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β-OXOANILIDE AS BUILDING BLOCKS IN HETEROCYCLIC SYNTHESIS: A NEW SYNTHESIS OF POLYFUNCTIONALLY SUBSTITUTED PYRIDINES, PYRANS AND PYRIMIDINES

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Abstract

β-Oxoanilide **1** reacted with acetyl isothiocyanate and ethoxycarbonyl isothiocyanate to give pyridine derivatives **6a,b** and pyrimidinethiol **8** respectively. While with arylidine malononitrile gave the pyran derivative **12**. Similarly, treatment of **1** with arylidine cyanoacetamide or arylidine cyanothioacetamide afforded the pyridine derivatives **13a,b**, **14a,b** respectively. Condensation of **1** with aromatic aldehyde obtained the cyclohexenones **19a-c**. The reaction of **1** with a mixture of aromatic aldehyde and urea or thiourea gave the pyrimidine derivatives **23a,b**. Treatment of compound **1** with arylidine acetophenone yield the cyclohexene derivatives **26a,b.** Reaction of **1** with a mixture of ethyl cyanoacetate and sulfur yield the thiophene derivative **27**. Which was reacted with formamide, potassium thiocyanate and hydrazine to afford the thienopyrimidines **28**, **29** and the hydrazide derivative **30.** respectively.

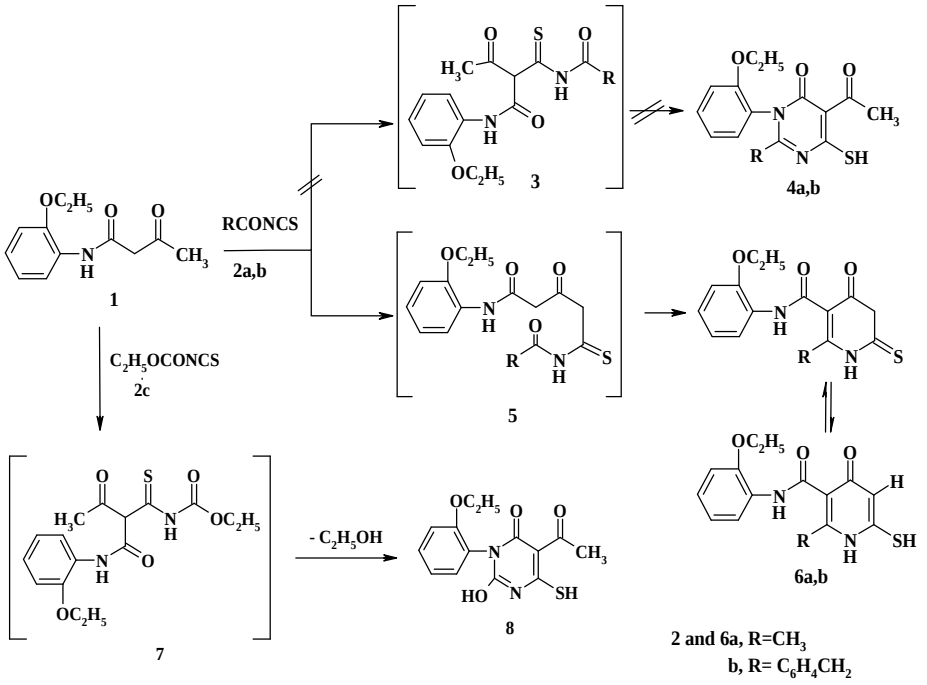
Introduction

Interest in the chemistry of azines and condensed azines has recently been revived[1-3]. Due to their biological activities[4,5]. In the last few years we have been involved in program directed for developing new approaches for the synthesis of polyfunctionally substituted azines utilizing inexpensive and readily obtainable starting materials[6-8]. In this work we report the use of the title reagent in several heterocyclic transformation to obtain pyridines, pyrimidines, pyrans and condensed pyrimidines.

Results and Discussion.

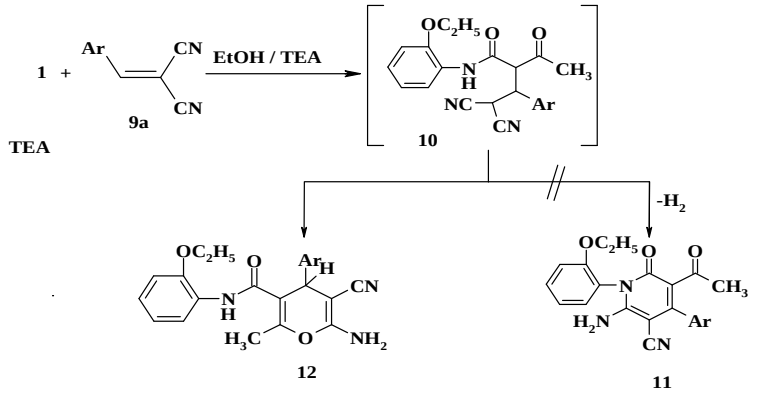
So it has been found that reactions of ***β*-**oxoanilide **1** (prepared as literature procedure)[9] reacted with acetyl isothiocyanate **2a** in refluxing dry acetone afforded the unexpected pyridine derivative **6a** rather than the expected pyrimidine derivative **4a**. Structure **6a** was assigned for the reaction product based on spectroscopic data (IR, ^{1}H NMR and ^{13}C NMR). The ^{1}H NMR spectrum displayed two singlet signals at δ 11.42 and 13.00 ppm for 2NH and one singlet signal at δ 2.19 ppm assigned for CH_3 and singlet signal at δ 8.78 ppm for CH-pyridine in addition to the triplet signal at δ 1.40 ppm for OCH_2CH_3 and quartet signal at δ 4.15 ppm for CH_2 of OCH_2CH_3 besides the expected signals. Also, ^{13}C NMR spectrum revealed a signal at δ 14.60 for CH_3 and δ 23.79 for phenetidine CH_3, δ 64.35 for phenetidine CH_2, 172.55 and 177.17 for 2(CO), in addition to the entire carbon signal assigned to C-H and C-C in the structure. From the above data we are sure that the structure **6a** is the sole product for this compound. Similarly, interaction of ***β*-**oxoanilide **1** with phenylacetyl isothiocyanate afforded the pyridine derivative **6b**. Compound **6b** was established based on its spectral data, **(Scheme 1)**.

On the other hand ethoxycarbonyl isothiocyanate **2c** reacted with ***β***-oxoanilide **1** under the same condition to afford the expected pyrimidinethiol derivative **8** through the intermediate **7**. The structure of compound **8** was confirmed based on its spectral data (IR and ^{1}H NMR). The ^{1}H NMR spectrum revealed the presence of a singlet signal at δ 2.18 ppm ($COCH_3$), a singlet signal at δ 3.66 ppm (SH), a singlet signal at δ 7.01 ppm (OH), a multiplet at δ 7.28-7.62 ppm (aromatic-H), besides the ethyl protons as triplet signals at δ 1.37 ppm (CH_3) and quartet at δ 4.08 ppm (OCH_2) group, **(Scheme 1)**.



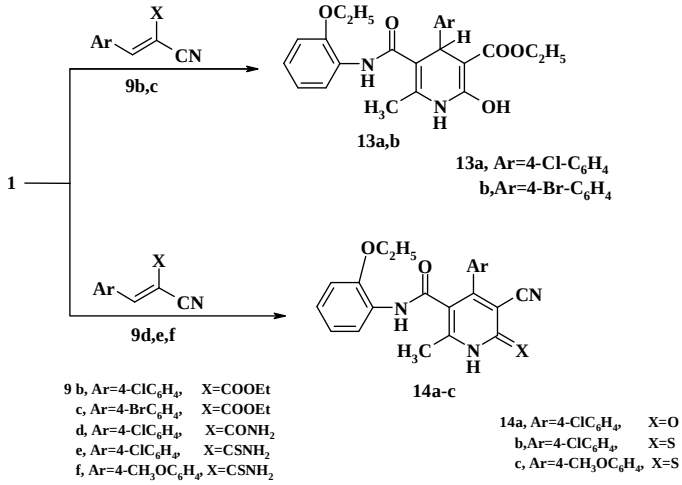
Scheme 1

A reaction of ***β***-oxoanilide **1** with electrophilic reagents under an alkaline conditions was also investigated. So, the reaction of **1** with 2-chlorobenzylidene malononitrile (**9a**) may afford the 4H-pyran derivative **12** or pyridine **11**; structure **11** was ruled out based on the spectral data (IR, ^{1}H NMR). The ^{1}H NMR spectrum revealed the presence of a singlet signal at δ 4.61 ppm assigned for 4H-pyran. **(Scheme 2).**



Scheme 2

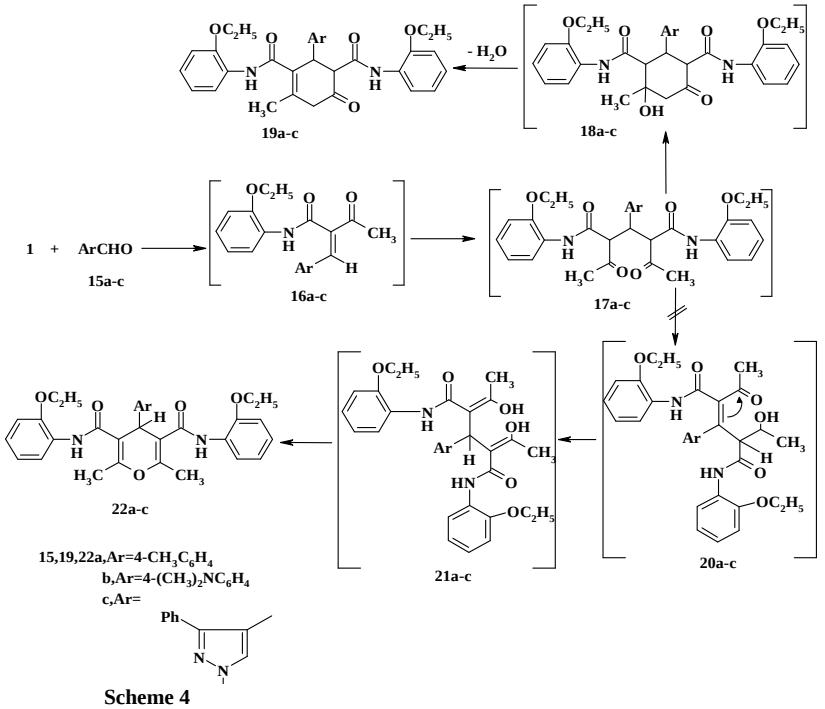
Further, ***β***-oxoanilide **1** reacted with arylidine ethyl cyanoacetate, arylidine cyanoacetamide and arylidine cyanothioacetamide to provide the pyridine derivatives. Reactions of **1** with arylidine ethyl cyanoacetate **9b,c** afforded the 4H pyridine **13a,b**; compound **13a** was established based on the spectral data (IR, ^{1}H NMR). So the IR spectrum show the disappearance of CN group and presence of CO ester at ν=1715 cm^{-1}. Also ^{1}H NMR revealed the presence of a singlet signal at δ 5.70 ppm assigned for 4H pyridine, singlet signal at δ 6.77 ppm assigned to OH group, δ 8.83 and 9.40 ppm for 2(NH) group. Also, the reaction of **1** with arylidines **9d-f** afforded the pyridone derivative **14a** and pyridinethione **14b,c** derivatives. Establishing of compounds **14a-c** based on its spectroscopic data. (**Scheme 3**).



Scheme 3

Condensation of **1** with aromatic aldehydes **15a-c** in refluxing ethanolic triethylamine obtained the arylidine derivatives **16a-c**, but under the reaction conditions we obtained the compounds which may be formulated as 4H-pyran derivatives **22a-c** or cyclohexenone derivatives **19a-c**. Compounds **22a-c** are the sole product based on its correct spectral data (IR, ^{1}H NMR and MS). The ^{1}H NMR of **19a** revealed a singlet signal at δ 1.31, 1.39, 2.17, 2.49 ppm assigned to 4CH_3, a signal at 5.80 ppm assigned to CH_2-cyclohexene group, a duplet at 7.59 and 7.87 ppm assigned to 2CH-cyclohexene group, a singlet at 8.71, 9.31 ppm assigned to 2NH group, besides the signal of ethyl group and aromatic group present in the structure. Also, ^{13}C NMR revealed a signal at 14.56, 14.75 assigned to 2CH_3 of ethyl group, signal at 20.68, 27.85 assigned to 2CH_3, signal at 62.60 assigned to CH_2 group, signal at 166.36, 204.78 assigned to 2CO group, these signals present beside all signals of CH and C-C in the structure.

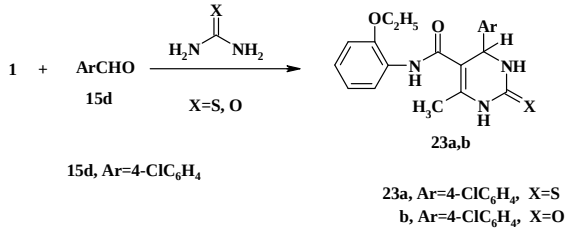
Moreover, the mass spectrum of structure **19a** revealed a molecular ion peak at m/z=525 (M^{-1}) corresponding to the molecular formula $C_{32}H_{34}N_2O_5$. We suggest that **19a-c** were formed via initial condensation between methylene of **1** and aromatic aldehyde **15a-c** to afford the arylidine **16a-c** and subsequently addition of methylene in another molecule of **1** to the double bond of the arylidine derivatives **16a-c** to give the Michael adduct **17a-c**. Which underwent interamolecular cyclization to give the adduct **18a-c** followed by losing of water to give the final product **19a-c**, (**Scheme 4**).



Scheme 4

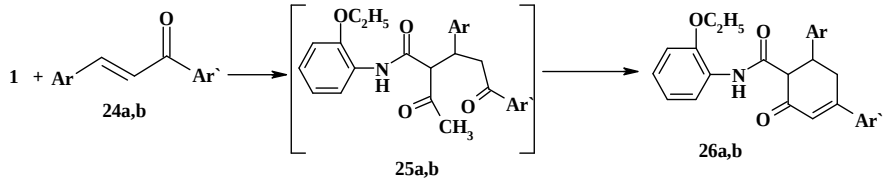
Scheme 4

The pyrimidine derivatives **23a,b** were prepared by the one-pot synthesis via a reaction of ***β***-oxoanilide **1**, aromatic aldehydes and thiourea or urea. Establishing of structure **23a,b** was based on its elemental analysis and spectral data. (**Scheme 5**).



Scheme 5

Also, the reaction of ***β***-oxoanilide **1** with non-symmetrical double bond system was investigated. Thus, compound **1** was reacted with arylidine acetophenones **24a,b** in ethanolic piperidine solution to yield condensation products via elimination of water. These were formulated as the cyclohexene derivatives **26a,b**. Formation of **26a,b** are assumed to proceed via Michael type addition between the methylene group in **1** and double bond in arylidine **24a,b** and subsequent cyclization of the intermediate **25a,b** by elimination of water. Establishing the structure of **26a,b** based on their spectral data (IR, ^{1}H NMR and ^{13}C NMR). ^{13}C NMR of compound **26a** as example revealed a signal at δ 14.60 assigned to CH_3 of ethyl group, a signal at δ 20.94 assigned to CH_3, a signal at δ 58.90 assigned to CH_2 group and signals at δ 167.45, 195.44 assigned to 2CO groups, (**Scheme 6**).



Scheme 6

Furthermore, the utility of ***β***-oxoanilide **1** for synthesis of π-excessive molecules has been investigated. Thus, reactions of a mixture of ***β***-oxoanilide **1**, elemental sulfur and ethyl cyanoacetate gave the thiophene derivative **27**. Compound **27** was confirmed by spectral data (IR, ^{1}H NMR and MS). Thus, the mass spectrum of **27** revealed a molecular ion peak at m/z=(348) (M^{+}) corresponding to molecular formula $C_{17}H_{20}N_2O_4S$. Moreover, the thiophene ring obtained possesse latent functional substituents which enable its further chemical transformation into thienoazines of an expected wide spectrum of biological activity. Treatment of thiophene **27** with formamide without solvent afforded the expected thienopyrimidinone derivative **28**. Similarly, treatment of **27** with potassium thiocyanate in refluxing dioxane containing 10% HCl afforded the thienopyrmidine

derivative **29**. Also, treatment of **27** with hydrazine hydrate afforded the hydrazide derivative **30** which was confirmed by compatible spectral data. (**Scheme 7**).

Experimental

All melting points are uncorrected. IR spectra (KBr) were recorded on a JASCO FT/IR-480 plus spectrometer (ν, cm^{-1}). The ^1H NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ at 200, 300 MHz on a Varian Gemini NMR spectrometer (δ, ppm) using TMS as an internal standard (carried out by the Micro Analytical Center, Cairo university). Mass spectra were obtained on GC Ms-QP 1000 EX mass spectrometer at 70 ev (carried out by the Micro Analytical Center, Cairo university). Elemental analysis were carried out by the Micro Analytical Research Center, faculty of science, department of chemistry, Assiut university.

Preparation of compounds 6a,b and 8.
General procedure:

To a solution of acetoacetanilide **1** (0.01 mole) in dry acetone (30 mL), acetyl isothiocyanate or phenylacetyl isothiocyanate or ethoxycarbonyl isothiocyanate was added. The reaction mixture was heated under reflux for 5 h. The solvent was removed by evaporation, the solid product so formed was collected by filtration and recrystallized from ethanol to give **6a,b** and **8** respectively.

2-Methyl-3-(2-ethoxyphenyl)aminocarbonyl-6-mercapto-4-oxo-1,4 dihydropyridine (6a).

It was obtained from acetoacetanilide **1** (0.01 mole) and acetyl isothiocyanate as yellow crystals in yield (60%); mp. = 180 ºC. IR (KBr) ν cm^{-1}: 3370 (NH), 3191 (NH), 1697 (C=O). ^1H NMR (DMSO-d_6) δ ppm: 1.40 (t, 3H, CH_3), 2.19 (s, 3H,

CH_3), 3.70 (s, 1H, SH), 4.15 (q, 2H, CH_2), 6.94-7.24 (m, 4H, Ar-H), 8.78 (s, 1H, CH pyridine), 11.42 (s, 1H, NH) and 13.00 (s, 1H, NH). ^{13}C NMR δ ppm: 14.60 (q); 23.79 (q); 64.35 (t); 112.21 (d); 112.21 (d); 119.75 (s); 119.75 (s); 122.12 (d); 122.12 (d); 125.25 (s); 126.26 (s); 127.25 (s); 149.40 (d); 172.55 (s, CO); 177.17 (s, CO). Anal. Calcd. for $C_{15}H_{16}N_2O_3S$ (304.37): C, 59.19; H, 5.30; N, 9.20; S, 10.53. Found: C, 59.10; H, 5.30; N, 9.10; S, 10.60.

2-Benzyl-3-(2-ethoxyphenyl)aminocarbonyl-6-mercapto-4-oxo-1,4-dihydropyridine (6b).

It was obtained from acetoacetanilide **1** (0.01 mole) and phenyl- acetyl isothiocyanate as colorless crystals in yield (65%); mp.=135 ºC. IR (KBr) ν cm^{-1}; 3195 (NH), 3127 (NH), 1695 (C=O), 1653 (C=O). ^{1}H NMR (DMSO-d_6) δ ppm: 1.31 (t, 3H, CH_3), 2.49 (s, 1H, SH), 3.80 (s, 2H, CH_2), 4.05 (q, 2H, CH_2), 6.92-7.35 (m, 9H, Ar-H), 8.65 (s, 1H, CH pyridine), 11.58 (s, 1H, NH) and 12.80 (s, 1H, NH). **MS**: m/z=380 (M^{+}). Anal. Calcd. For $C_{21}H_{20}N_2O_3S$ (380.47): C, 66.30; H, 5.30; N, 7.36; S, 8.43. Found; C, 66.20; H, 5.20; N, 7.30; S, 8.50.

5-Acetyl-2-hydroxy-1-(2-ethoxyphenyl)aminocarbonyl-4-mercapto-1*H*-pyrimidine-6-one (8).

It was obtained from acetoacetanilide **1** (0.01 mole) and ethoxy-carbonyl isothiocyanate (0.01 mole) as yellow crystals in yield (60%); mp.>360 ºC. IR (KBr) ν cm^{-1}; 3138 (br., OH), 1713 (C=O), 1671 (C=O). ^{1}H NMR (DMSO-d_6) δ ppm: 1.37 (t, 3H, CH_3), 2.18 (s, 3H, CH_3), 3.66 (s, 1H, SH), 4.08 (q, 2H, CH_2), 7.01 (s, 1H, OH) and 7.28-7.62 (m, 4H, Ar-H). Anal. Calcd. For $C_{14}H_{14}N_2O_4S$ (306.34): C, 54.89; H, 4.61; N, 9.14; S, 10.47. Found: C, 54.70; H, 4.50; N, 9.10; S, 10.50.

2-Amino-3-cyano-4-(2-chlorophenyl)-5-(2-ethoxyphenyl)aminocarbonyl-6-methyl-4*H*-pyran (12).

A solution of acetoacetanilide **1** (0.01 mole), 2-chloro benzylidene malononitrile (0.01 mole) and triethylamine (0.5 mL) in ethanol (30 mL) was heated under reflux for 6 h. The solid product formed on heating was collected by filtration to give **12** as white crystals, recrystallized from ethanol, yield (80%), mp.= 205 ºC. IR (KBr) ν cm^{-1}; 3467, 3321 (NH_2, NH), 2189 (CN), 1644 (C=O). ^{1}H NMR (DMSO-d_6) δ ppm: 1.37 (t, 3H, CH_3), 2.30 (s, 3H, CH_3), 4.15 (q, 2H, CH_2), 4.61 (s, 1H, 4H pyrane), 5.98 (s, 2H, NH_2) and 7.05-7.65 (m, 9H, Ar-H+NH). **MS**: m/z=409 (M^{+}). Anal. Calcd. For $C_{22}H_{20}ClN_3O_3$ (409.88): C, 66.40; H, 4.78; N, 11.06; Cl, 9.33. Found: C, 66.40; H, 4.60; N, 11.00; Cl, 9.40.

Preparation of compounds 13a,b:
General procedure:

A mixture of acetoacetanilide **1** (0.01 mole), benzylidene ethyl cyanoacetate (0.01 mole) and triethylamine (0.5 mL) was refluxed in ethanol (30 mL) for 6 h. The solid product formed on heating was collected by filtration and recrystallized from ethanol to give **13a,b**.

4-(4-Chlorophenyl)-5-(2-ethoxyphenyl)carbamoyl-2-hydroxy-6-methyl-1,4-dihydropyridine-3-ethylcarboxylate (13a).

It was obtained from acetoacetanilide **1** (0.01 mole) and 4-chloro benzylidene ethyl cyanoacetate (0.01 mole) as white crystals in yield (80%), mp.=220 ºC. IR (KBr) ν cm^{-1}; 3418 (OH), 3388 (NH), 3373 (NH), 1715 (C=O), 1674 (C=O). ^1H NMR (DMSO-d_6) δ ppm: 1.29 (t, 3H, CH_3), 1.36 (t, 3H, CH_3), 2.51 (s, 3H, CH_3), 3.99 (q, 2H, CH_2), 4.00 (q, 2H, CH_2), 5.70 (s, 1H, 4H pyridine), 6.77 (s, 1H, OH), 6.78-7.81 (m, 8H, Ar-H), 8.83 (s, 1H, NH) and 9.40 (s, 1H, NH). Anal. Calcd. For $C_{24}H_{25}ClN_2O_5$ (456.93): C, 63.09; H, 5.51; N, 6.13; Cl, 7.76. Found: C, 63.00; H, 5.40; N, 6.00; Cl, 7.80.

4-(4-Bromophenyl)-5-(2-ethoxyphenyl)carbamoyl-2-hydroxy-6-methyl-1,4-dihydropyridine-3-ethylcarboxylate (13b).

It was obtained from acetoacetanilide **1** (0.01 mole) and 4-bromo benzylidene ethyl cyanoacetate (0.01 mole) as white crystals in yield (70%); mp.=215 ºC. IR (KBr) ν cm^{-1}; 3421 (OH), 3388 (NH), 3372 (NH), 1714 (C=O), 1672 (C=O). ^1H NMR (DMSO-d_6) δ ppm: 1.30 (t, 3H, CH_3), 1.39 (t, 3H, CH_3), 2.49 (s, 3H , CH_3), 4.00 (q, 2H, CH_2), 4.05 (q, 2H, CH_2), 5.7 (s, 1H, 4H pyridine), 6.78 (s, 1H, OH), 6.80-7.41 (m, 8H, Ar-H), 8.79 (s, 1H, NH) and 9.38 (s, 1H, NH). Anal. Calcd. For $C_{24}H_{25}BrN_2O_5$ (501.38): C, 57.49; H, 5.03; N, 5.59; Br, 15.94. Found: C, 57.40; H, 5.00; N, 5.40; Br, 15.90.

Preparation of compounds 14a-c:
General procedure:

To a solution of acetoacetanilide **1** (0.01 mole) in ethanol (30 mL) containing triethylamine (0.5 mL), benzylidene cyanoacetamide or benzylidene cyanothioacetamide (0.01 mole) was added respectively. The reaction mixture was heated under reflux for 4 h. The solid product formed on heating was collected by filtration and recrystallized from ethanol to give **14a-c**.

3-Cyano-4-(p-chlorophenyl)-5-(2-ethoxyphenyl)aminocarbonyl-6-methyl-6-oxo-1,2-dihydropyridine (14a).

It was obtained from acetoacetanilide **1** (0.01 mole) and 4-chloro benzylidene cyanoacetamide (0.01 mole) as pale yellow crystals in yield (70%); mp.=250 ºC. IR (KBr) ν cm^{-1}; 3270 (NH), 3133 (NH), 2225 (CN), 1654 (C=O). ^1H NMR (DMSO-d_6) δ ppm: 1.34 (t, 3H, CH_3), 2.41 (s, 3H, CH_3), 4.0 (q, 2H, CH_2), 6.83-7.56 (m, 9H, Ar-H +NH) and 9.53 (s, 1H, NH). Anal. Calcd. For $C_{22}H_{18}ClN_3O_3$ (407.86): C, 64.79; H, 4.45; N, 10.30; Cl, 8.69. Found: C, 64.70; H, 4.40; N, 10.30; Cl, 8.70.

3-Cyano-4-(p-chlorophenyl)-5-(2-ethoxyphenyl)aminocarbonyl-6-methyl-6-thioxo-1,2-dihydropyridine (14b).

It was obtained from acetoacetanilide **1** (0.01 mole) and 4-chloro benzylidene cyanothioacetamide (0.01 mole) as yellow crystals in yield (80%), mp.=264 ºC. IR (KBr) ν cm^{-1}: 3436 (NH), 3242 (NH), 2230 (CN), 1650 (C=O). ^1H NMR (DMSO-d_6) δ ppm: 1.35 (t, 3H, CH_3), 2.53 (s, 3H, CH_3), 4.06 (q, 2H, CH_2), 6.86-7.61 (m, 8H, Ar-H), 9.65 (s, 1H, NH), and 14.38 (s, 1H, NH). Anal Calcd. For $C_{22}H_{18}ClN_3O_2S$

(423.92): C, 62.33; H, 4.28; N, 9.91; Cl, 8.36; S, 7.56. Found: C, 62.20; H, 4.20; N, 9.90; Cl, 8.40; S, 7.60.

3-Cyano-4-(p-methoxyphenyl)-5-(2-ethoxyphenyl)aminocarbonyl-6-methyl-6-thioxo-1,2-dihydropyridine (14c).

It was obtained from acetoacetanilide **1** (0.01 mole) and 4-methoxy benzylidene cyanothioacetamide (0.01 mole) as yellow crystals in yield (80%), mp.=260 ºC. IR (KBr) ν cm^{-1}; 3430 (NH), 3273 (NH), 2225 (CN), 1651 (C=O). ^{1}H NMR (DMSO-d_6) δ ppm: 1.33 (t, 3H, CH_3), 2.47 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.0 (q, 2H, CH_2), 6.79-7.43 (m, 8H, Ar-H), 9.56 (s, 1H, NH) and 14.38 (s, 1H, NH). **MS**: m/z=419 ($M^{\cdot +}$). Anal. Calcd. For $C_{23}H_{21}N_3O_3S$ (419.51). C, 65.85; H, 5.05; N, 10.02; S, 7.64. Found: C, 65.70; H, 5.00; N, 10.00, S, 7.70.

Preparation of compounds 19a-c:
***General procedure*:**

A solution of acetoacetanilide **1** (0.01 mole), aromatic aldehyde (0.01 mole) and catalytic amount of triethylamine (0.5 mL) in ethanol (30 mL) was refluxed for 10 h. The solid product formed on heating was collected by filtration, recrystallized from the ethanol to give **19a-c**.

4-Methyl-1,3-bis-[(2-ethoxyphenyl)aminocarbonyl]-6-oxo-2-p-tolyl-cyclohex-3-ene (19a).

It was obtained from acetoacetanilide **1** (0.01 mole) and 4-methyl benzaldehyde as colorless crystals in yield (80%). mp.=218 ºC. IR (KBr) ν cm^{-1}; 3412, 3386 (2NH), 1713, 1674 (3C=O). ^{1}H NMR (DMSO-d_6) δ ppm: 1.31 (t, 3H, CH_3), 1.39 (t, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 4.02 (q, 2H, CH_2), 4.02 (q, 2H, CH_2), 5.80 (s, 2H, CH_2 cyclohexene), 6.77-7.17 (m, 12H, Ar-H), 7.59 (d, 1H, CH cyclohexene), 7.87 (d, 1H, CH cyclohexene), 8.71 (s, 1H, NH) and 9.31 (s, 1H, NH). ^{13}C NMR: 14.56 (q); 14.75 (q); 20.68 (q); 27.85 (q); 44.86 (q); 54.18 (t); 62.60 (t); 64.16 (d); 72.59 (d); 72.59 (d); 112.32 (s); 112.64 (s); 120.31 (d); 121.03 (s); 123.99 (d); 127,46 (s); 127.74 (d); 128.12 (s); 128.60 (d); 135.58 (s); 135.59 (s); 137.17 (s); 147.80 (s); 166.36 (s, CO); 170.00 (s, CO); 204.78 (s, CO). MS: m/z=525 (M^{-1}). Anal. Calcd. For $C_{32}H_{34}N_2O_5$ (526.64): C, 72.98; H, 6.51; N, 5.32. Found: C, 72.80; H, 6.40; N, 5.20.

2-(4-(Dimethylaminophenyl)-1,3-bis-[(2-ethoxyphenyl)aminocarbonyl]-4-methyl-6-oxo-cyclohex-3-ene (19b) .

It was obtained from acetoacetanilide **1** (0.01 mole) and 4-dimethylamino benzaldehyde as colorless crystals in yield (70%). mp. =230 ºC. IR (KBr) ν cm^{-1}; 3411, 3383 (2NH), 1713 (C=O), 1674 (2C=O). ^{1}H NMR (DMSO-d_6) δ ppm: 1.35 (t, 3H, CH_3), 1.43 (t, 3H, CH_3), 2.81 (s, 3H , CH_3), 3.19 (s, 6H , $N(CH_3)_2$), 4.01 (q, 2H, CH_2), 4.28 (q, 2H, CH_2), 5.65 (hump, 2H, CH_2 cyclohexene), 6.54-7.14 (m, 12H, Ar-H), 7.68 (d, 1H, CH cyclohexene), 7.95 (d, 1H, CH cyclohexene), 8.71 (s, 1H, NH) and 9.33 (s, 1H, NH). Anal. Calcd. For $C_{33}H_{37}N_3O_5$ (555.68): C, 71.33; H, 6.71; N, 7.56. Found: C, 71.20; H, 6.60; N, 7.60.

2-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-1,3-bis-[(2-ethoxyphenyl)aminocarbonyl]-4-methyl-6-oxo-cyclohex-3-ene (19c).

It was obtained from acetoacetanilide **1** (0.01 mole) and 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde as colorless crystals from ethanol in yield (80%). mp.=205 ºC. IR (KBr) ν cm^{-1}; 3401 (NH), 3344 (NH), 1705, 1674 (3C=O). ^{1}H NMR (DMSO-d_6) δ ppm: 1.19 (t, 3H, CH_3), 1.30 (t, 3H, CH_3), 2.53 (s, 3H, CH_3), 3.96 (q, 2H, CH_2), 4.39 (q, 2H, CH_2), 5.80 (s, 2H, CH_2 cyclohexene), 6.75-7.58 (m, 18H, Ar-H), 7.76 (d, 1H, CH cyclohexene), 7.86 (d, 1H, CH cyclohexene), 8.73 (s, 1H, CH pyrazole), 8.95 (s, 1H, NH) and 9.18 (s, 1H, NH). Anal. Calcd. For $C_{40}H_{38}N_4O_5$ (654.77): C, 73.38; H, 5.85; N, 8.56. Found: C, 73.30; H, 5.80; N, 8.50.

Preparation of compounds 23a,b:
General procedure:

To a solution of acetoacetanilide **1** (0.01 mole) in ethanol (30 mL) containing a few drops of hydrochloric acid (5 mL), thiourea or urea (0.01 mole) and aromatic aldehyde (0.01 mole) were added. The reaction mixture was heated under reflux for 4 h. The solid product which produced on hot was collected by filtration and recrystallized from ethanol to give **23a,b.**

4-(4-Chlorophenyl)-5-(2-ethoxyphenyl)aminocarbonyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine (23a).

It was obtained from acetoacetanilide **1** (0.01 mole), 4-chloro benzaldehyde (0.01 mole) and thiourea (0.01 mole) as yellow crystals; yield (80%); mp.=205 ºC. IR (KBr) ν cm^{-1}; 3434 (NH), 3254 (NH), 3162 (NH), 1644 (C=O). ^{1}H NMR (DMSO-d_6) δ ppm: 1.27 (t, 3H, CH_3), 2.22 (s, 3H, CH_3), 4.0 (q, 2H, CH_2), 5.33 (s, 1H, CH pyrimidine), 6.85-7.46 (m, 8H, Ar-H), 8.57 (s, 1H, NH), 9.45 (s, 1H, NH) and 10.00 (s, 1H, NH). MS: m/z=401(M^+), 403 (M^{+2}). Anal. Calcd. For $C_{20}H_{20}ClN_3O_2S$ (401.92): C, 59.77; H, 5.02; N, 10.45; Cl, 8.82; S, 7.98. Found: C, 59.60; H, 5.00; N, 10.40; Cl, 8.90; S, 7.90.

4-(4-Chlorophenyl)-5-(2-ethoxyphenyl)aminocarbonyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (23b).

It was obtained from acetoacetanilide **1** (0.01 mole), 4-chloro benzaldehyde (0.01 mole) and urea (0.01 mole) as white crystals; yield (60%); mp. = 230 ºC. IR (KBr) ν cm^{-1}: 3418 (NH), 3269 (NH), 3131 (NH), 1696 (C=O), 1639 (C=O). ^{1}H NMR (DMSO-d_6) δ ppm: 1.07 (t, 3H, CH_3), 2.21 (s, 3H, CH_3), 3.96 (q, 2H, CH_2), 5.38 (s, 1H, CH pyrimidine), 6.84-7.51 (m, 9H, Ar-H+NH), 8.66 (s, 1H, NH) and 8.91 (s, 1H, NH). Anal. Calcd. For $C_{20}H_{20}ClN_3O_3$ (385.85): C, 62.26; H, 5.22; N, 10.89; Cl, 9.19. Found: C, 62.10; H, 5.20; N, 10.80; Cl, 9.20.

Preparation of compounds 26a,b:
General procedure:

To a solution of acetoacetanilide **1** (0.01 mole) in ethanol (40 mL) containing catalytic amount of piperdine (4 drops), chalcones deriveatives **24a,b** (0.01 mole) were added. The reaction mixture was heated under reflux for 10 h. The solid product formed on heating was collected by fIltration, recrystallized from ethanol to give **26a,b**.

6-(4-Chlorophenyl)-1-(2-ethoxyphenyl)aminocarbonyl-2-oxo-4-p-tolyl-cyclohex-3-ene (26a).

It was obtained from acetoacetanilide **1** (0.01 mole) and 3-(4-chlorophenyl)-1-(4-methylphenyl*)*-propenone **24a** (0.01 mole) as white crystals from ethanol in yield (60%), mp. = 170 ºC. IR (KBr**)** ν cm^{-1}; 3270 (NH), 1665 (2C=O). ^{1}H NMR (DMSO-d_6**)** δ ppm: 1.38 (t, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.04 (t, 1H, CH cyclohexene), 3.32 (d, 1H, CH cyclohexene), 4.02 (q, 2H, CH_2), 4.39 (d, 2H, CH_2 cyclohexene), 6.54 (s, 1H, CH cyclohexene), 6.81-7.80 (m, 12H, Ar-H) and 9.04 (s, 1H, NH). ^{13}C NMR: 14.60 (q); 20.94 (q); 58.90 (t); 64.15 (t); 112.64 (d); 120.24 (d)); 121.67 (d); 122.81 (s); 124.42 (d); 124.42 (d); 126.51 (s); 127.41 (s); 128.32 (d); 129.52 (s); 129,64 (d); 129.64 (d); 131.38 (s); 134.51 (s), 140.55 (s); 141.43 (d); 148.38 (d); 158.48 (d); 167.45 (s, CO); 195.44 (s, CO). Anal. Calcd. For $C_{28}H_{26}ClNO_3$ (459.98): C, 73.11; H, 5.70; N, 3.05; Cl, 7.71. Found: C, 73.00; H, 5.60; N, 3.00; Cl, 7.80.

4-(4-Bromophenyl)-6-(4-chlorophenyl)- 1-(2-ethoxyphenyl)aminocarbonyl-2-oxo-cyclohex-3-ene (26b).

It was obtained from acetoacetanilide **1** (0.01 mole) and 1-(4-bromophenyl)-3-(4-chlorophenyl)-propenone **24b** (0.01 mole) as yellow crystals in yield (80%), mp. =180 ºC. IR (KBr) ν cm^{-1}; 3374 (NH), 1688 (C=O), 1653 (C=O). ^{1}H NMR ($CDCl_3$): 1.52 (t, 3H, CH_3), 3.00 (t, 1H, CH cyclohexene), 3.93 (d, 1H, CH cyclohexene), 4.12 (q, 2H, CH_2), 4.70 (d, 2H, CH_2 cyclohexene), 6.59 (s, 1H, CH cyclohexene), 6.84-8.31 (m, 12H, Ar-H) and 8.66 (s, 1H, NH). MS: m/z=523 (M^+), 525 (M^{+2}). Anal. Calcd. For $C_{27}H_{23}BrClNO_3$ (524.85): C, 61.79; H, 4.42; N, 2.67; Br, 15.22; Cl, 6.75. Found: C, 61.70; H, 4.30; N, 2.60; Br, 15.30; Cl, 6.80.

Compound (27): Ethyl 2-amino-5-((2-ethoxyphenyl)carbamoyl)-4-methylthiophene-3-carboxylate.

A solution of acetoacetanilide **1** (0.01 mole), ethyl cyanoacetate, elemental sulfur and few drops of triethylamine (4 drops) in absolute ethanol (30 mL) was refluxed for (4-8) h. The reaction mixture left to cool, the solid which formed collected by filtration, washed with ethanol, dried and recrystallized from ethanol to give **27** as brown crystals in yield (80%), mp. =175 ºC, IR (KBr) ν cm^{-1}; 3432, 3316 (NH_2, NH), 1647 (C=O), 1633 (C= O). ^{1}H NMR (DMSO-d_6) δ ppm: 1.29 (t, 3H, CH_3), 1.40 (t, 3H, CH_3), 2.49 (s, 3H, CH_3), 3.75 (s, 2H, NH_2), 4.09 (q, 2H, CH_2), 4.14 (q, 2H, CH_2), 6.90-8.08 (m, 4H, Ar-H), and 8.50 (s, 1H, NH). **MS**: m/z=348 (M^+). Anal. Calcd. For $C_{17}H_{20}N_2O_4S$ (348.42): C, 58.60; H, 5.79; N, 8.04; S; 9.20. Found: C, 58.50; H, 5.70; N, 8.00; S, 9.20.

Compound (28): N-(2-ethoxyphenyl)-5-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxamide.

A mixture of compound **27** (0.01 mole) and formamide (10 mL) was heated under reflux for 10 h. The solid obtained on hot was crystallized from ethanol to give **28**, as brown powder in yield (65%), mp. =270 ºC. IR (KBr) ν cm^{-1}; 3423 (NH), 3274 (NH), 1670 (C=O). ^{1}H NMR (DMSO-d_6) δ ppm: 1.41 (t, 3H, CH_3), 2.87 (s, 3H, CH_3), 4.12 (q, 2H, CH_2), 6.93-8.01 (m, 4H, Ar-H), 8.17 (s, 1H, CH pyrimidine), 9.09

(s, 1H, NH) and 12.56 (hump, 1H, NH). Anal. Calcd. For $C_{16}H_{15}N_3O_3S$ (329.38): C, 58.35; H, 4.59; N, 12.76; S, 9.73. Found: C, 58.20; H, 4.50; N, 12.70; S, 9.80.

Compound (29): N-(2-ethoxyphenyl)-5-methyl-4-oxo-2-thioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidine-6-carboxamide.

A mixture of compound **27** (0.01 mole) and potassium thiocyanate (0.15 mole) was stirred under reflux in dioxane containing (10%) HCl for 15 h. poured onto (200 mL) water, the solid precipitated was filtered off, and crystallized from ethanol, as brown crystals, in yield (70%). mp.=260 ºC. IR (KBr) ν cm^{-1}; 3423 (br., 3NH), 1627, 1686 (2C=O). ^{1}H NMR (DMSO-d_6) δ ppm: 1.41 (t, 3H, CH_3), 2.79 (s, 3H, CH_3), 4.14 (q, 2H, CH_2), 6.92-8.01 (m, 4H, Ar-H), 8.98 (s, 1H, NH), 12.49 (s, 1H, NH) and 13.49 (hump, 1H, NH). MS: m/z=361 ($M^{\cdot+}$). Anal. Calcd. For $C_{16}H_{15}N_3O_3S_2$ (361.44): C, 53.17; H, 4.18; N, 11.63, S, 17.74. Found: C, 53.10; H, 4.00; N, 11.60; S, 17.80.

Compound (30): 5-Amino-N-(2-ethoxyphenyl)-4-(hydrazinecarbonyl)-3-methylthiophene-2-carboxamide.

A mixture of compound **27** (0.01 mole) and hydrazine hydrate (5 mL) in ethanol (20 mL) was refluxed for 10 h. The reaction mixture was poured onto ice-cold water, filtered off, recrystallized from ethanol to give **30** as gray crystals in yield (60%), mp. =190 ºC. IR (KBr) ν cm^{-1}; 3432, 3298 (2NH_2, NH), 3160 (NH), 1634 (2C=O). ^{1}H NMR (DMSO-d_6) δ ppm: 1.40 (t, 3H, CH_3), 2.62 (s, 3H, CH_3), 3.75 (s, 2H, NH_2), 4.13 (q, 2H, CH_2), 6.88-7.09 (m, 4H, Ar-H), 7.78 (s, 2H, NH_2), 8.50 (s, 1H, NH) and 8.87 (s, 1H, NH). Anal. Calcd. For $C_{15}H_{18}N_4O_3S$ (334.40): C, 53.88; H, 5.43; N, 16.75; S, 9.59. Found: C, 53.70; H, 5.40; N, 16.70; S, 9.60.

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