-d_6, δ ppm): 2.15 (m, 2H, CH_2), 2.69 (t, 2H, CH_2), 3.12 (t, 2H, CH_2), 7.34 (m, 1H, Ar-H), 7.56 (m, 2H, Ar-H), 7.97 (m, 4H, Ar-H), 7.99 (s, H, N=CH), 8.54 (s, 1H, N=CH),11.11 (bros, 1H, OH).IR (KBr, υ cm^{-1}) :2510 (OH), 1710 (C=O), 1620 (C=O).

Anal. for $C_{17}H_{13}N_3O_3S$ (339.37) Calcd%: C, 60.17; H, 3.86; N,12.38. Found%: C, 60.07; H, 3.76; N, 12.25.

2-anilino-3-(2-hydroxybenzylidene)amino-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]Pyrimidine (10b): This compound was obtained from ethanol as white crystals, (Yield%:41), mp.149-150 °C.^{1}H-NMR (DMSO-d_6, δ ppm): 2.14 (m, 2H, CH_2), 2.69 (t, 2H, J = 6, CH_2), 3.13 (t, 2H, J=6,CH_2), 7.32 -7.65 (m, 5H, Ar-H), 7.85 (m, 4H, Ar-H), 8.01 (s, 1H, CH=N), 8.02 (brs,1H, NH), 11.10 (bros, 1H, OH).IR (KBr, υ cm^{-1}) :3130 (NH), 2510 (OH), 1720 (C=O), 1630 (C=O).

Anal. for $C_{23}H_{18}N_4O_3S$ (430.48) Calcd%:C, 64.17; H, 4.21; N,13.01.Found%: C, 64.19; H, 4.26; N, 12.91.

3-(4-methoxybenzylidene)amino-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine(11a): This compound was obtained from ethanol as a brown crystals, (Yield%: 81), mp.111 -112°C. ^{1}H-NMR ($CDCl_3$, δ ppm): 2.11 (m, 2H, CH_2), 2.89 (m, 2H, CH_2), 3.02 (m, 2H, CH_2), 3.42 (s, 3H, O-CH_3), 6.94-7.16 (m, 4H, Ar-H), 8.59 (s, H, N=CH), 8.94 (s, 1H, N=CH). IR (KBr, υ cm^{-1}) :1710 (C=O), 1620 (C=O).

Anal. for $C_{18}H_{15}N_3O_3S$ (353.40) Calcd%: C, 61.18; H, 4.28;N, 11.89. Found%: C, 61.15; H, 4.17; N, 12.00.

2-anilino-3-(4-methoxybenzylidene)amino-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]Pyrimidine (11b): This compound was obtained from ethanol as a yellow crystals, (Yield%: 92), mp.129-30°C. ^{1}H-NMR ($CDCl_3$, δ ppm): 2.11 (m, 2H, CH_2), 2.89 (m, 2H, CH_2), 3.02 (m, 2H, CH_2), 3.42 (s, 3H, CH_3), 6.99-7.16 (m, 4H, Ar-H), 7.85 (m, 4H, Ar-H), 8.56 (s, 1H, CH=N), 8.72 (brs, 1H, NH). IR (KBr, υ cm^{-1}) :3130 (NH), 1710 (C=O), 1620 (C=O).

Anal. for $C_{24}H_{20}N_4O_3S$ (444.51) Calcd%: C, 64.85; H, 4.54; N, 12.60. Found%: C, 64.81; H, 4.64; N,12.71.

3-(4-hydroxybenzylidene)amino-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine(12a): This compound was obtained from ethanol as a brownish crystals, (Yield%: 82), mp.168 -169°C. ^{1}H-NMR (DMSO-d_6, δ ppm): 2.14 (dd, 2H, CH_2), 2.67 (t, 2H, J = 6, CH_2), 3.09 (t, 2H, J=6, CH_2), 7.13-7.37 (m, 5H, Ar-H), 8.5 (s, 1H, CH), 11.12 (bros, 1H, OH). IR (KBr, υ cm^{-1}) :2510 (OH), 1730 (C=O), 1640 (C=O).

Anal. for $C_{17}H_{13}N_3O_3S$(339.37) Calcd%: C, 60.17; H, 3.86; N, 12.38. Found%: C, 60.01; H, 3.89; N, 12.36.

2-anilino-3-(4-hydroxybenzylidene)amino-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*] Pyrimidine (12b): This compound was obtained from ethanol as a white crystals, (Yield%: 29), mp.108 -109 °C.^{1}H-NMR ($CDCl_3$, δ ppm): 2.14 (dd, 2H, CH_2), 2.67 (t, 2H, J=6, CH_2), 3.09 (t, 2H, J=6,CH_2), 7.38 (m, 2H, Ar-H), 7.45-7.67 (m, 5H, Ar-H), 8.5 (brs, 1H, NH), 11.11 (bros, 1H, OH). IR (KBr, υ cm^{-1}) :3130 (NH), 2510 (OH), 1710 (C=O), 1660 (C=O).

Anal. for $C_{23}H_{18}N_4O_3S$ (430.48) Calcd%: C, 6 4.17; H,4.21; N, 13.01. Found%:C, 64.07; H, 4.09; N, 13.11.

Compounds 13, 14, 15 (A,b) and 19a,b

General Procedure: A mixture of **4a** or **4b** or **5a** or **5b** or **8a** or **8b** or **9a** or **9b** (0.05 mol) and (0.04 mol) of phenylhydrazine in ethanol (20 ml) was heated under reflux for 2h on a boiling water bath. Pour this phenylhydrazone intermediate into a 25-mL Erlenmeyer flask containing 6.0g of methanesulfonic acid which has previously been heated in a hot water bath for 10 min. Heat and stir for an additional 10 min. After that the hot reaction solution is added to 25 mL of ice/water and stirred. Collect the product by vacuum filtration using a Hirsch funnel and wash the crystals several times with distilled water. After drying, the solid obtain, was recrystallized from an appropriate mixed solvent. Determine the final weight and yield and mp.

3-(Phenylmethylidene)amino-3,5,6,11-tetrahydro-4*h*-pyrimido[5',4':4,5]thieno[2,3-*a*]carbazol-4-one (13a): The solid product of **13a** was collected, dried and recrystalized from ethanol/water to give a colorless crystals (Yield%: 78), mp 204-205°C.^{1}H-NMR ($CDCl_3$, δ ppm): 2.13 (t, 2H, J=6, CH_2), 2.84 (t, 2H, J=6, CH_2), 7.21-7.50 (m, 5H, Ar-H), 7.38-8.40 (m, 4H, Ar-H), 8.82 (s, 1H, N=CH), 8.28 (brs, 1H, NH). IR (KBr, υ cm^{-1}) :3050 (NH), 1730 (C=O), 1630 (C=O).

Anal. for $C_{23}H_{16}N_4OS$ (396.47) Calcd%: C, 69.68; H, 4.07; N, 14.13. Found%: C, 69.66; H, 4.10; N, 14.11.

2-anilino-3-(Phenylmethylidene)amino-3,5,6,11-tetrahydro-4*h*-pyrimido[5',4':4,5]thieno[2,3-*a*] Carbazol 4-one (13b): The solid product of **13b** was collected, dried and recrystalized from dioxin/ethanol to give a yellowish crystals (Yield%: 76), mp 241-242°C. ^{1}H-NMR (DMSO-d_6, δ ppm): 2.15 (t, 2H,J=6, CH_2), 2.94 (t, 2H, J=6, CH_2), 7.19-7.55 (m, 10H, Ar-H), 7.36-8.40 (m, 4H, Ar-H), 8.81 (s, H, N=CH), 8.98 (brs, 2H, 2NH). IR (KBr, υ cm^{-1}) :3060 (NH), 3090 (Ar-H), 1680 (C=O).

Anal.for $C_{29}H_{21}N_5OS$ (487.58) Calcd%: C, 71.44; H, 4.34; N, 14.36. Found%: C, 71.36; H, 4.28; N, 14.44.

3-[(4-methylphenyl)methylidene]amino-3,5,6,11-tetrahydro-4*H*-pyrimido[5',4':4,5]thieno[2,3-*a*] carbazol 4-one (14a): The solid product of **14a** was collected, dried and recrystalized from ethanol to give a yellow crystals (Yield%: 38), mp. 210-211 °C.^{1}H-NMR (DMSO-d_6, δ ppm): 2.22 (t, 2H,J=6, CH_2), 3.01 (t, 2H,J=6, CH_2), 2.64 (s, 3H, CH_3), 7.12 (d, 2H, Ar-H), 7.22 (d, 2H, J=4.0, Ar-H), 7.32-7.80 (m, 2H, J=4.0, Ar-H), 8.06 (s, 1H, N=CH), 8.30 (s, 1H, N=CH), 9.39 (brs, 1H, NH). IR (KBr, υ cm^{-1}) :3050 (NH), 1730 (C=O), 1630 (C=O).

Anal. for $C_{24}H_{18}N_4OS$ (410.49) Calcd%: C,70.22; H, 4.42; N, 13.65. Found%: C, 70.28; H, 4.33; N, 13.70.

2-anilino-3-[(4-methylphenyl)methylidene]amino-3,5,6,11-tetrahydro-4*h*-pyrimido[5',4':4,5]thieno [2,3-*a*]carbazol-4-one (14b): The solid product of **14b** was

collected, dried and recrystalized from ethanol to give of off-white crystals (Yield%: 68), mp 216–217°C.^{1}H-NMR (DMSO-d_6, δ ppm): 2.22 (t, 2H,J=6, CH_2), 3.08 (t, 2H,J=6, CH_2), 2.66 (s, 3H, CH_3), 6.31-7.12 (m, 9H, Ar-H), 7.32 (m, 2H, Ar-H), 7.38 (m, 2H, Ar-H), 8.39 (s, 1H, N=CH), 9.39 (s, 2H, 2NH).IR (KBr, υ cm^{-1}) :3250 (NH), 3080 (Ar-H), 1660 (C=O).

Anal. for $C_{30}H_{23}N_5OS$ (501.60) Calcd%: C, 71.83; H, 4.62; N, 13.96. Found%: C, 71.91; H, 4.67; N, 14.06.

3-[(4-nitrophenyl)methylidene]amino-3,5,6,11-tetrahydro-4*h*-pyrimido[5',4':4,5]thieno[2,3-*a*]Carbazol-4-one (15a): The solid product of **15a** was collected, dried and recrystalized from ethanol to give a white crystals (Yield%: 68), mp 277-278°C .^{1}H-NMR ($CDCl_3$, δ ppm): 2.12 (m, 2H, CH_2), 2.61 (t, 2H, CH_2), 7.23 -8.09 (m, 8H, Ar-H), 8.19 (s, H, N-CH), 8.54 (s, 1H, N=CH), 9.14 (s, 1H, N=CH). IR (KBr, υ cm^{-1}) :3250 (NH), 1650 (C=O).

Anal. for $C_{23}H_{15}N_5O_3S$ (441.46) Calcd%: C, 62.58; H, 3.42; N, 15.86. Found%: C, 62.64; H, 3.47; N,15.79.

2-anilino-3-[(4-nitrophenyl)methylidene]amino-3,5,6,11-tetrahydro-4*h*-pyrimido[5',4':4,5]thieno[2,3-*a*]carbazol-4-one (15b): The solid product of **15b** was collected, dried and recrystalized from benzene/dioxane to give a white solid (Yield%: 38), mp 280–281°C.^{1}H-NMR ($CDCl_3$, δ ppm): 2.31 (t, 2H,J=6, CH_2), 2.67 (t, 2H, J= 6, CH_2), 7.01 (d, 2H, J=4.0, Ar-H), 7.49 (d, 2H, J =12, Ar-H), 7.65 (m, 5H, Ar-H), 7.99 (m, 4H, Ar-H), 8.81 (s, 1H, N=CH), 8.39 (brs, 2H, 2NH).IR (KBr, υ cm^{-1}) :3250 (NH), 1650 (C=O).

Anal.for $C_{29}H_{20}N_6O_3S$ (532.57) Calcd%: C, 65.40; H, 3.79; N, 15.78. Found%: C, 65.38; H, 3.87; N, 15.70.

3-(Cyclohexylidenamino)-3,5,6,11-tetrahydro-4*h*-pyrimido[5',4':4,5]thieno[2,3-*a*]carbazol-4-one (19a): The solid product of **19a** was collected, dried and recrystalized from (CH2Cl2–pet. ether) to give a white solid, (Yield%: 60), mp 254–256°C. ^{1}H-NMR (DMSO-d_6, δ ppm): 2.13 (m, 2H, CH_2), 2.18-2.67 (m, 10H, $5CH_2$), 2.68 (t, 2H, *J* = 6 Hz,CH_2), 7.32-7.80 (m, 4H, Ar-H), 8.06 (s, 1H, N=CH), 8.31 (s, 1H, N=CH), 9.41 (brs, 1H, NH). IR (KBr, υ cm^{-1}) :3250 (NH), 1640 (C=O).

Anal.for $C_{22}H_{20}N_4OS$ (388.49) Calcd%: C, 68.02; H, 5.19; N,14.42. Found%: C, 67.99; H, 5.09; N, 14.51.

2-anilino-3-(Cyclohexylidenamino)-3,5,6,11-tetrahydro-4*h*-pyrimido[5',4':4,5]thieno[2,3-*a*]carbazol-4-one(19b): The solid product of **19b** was collected, dried and obtained after recrystallization from ethanol as a white solid, (Yield%: 88), mp 200–201°C.^{1}H-NMR ($CDCl_3$, δ ppm): 2.09 (m, 2H, CH_2), 2.20-2.57 (m, 10H, $5CH_2$), 2.61 (t, 2H, *J* = 6 Hz, CH_2), 6.62 -7.19 (m, 5H, Ar-H), 7.32 (m, 2H, Ar-H), 7.38 (m, 2H, Ar-H), 8.19 (s, 1H, N=CH), 9.09 (bros, 2H, 2NH). IR (KBr, υ cm^{-1}) :3180 (NH), IR (KBr, υ cm^{-1}) :3250 (NH), 1640 (C=O).

Anal.for $C_{28}H_{25}N_5OS$ (479.60) Calcd%: C, 70.12; H, 5.25; N, 14.60. Found%: C, 70.11; H, 5.20; N, 14.69.

Compounds 16, 17, 18 (A,b) and 20a,b

General Procedure: Dissolve NaOH (0.066 mol) in a mixture of methanol (6 mL) and water (1 mL) in a round flask. Dissolve the appropriated cabazol compounds **13-15 (a,b)** or **19** (**a,b**) from the previous step (0.054 mol) in DMSO (6 mL). The NaOH solution was transferred into the flask containing the cabazol compounds solution and the Me_2SO_4 (0.081 mol) was added by pipetter and allow the mixture to stirring for 10 min and dilution of reaction mixture with water. After 30 min, add additional NaOH (0.021 mol) and Me_2SO_4 (0.021 mol) and stirring the reaction mixture for 30 min. The precipitated formed was filtered by a Buchner funnel and rinse with water (2×10 mL).

11-methyl-3-(Benzylidene)amino-3,5,6,11-tetrahydro-4*h*-pyrimido[5',4':4,5]thieno[2,3-*a*]carbazol-4-one (16a): The solid product of **16a** was collected, dried and recrystalized from benzene to give brownish crystals (Yield%: 60), mp 187-188 °C**.** The 1H NMR spectrum of **16a** is very similar to that of **13a** with the exception of a methyl singlet near 3.71 ppm.

Anal.for $C_{24}H_{18}N_4OS$ (410.49) Calcd%: C, 70.22; H, 4.42; N, 13.65. Found%: C, 70.32; H, 4.46; N, 13.56.

2-anilino-11-methyl-3-(Benzylidene)amino-3,5,6,11-tetrahydro-4*h*-pyrimido[5',4':4,5]thieno[2,3-*a*] Carbazol 4-one (16b): The solid product of **16b** was collected, dried and recrystalized from dioxane to give a yellow crystals (Yield % : 77), mp 201-202 °C**.** The same spectrum for compound **13b** but show the signal at 3.73 ppm due to the N-methyl group.

Anal.for $C_{30}H_{23}N_5OS$ (501.60) Calcd%: C, 71.83; H, 4.62; N, 13.96. Found%: C, 71.91; H, 4.56; N, 14.02.

11-methyl-3-(4-methybenzylidene)amino-3,5,6,11-tetrahydro-4*h*-pyrimido[5',4':4,5]thieno[2,3-*a*] Carbazol 4-one (17a): The solid product of **17a** was collected, dried and recrystalized from ethanol/ water to give a yellow crystals (Yield%: 61), mp 173-175 °C. The same spectrum for compound **14a** but show the signal at 3.75 ppm due to the N-methyl group

Anal. for $C_{25}H_{20}N_4OS$ (424.52) Calcd%: C, 70.73; H, 4.75; N, 13.20. Found%: C, 70.74; H, 4.69; N, 13.29.

2-anilino-11-methyl-3-(4-methybenzylidene)amino-3,5,6,11-tetrahydro-4*h*-pyrimido[5',4':4,5]thieno [2,3-*a*]carbazol-4-one (17b): The solid product of **17b** was collected, dried and recrystalized from ethanol/ water to give yellow crystals (Yield%: 40), mp 115-116 °C. The same spectrum for compound **14b** but show the signal at 3.70 ppm due to the N-methyl group

Anal. for $C_{31}H_{25}N_5OS$ (515.63) Calcd%: C,72.21; H, 4.89; N, 13.58. Found%: C, 72.27; H, 4.84; N, 13.49.

11-methyl-3-(3-nitrobenzylidene)amino-3,5,6,11-tetrahydro-4*h*-pyrimido[5',4':4,5]thieno[2,3-*a*]Carbazol-4-one (18a): The solid product of **18a** was collected, dried and recrystalized from ethanol/ water to give yellow crystals (Yield%: 78), mp 111-112°C. The same spectrum for compound **15a** but show the signal at 3.74 ppm due to the N-methyl group

Anal. for $C_{24}H_{17}N_5O_3S$ (455.49) Calcd%: C, 63.29; H, 3.76; N, 15.38. Found%:C, 63.33; H, 3.66; N, 15.40.

2-anilino-11-methyl-3-(3-nitrobenzylidene)amino-3,5,6,11-tetrahydro-4*h*-pyrimido[5',4':4,5]thieno [2,3-*a*]carbazol-4-one (18b): The solid product of **18b** was collected, dried and recrystalized from ethanol to give yellow crystals (Yield%: 39), mp 139-141°C. The same spectrum for compound **15b** but show the signal at 3.74 ppm due to the N-methyl group

Anal. for $C_{30}H_{22}N_6O_3S$ (546.60) Calcd% : C, 65.92; H,4.06; N,15.37.Found%: C, 65.96; H, 4.11; N,15.27.

3-(Cyclohexylidenamino)-11-methyl-3,5,6,11-tetrahydro-4*h*-pyrimido[5',4':4,5]thieno[2,3-*a*]carbazol-4-one(20a): The solid product of **20a** was collected, dried and recrystalized from ethanol/ water to give yellow crystals (Yield%: 65), mp 195–196°C. The same ^{1}H-NMR data of compound **19a** were also deduced the signal at 3.79 ppm due to the N-methyl group

Anal. for $C_{23}H_{22}N_4OS$ (402.51) Calcd%: C, 68.63; H, 5.51; N,13.92. Found%: C, 68.73; H, 5.49; N, 14.00.

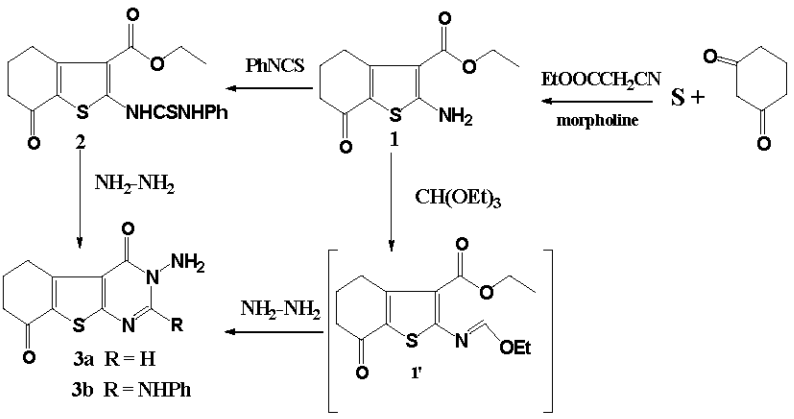
2-anilino-3-(Cyclohexylidenamino)-11-methyl-3,5,6,11-tetrahydro-4*h*-pyrimido[5',4':4,5]thieno[2,3-*a*]Carbazol-4-one (20b): The solid product was collected, dried and recrystallization from CH_2Cl_2–Et O_2 as a white solid,(Yield%: 68) mp 160–161 °C. After recrystallization of **20b** the same ^{1}H-NMR data of compound **19b** were also deduced the signal at 3.78 ppm due to the N-methyl group.

Anal. for $C_{29}H_{27}N_5OS$ (493.62) Calcd%: C, 70.56; H, 5.51; N, 14.19. Found%: C, 70.61; H, 5.48; N, 14.16.

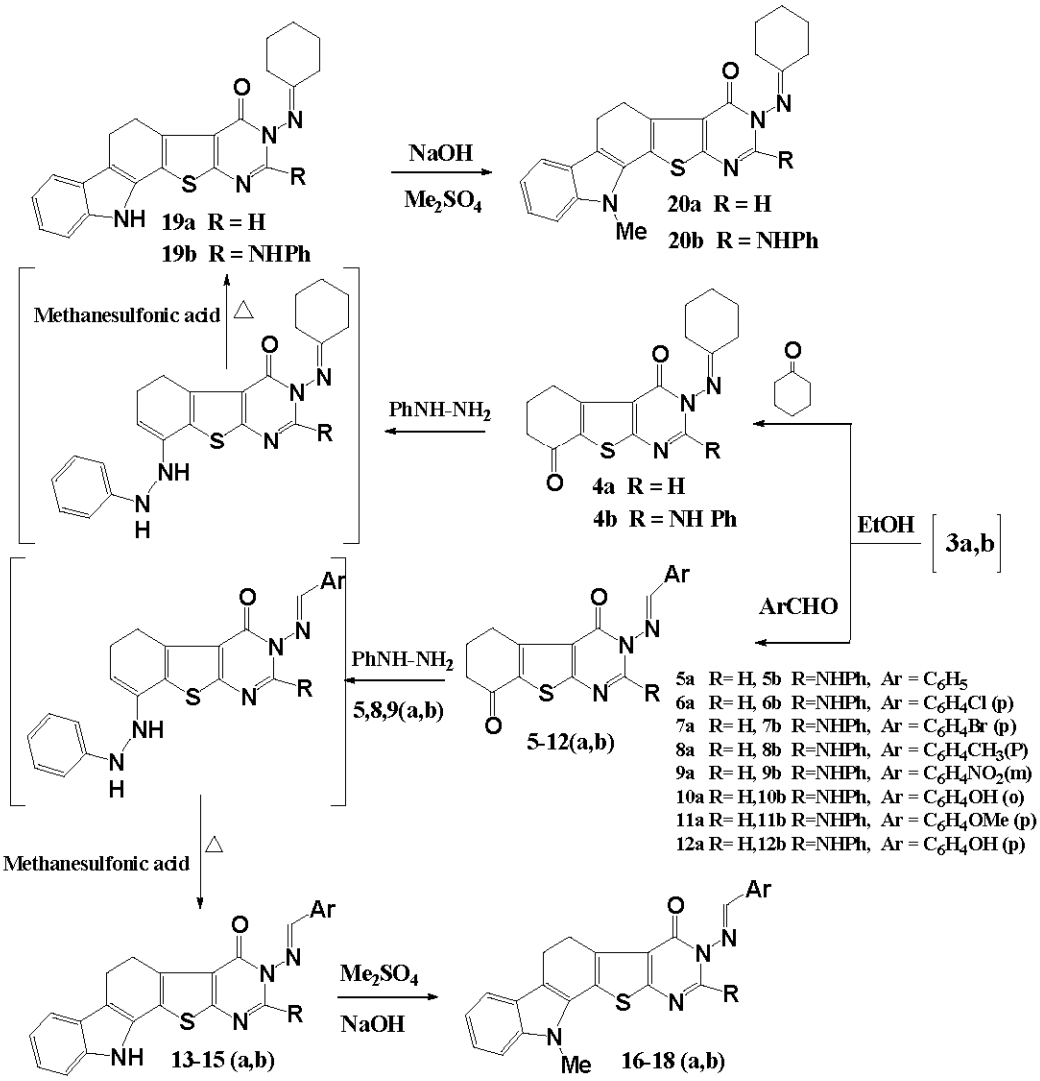
RESULTS AND DISCUSSION

The starting material ethyl 2-amino-7-oxo-4,5,6,7-tetrahydrobenzo thiophene-3-carboxylate **(1)** was prepared by condensation of 1,3-dioxocylohexane, elemental sulfur and ethyl cyano-acetate in the presence of morpholine as a basic medium according to Gewald base reaction [11]. The published procedure and many methods for synthesis of 4,8-dioxo-3,4,5,6,7,8-hexahydro benzo thienopyrimidine, for example the oxidation of the thiophene moiety α-position in 4-oxo-3,4,5,6,7,8-hexahydrobenzothieno[2,3-d]pyrimidine with K_2Cr Q $_7$ gave 4,8-dioxo-3,4,5,6,7,8-hexahydrobenzothieno[2,3-d]pyrimidine[12]. In the present study, the amino ester **(1)** was converted to 4,8-dioxothienopyrimidine **(3a,b)** as a new method (Scheme 1).

Cyclohexanone ,benzaldehyde and other aromatic aldehydes containing electron-withdrawing groups (such as nitro-group, halide) or electrondonating groups (such as hydroxy group, alkoxyl group) were employed and reacted with 4,8-dioxo thienopyrimidine **(3a,b)** for preparation of the corresponding 3-(Cyclohexylidene) amino-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzothieno[2,3-d] pyrimidine **(4a,b)** and 3-(Arylidene) amino-4,8-dioxo-3,4,5,6,7,8-hexahydrobenzothieno[2,3-d]pyrimidine [**5-12(a,b)**] respectively in good to excellent yields. Numerous methods have been developed for the synthesis of substituted indoles and indole-containing polycyclic ring systems [13]. In our research, the hydrazones derivatives were intermediate products by Fischer indole synthesis via condensation of phenylhydrazine with 4,8-dioxo-3,4,5,6,7,8-hexa hydrobenzothieno[2,3-d]pyrimidine derivatives **[4a,b** and **5,8,9(a,b)]** that using as a synthon of carbazole compounds **[19a,b** and **13-15 (a,b)]**. These compounds**[19a,b** and **13-15(a,b)]** were methylated by deprotonating the N-H with NaOH followed by treatment with dimethyl sulfate . Additional portions of NaOH and dimethyl sulfate may be needed to force the reaction to complete and the dilution of the reaction with water precipitates the product, that isolated by filtration. The ^{1}H NMR spectra of **20(a,b)** and **16-18 (a,b)** were similar to that of **19(a,b)** and**13-15 (a,b)**, respectively with the exception of a methyl singlet at 3.70-3.79 ppm (Scheme 2).



Scheme 1:



13a,16a R= H,13b,16b R=NHPh, Ar = C_6H_5
14a,17a R= H,14b,17b R=NHPh, Ar = $C_6H_4CH_3$(P)
15a,18a R= H,15b,18b R=NHPh, Ar = $C_6H_4NO_2$(m)

Scheme 2:

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