JACOBS PUBLISHERS

OPEN ACCESS

Jacobs Journal of Organic Chemistry

Research Article

# Synthesis of Pyran, Pyridine, Thiophene, Pyrimidine and Thiazole Derivatives with Antitumor Activities

Rafat M. Mohareb[1*], Ensaf S. Alwan[1,2]

[1]*Department of Chemistry, Cairo University, Giza, A. R. Egypt*

[2]*Department of Quality Assurance, Yemen Drug Company for industry and Commerce (YEDCO) , Sana'a, Yemen*

**Corresponding author: Dr. Rafat M. Mohareb, Department of Chemistry, Cairo University, Giza, A. R. Egypt,*

*Email: raafat_mohareb@yahoo.com*

*Received:* 06-06-2016

*Accepted:* 09-09-2016

*Published:* 11-08-2016



## Abstract

The aim of present study was the uses of 4- methyl cyanoacetanilide (1) in the synthesis of pyridine, pyran, thiophene, thiazole, pyrimidine, chromen derivatives together with their antitumor evaluations. The work has resulted in the synthesis of a variety of 2- aminopyran, 2- hydroxypyran, 2-amino pyridine, 2-hydroxypyridine, 4,5,6,7-tetrahydrobenzo[b]thiophene, N-benzal,N-acetyl, N-phenylthiourea, thiazole, pyrimidine, phenylhydrazone, benzalydine, ethoxyethine and N- phenylmethino derivatives. The antitumor activities of the newly synthesized product were evaluated against cancer.

**Keywords :** Pyridine; Pyran; Thiophene; Pyrimidine; Antitumor Activities

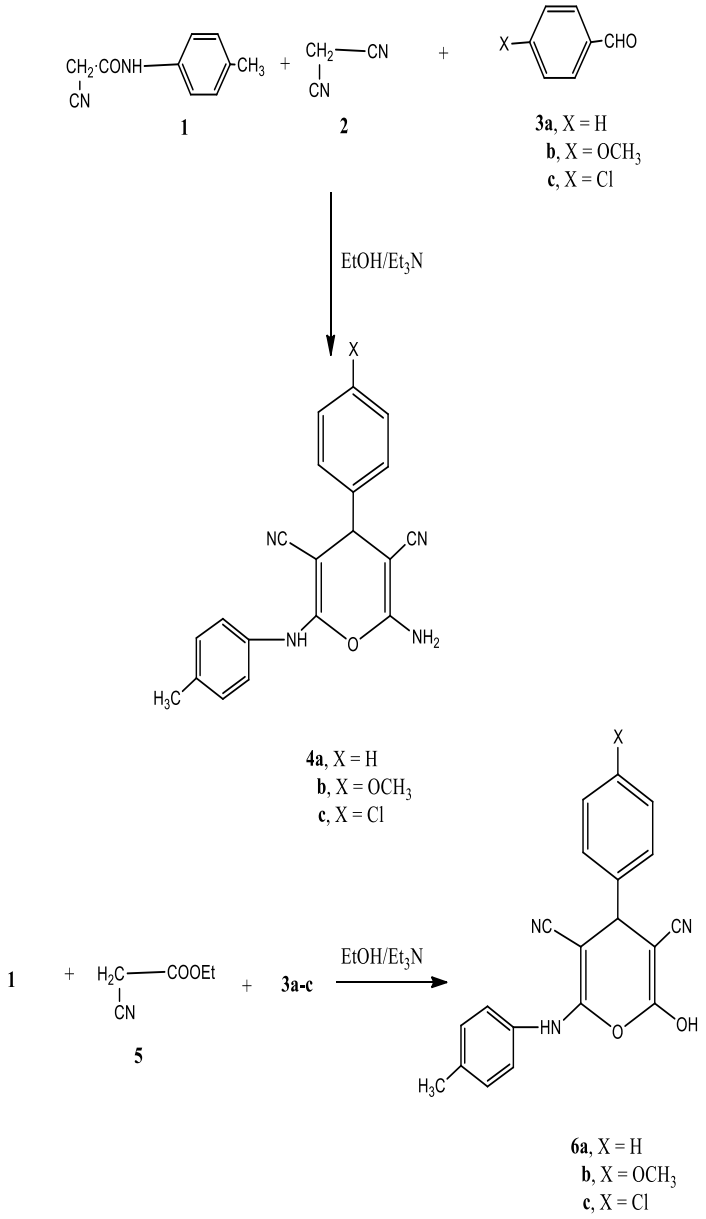
## Introduction

Multicomponent reactions (MCRs) have emerged as a valuable tool in the preparation of structurally diverse chemical libraries of heterocyclic compounds [1]. They are inherently atom economical processes in which relatively complex products can be obtained in a one-pot reaction from simple starting materials, and thus they exemplify many of the desired features of an ideal synthesis. MCRs are generally much more environmentally friendly and offer access to large compound libraries with diverse functionalities with the avoidance of protection and deprotection steps for possible combinatorial surveying of structural variations. In view of the increasing interest in the preparation of a large variety of heterocyclic compound libraries, the development of new synthetically valuable MCRs with several diversity points remains a challenge for both academic and industrial institutions [2]. Thiophene and its derivatives are an important class of heterocyclic compounds possessing broad biological activities, such as anti-inflammatory [3], analgesic [3], antioxidant [4], antitubercular [5], antidepressant [6], sedative [6], antiamoebic [7], oral analgesic [8], anti-metabolite [9] and antineoplastic properties [10]. From the aforementioned reports, it seemed that the development of an efficient, rapid, and clean synthetic route towards focused libraries of such compounds is of great importance to both medicinal and synthetic chemists. Hence in this paper, we report a one-pot, three-component reaction for the synthesis of pyran derivatives through the reaction of α-cyano-4-methylacetanilide (**1**) with cyanomethylene derivatives and aromatic aldehydes. All the synthesized compounds were characterized using FT-IR, $^1$H NMR, $^{13}$C NMR, and mass spectrometry and were subjected to screening towards cancer cell lines.

## Results and Discussion

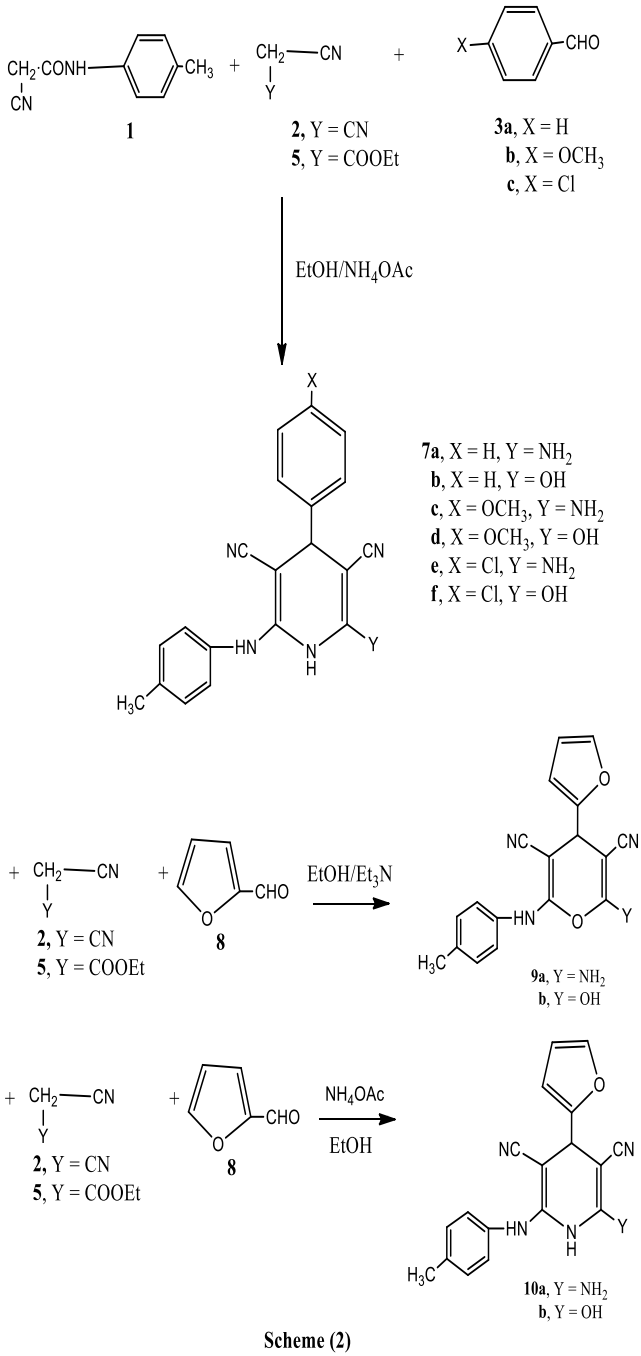
In the present work, the multicomponent reaction of 4-methylcyanoacetanilide (**1**) reacted with malononitrile(**2**) and any of benzaldehyde (**3a**), 4-methoxybenzaldehyde (**3b**), and 4-chlorobenzaldehyde (**3c**), in ethanolic/triethylamine gave the 2-amino pyran derivatives **4a-c**, respectively. The analytical and spectral data of the compounds **4a-c** were the tools of their structural elucidation. Thus, the $^1$H NMR spectrum of compound **4a** showed a singlet at δ 3.11 ppm due to the presence of $CH_3$ group, a singlet, $D_2O$ exchangeable at δ 4.82 ppm indicating the presence of $NH_2$ group, a singlet at δ 6.05 ppm for the pyran H-4, a multiplet at δ 7.28-7.39 ppm for the two phenyl protons and a singlet, $D_2O$ exchangeable, at δ 8.29 ppm

for the NH group. Similarly, the multi-component reaction of compound (**1**) with ethyl cyanoacetate (**5**) and any of benzaldehyde (**3a**), 4-methoxybenzaldehyde (**3b**), and 4-chlorobenzaldehyde (**3c**) gave the 2-hydroxypyran derivatives **6a-c**, respectively (Scheme 1).




**Scheme (1)**

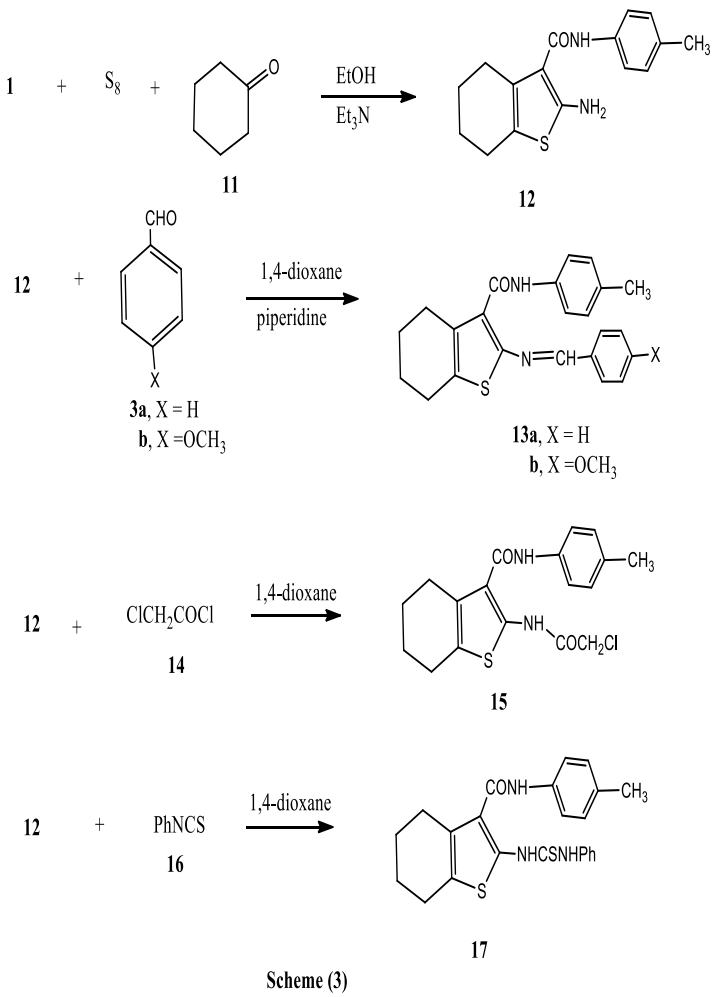
On the other hand, carrying the multi-component reactions of compound **1** with either of malononitrile (**2**) or ethyl cyanoacetate (**5**) and any of the aromatic aldehydes **3a-c** but in the presence of ammonium acetate instead of triethylamine gave the pyridine derivatives **7a-f**, respectively. The analytical and spectral data of compounds **7a-f** were consistent with their respective structures. Thus, the $^1$H NMR spectrum of compound **7a** (as an example) showed a singlet at δ 3.16 ppm due to the presence of $CH_3$ group, a singlet, $D_2O$ exchangeable, at δ 4.89 ppm indicating the presence of $NH_2$ group, a singlet at δ 6.14 ppm for the pyridine H-4, a multiplet at δ 7.26-7.35 ppm for the two phenyl protons and two singlets, $D_2O$ exchangeable, at δ 8.33 & 8.38 ppm for the two NH group. The multi-component reaction of compound 1 with furfural (**8**) and either of malononitrile (**2**) or ethyl cyanoacetate (**5**) in ethanolic/triethylamine gave the pyran derivatives **9a,b**; respectively. Carrying the same reaction of compound **1** with either of malononitrile (**2**) or ethyl cyanoacetate (**5**) but in the presence of ammonium acetate instead of triethylamine gave the pyridine derivatives **10a** and **10b**, respectively (Scheme 2).




**Scheme (2)**

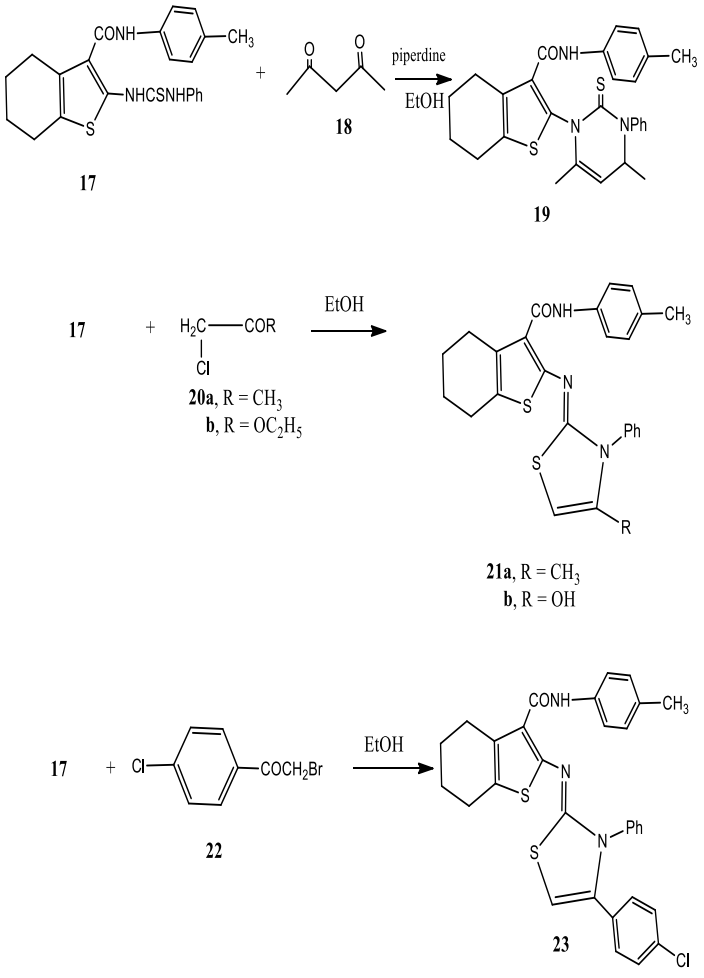
Next, we moved towards the uses of compound (**1**) to form thiophene derivatives using the Gewald's thiophene synthesis. Thus, the reaction of compound **1** with elemental sulfur

and cyclohexanone (**11**) in ethanolic/triethylamine gave the 4,5,6,7-tetrahydrobenzo[*b*]thiophene derivative **12**. Compound **12** was used as the key starting product for the synthesis of acyclic and heterocyclic derivatives incorporated thiophene moiety. Thus, the reaction of compound **12** with any of benzaldehyde (**3a**) or 4-methoxybenzaldehyde (**3b**) in 1,4-dioxane containing a catalytic amount of piperidine gave the N-benzal derivatives **13a** and **13b**, respectively. On the other hand, the reaction of compound **12** with α-chloroacetylchloride (**14**) in 1,4dioxane gave the N-acetyl derivative **15**. The analytical and spectral data of the latter product were used to elucidate its structure. Thus, the $^1$H NMR spectrum of compound **15** revealed two multiplets at δ 1.60-1.84 and 2.22-2.40 ppm indicating the psesence of the four $CH_2$ group, a singlet at δ 3.15 ppm due to the presence of $CH_3$, a singlet at δ 5.24 ppm due to the presence of $CH_2$ group, two doublets at δ 7.25-7.39 ppm for the phenyl protons and two singlets, $D_2O$ exchangeable, at δ 8.24, 8.30 ppm for the two NH group. Moreover, the reaction of compound **12** with phenylisothiocyanate **(16)** in 1,4-dioxane gave the N-phenylthiourea derivative **17** (Scheme 3).




**Scheme (3)**

Compounds **17** was used for further heterocyclization reactions to give thiazole derivatives with potential antitumor activity. Thus compound **17** reacted with acetylacetone **(18)** in ethanol containing a catalytic amount of piperidine to give the pyrimidine derivative **19**. The analytical and spectral data of the latter product are in agreement with its structure. Thus, the $^1$H NMR spectrum of compound **19** showed two multiplets at δ 1.60-1.84 and 2.20-2.38 ppm indicating the presence of four $CH_2$ group, three singlets at δ 2.87, 3.05, 3.13 ppm due to the presence of three $CH_3$ group, a multiplet at δ 6.22 ppm for the pyrimidine H-4, H-5, a multiplet at δ 7.28-7.36 ppm for the two phenyl protons and a singlet, $D_2O$ exchangeable, at δ 8.28 ppm for the NH group. Compound **17** with its thiourea moiety capable for the synthesis of thiazole derivatives. Thus, the reaction of compound **17** with either of α-chloroacetone **(20a)** or ethyl chloroacetate **(20b)** in ethanol solution under reflux gave the thiazole derivatives **21a** and **21b**, respectively. Moreover, the reaction of compound **17** with ω-bromo-4-chloroacetophenone **(22)** in ethanol solution gave the thiazole derivative **23** (Scheme 4).

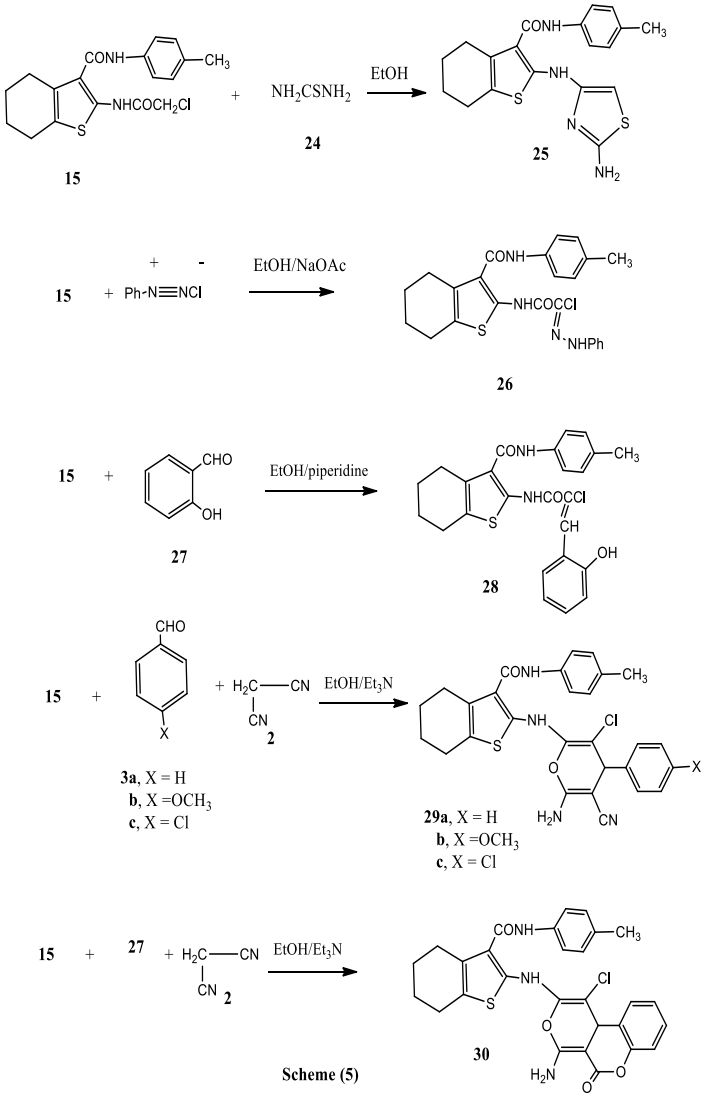



**Scheme (4)**

The 2-(2-chloroacetamido)-N-(p-tolyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide **(15)** showed interesting reactivity toward some chemical reagents. Thus, it reacted with

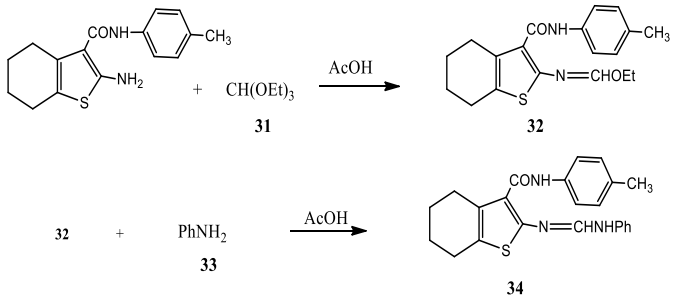
thiourea **(24)** in ethanol solution to give thiazole derivative **25**. On the other hand, the reaction of compound **15** with benzenediazonium chloride in ethanolic/sodium acetate at 0-5 ºC give phenylhydrazone derivative **26**, moreover, the reaction of compound **15** with salicylaldehyde **(27)** in ethanolic/piperidine gave the benzylidine derivative **28**.

The multi-component reaction of compound **15** with malononitrile **(2)** and either of the aromatic aldehydes namely benzaldehyde **(3a)**, 4-methoxybenzaldehyde **(3b)** or 4-chlorobenzaldehyde **(3c)** in ethanolic/triethylamine gave the pyran derivatives **29a-c**, respectively. On the other hand, the reaction of compound **15** with malononitrile **(2)** and salicylaldehyde **(27)** in ethanolic/triethylamine gave the 5,10b-dihydropyrano[3,4-*c*]chromen-2-yl derivative **(30).** Formation of compound **30** was assumed on the intermediate formation of the expected pyran derivative followed by the Micheal addition of the 2-hydroxy group of salicylaldehyde to the 3-cyanopyrane moiety to give compound **30** (Scheme 5).




Scheme (5)

The multi-component reaction of compound **12** with triethylorthoformate **(31)** in acetic acid solution gave ethoxyethine derivative **32**. Compound **32** reacted with aniline **(33)** in acetic acid solution to give N- phenylmethino derivative **34** (Scheme 6).




Scheme (6)

## Antitumor evaluations

Fetal bovine serum (FBS) and L-glutamine, were from Gibco Invitrogen Co. (Scotland, UK). RPMI-1640 medium was from Cambrex (New Jersey, USA). Dimethyl sulfoxide (DMSO), doxorubicin, penicillin, streptomycin and sulforhodamine B (SRB) were from Sigma Chemical Co. (Saint Louis, USA).

Cell cultures: Three human tumor cell lines, MCF-7 (breast adenocarcinoma), NCI-H460 (non-small cell lung cancer), and SF-268 (CNS cancer) were used. MCF-7 was obtained from the European Collection of Cell Cultures (ECACC, Salisbury, UK) and NCI-H460 and SF-268 were kindly provided by the National Cancer Institute (NCI, Cairo, Egypt). They grow as monolayer and routinely maintained in RPMI-1640 medium supplemented with 5 % heat inactivated FBS, 2 mM glutamine and antibiotics (penicillin 100 U/mL, streptomycin 100 µg/mL), at 37°C in a humidified atmosphere containing 5 % $CO_2$. Exponentially growing cells were obtained by plating 1.5 x $10^5$ cells/mL for MCF-7 and SF-268 and 0.75 x $10^4$ cells/mL for NCI-H460, followed by 24 h of incubation. The effect of the vehicle solvent (DMSO) on the growth of these cell lines was evaluated in all the experiments by exposing untreated control cells to the maximum concentration (0.5 %) of DMSO used in each assay.

## Tumor Cell Growth Assay

The effects of **4a-34** on the in vitro growth of human tumor cell lines were evaluated according to the procedure adopted by the National Cancer Institute (NCI, USA) in the 'In vitro Anticancer Drug Discovery Screen' that uses the protein-binding dye sulforhodamine B to assess cell growth. Briefly, exponentially, cells growing in 96-well plates were then exposed for 48 h to five serial concentrations of each compound, starting from a maximum concentration of 150 µM. Following this exposure period adherent cells were fixed, washed, and stained. The bound stain was solubilized and the absorbance was measured at 492 nm in a plate reader (Bio-Tek Instruments Inc., Power wave XS, Wincoski, USA). For each test compound and

cell line, a dose–response curve was obtained and the growth inhibition of 50 % ($GI_{50}$), corresponding to the concentration of the compounds that inhibited 50 % of the net cell growth, was calculated as described by the National Cancer Research Center in Cairo, Egypt. Doxorubicin was used as a positive control and tested in the same manner.

| Compound | $GI_{50}$ (μmol $L^{-1}$) | | |
|---|---|---|---|
| | MCF-7 | NCI-H460 | SF-268 |
| **4a** | 0.06 ± 0.004 | 0.03 ± 0.003 | 0.1 ± 0.02 |
| **4b** | 0.01 ± 0.002 | 0.01 ± 0.004 | 0.04 ± 0.01 |
| **4c** | 0.03 ± 0.002 | 0.02 ± 0.003 | 0.05 ± 0.002 |
| **6a** | 0.3 ± 0.1 | 0.2 ± 0.08 | 0.5 ± 0.01 |
| **6b** | 0.9 ± 0.2 | 0.1 ± 0.02 | 0.3 ± 0.05 |
| **6c** | 2.84 ± 0.14 | 4.62 ± 1.04 | 6.08 ± 1.16 |
| **7a** | 28.6 ± 12.2 | 12.6 ± 8.6 | 52.4 ± 14.6 |
| **7b** | 26.4 ± 2.2 | 34.1 ± 0.8 | 18.8 ± 4.8 |
| **7c** | 18.1 ± 0.6 | 16.3 ± 1.4 | 12.3 ±1.5 |
| **7d** | 0.01 ± 0.003 | 0.02 ± 0.001 | 0.01 ± 0.001 |
| **7e** | 16.29 ± 4.06 | 20.81 ± 8.29 | 18.29 ± 6.39 |
| **7f** | 22.6 ± 1.4 | 24.9 ± 2.8 | 13.8 ± 3.8 |
| **9a** | 0.02 ± 0.005 | 0.06 ± 0.004 | 0.02 ± 0.003 |
| **9b** | 55.1 ± 2.7 | 23.2 ± 4.8 | 14.4 ± 2.6 |
| **10a** | 36.2 ± 6.24 | 26.19 ± 6.22 | 22.40 ± 3.21 |
| **10b** | 0.42 ± 0.2 | 0.14 ± 0.02 | 0.92 ± 0.08 |
| **12** | 22.6 ± 2.6 | 24.3 ± 0.8 | 30.9 ± 3.8 |
| **13a** | 10.8 ± 2.6 | 4.5 ± 0.8 | 4.8 ± 1.8 |
| **13b** | 0.73 ± 0.50 | 0.25 ± 0.08 | 1.03 ± 0.02 |
| **15** | 32.8 ± 0.6 | 36.5 ± 0.8 | 30.7 ± 1.6 |
| **17** | 70.7 ± 18.5 | 40.2 ± 12.8 | 52.4 ± 8.6 |
| **19** | 31.41± 2.83 | 20.80 ± 4.33 | 18.21 ±3.70 |
| **21a** | 0.02 ± 0.008 | 0.03 ± 0.006 | 0.05 ± 0.00 |
| **21b** | 22.4 ± 2.2 | 32.6 ± 1.4 | 26.8 ± 6.4 |
| **23** | 28.75 ± 6.16 | 24.58 ± 16.07 | 18.41 ± 4.22 |
| **25** | 60.6 ± 16.9 | 38.9 ± 10.8 | 50.8 ± 8.6 |
| **26** | 0.02± 0.005 | 0.01 ±0.007 | 0.20 ± 0.03 |
| **28** | 0.63± 0.07 | 0.80 ± 0.14 | 0.018 ± 0.002 |
| **29a** | 2.84 ± 2.04 | 3.62 ± 1.04 | 6.08 ± 2.16 |
| **29b** | 1.29 ± 0.04 | 5.29 ± 1.84 | 3.14 ± 1.06 |
| **29c** | 36.0 ± 1.8 | 43.0 ± 0.8 | 30.5 ± 1.1 |
| **30** | 0.31± 0.020 | 0.21 ±0.03 | 0.39 ± 0.13 |
| **32** | 30.6 ± 10.2 | 32.6 ± 8.6 | 24.4 ± 12.8 |
| **34** | 0.01 ± 0.006 | 0.03 ± 0.001 | 0.02 ± 0.004 |
| Doxorubicin | 0.04 ± 0.008 | 0.09 ± 0.008 | 0.09 ± 0.007 |

**Table 1.** Effect of the newly synthesized compounds on the growth of three human tumor cell lines.

Results are given in concentrations that were able to cause 50 % of cell growth inhibition ($GI_{50}$) after a continuous exposure of 48 h and show means ± SEM of three-independent experiments performed in duplicate.

The effect of compounds **4a** to **34** was evaluated on in vitro growth of three human tumor cell lines representing different tumor namely (MCF-7), (NCI-H460), (SF-268) after a continuous exposure for 48 h, these effects were indicated through figure 1.

The results were summarized in the previous table.

The results indicate that:

Compounds **4b, 4c, 7d, 9a, 21a, 34** showed the highest inhibitory effect against all the three tumor cell lines. Compounds 4a, 26 showed high inhibitory effect against (MCF-7), (NCI-H460). Compounds **6a, 6b, 10b, 13b, 30** showed moderate inhibitory effect against the three cell line. Compound **28** showed the moderate inhibitory effect against (MCF-7), (NCI-H460), and high inhibitory effect against (SF-268). (Compounds **6c, 7a, 7b, 7c, 7e, 7f, 9b, 10a, 12, 13a, 15, 17, 19, 21b, 23, 25, 29a, 29b, 29c, 32** showed the lowest inhibitory effect against the three cell lines. Comparing the inhibitory effect of the compound **4a, 4b, 4c** it is obvious that the highest inhibitory effect of compounds **4b** and **4c** against all the three tumor cell lines attributed to the presence of 4-methoxy group, chlorine atom respectively which are not presence in compound **4a** which showed high inhibitory effect against (MCF-7), (NCI-H46). Considering pyridine derivatives **7a-7f** it is obvious that compound **7d** with its hydroxyl and 4-methoxy groups showed highest inhibitory effect against all the three tumor cell lines. The high inhibitory effect of compound **9a** relative compound **9b** against all the three tumor cell lines attributed to the presence of amine group moieties. Also the high inhibitory effect of compound **21a** relative to **21b** against all the three tumor cell lines attributed to the presence of methyl group. On the other hand the high inhibitory effect of compound **26** against (MCF-7), (NCI-H460 ) attributed to the presence of chlorine atom and phenylhydrazone group. Finally the high inhibitory effect of compound **34** against of the three tumor cell lines attributed to the presence of N- phenylmethino group (Figure 1).

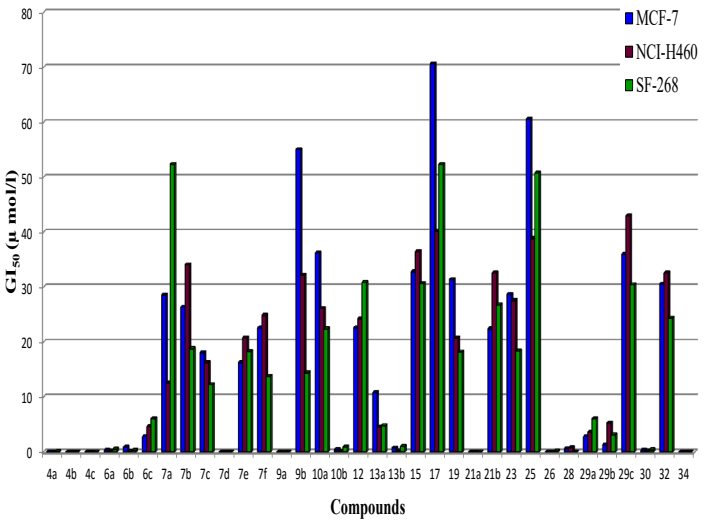



**Figure 1.** $GI_{50}$ of the new synthesized compounds against MCF-7, NCI-H460 and SF-268.

## Experimental

### General

All melting points were determined on an Electrothermal digital melting point apparatus and are uncorrected. IR spectra (KBr discs) were recorded on a FTIR plus 460 or PyeUnicam SP-1000 spectrophotometer. $^1$H NMR spectra were recorded with Varian Gemini-200 (200 MHz) and Jeol AS 500 MHz instruments spectra were performed in DMSO-*d*6 as solvent using TMS as internal standard and chemical shifts are expressed as δ ppm. MS (EI) spectra were recorded with Hewlett Packard 5988 A GC/MS system and GCMS-QP 1000 Ex Shimadzu instruments. Analytical data were obtained from the Micro-analytical Data Unit at Cairo University and were performed on Vario EL III Elemental analyzer. The Anti-tumor evaluation has been carried out through the National Cancer Research Center in Cairo, Egypt where the $GI_{50}$ values were calculated.

*2-Amino-4-phenyl-6-(p-tolylamino)-4H-pyran-3,5-dicarbonitrile **(4a)**, 2-amino-4-(4-methoxyphenyl)-6-(p-tolylamino)-4H-pyran-3,5-dicarbonitrile **(4b)** and 2-amino-4-(4-chlorophenyl)-6-(p-tolylamino)-4H-pyran-3,5-dicarbonitrile**(4c)**.*

**General procedure:** To a solution of compound **1** (1.74 g, 0.01 mol) in ethanol (50 mL) containing triethylamine (0.50 mL), malononitrile (0.66 g, 0.01 mol ) either of benzaldehyde (1.06 g, 0.01 mol), 4-methoxybenzaldehyde (1.36 g, 0.01 mol) or 4-chlorobenzaldehyde (1.41 g, 0.01 mol) was added. The reaction mixture in each case was heated under reflux for 4 h then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

Compound **4a**: Yellow crystals from ethanol, yield 73 % (2.4 g), m.p>300°C. *Anal*. Calculated for $C_{20}H_{16}N_4O$ (328.37): C, 73.15; H, 4.91; N, 17.06. Found: C, 73.08; H, 5.11; N; 16.89. MS: m/e 328 ($M^+$, 22 %), IR, υ: 3472-3332 ($NH_2$, NH), 3054 (CH, aromatic), 2227, 2222 (2CN), 1632 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): δ = 3.11 (s, 3H, $CH_3$), 4.82 (s, 2H, $D_2O$ exchangeable, NH2), 6.05 (s, 1H, pyran H-4), 7.28-7.39 (m, 9H, $C_6H_4$,$C_6H_5$), 8.29 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$C_6H_4$, 75 MHz): δ = 19.6 ($CH_3$), 80.4 (pyran C-4), 116.8, 117.0 (2CN), 119.3, 119.8, 120.2, 120.6, 122.4, 125.3, 126.0, 128.6, 129.8, 130.1, 132.2, 132.3 ($C_6H_5$, $C_6H_4$, pyran C).

Compound **4b**: Yellow crystals from ethanol yield 56 % (2.00 g), m.p 165 °C. *Anal*. Calculated for $C_{21}H_{18}N_4O_2$ (358.39): C, 70.38; H, 5.06; N, 15.63. Found: C, 70.19; H, 5.20; N; 15.83. MS: m/e 358 (M+, 16 %), IR, υ: 3478-3328 ($NH_2$, NH), 3054 (CH, aromatic), 2226, 2222 (2CN), 1631 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): δ = 3.09, 3.20 (2s, 6H, 2$CH_3$), 4.86 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.08 (s, 1H, pyran H-4), 7.26-7.45 (m, 8H, 2$C_6H_4$), 8.26 (s, $^1$H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$C_6H_4$,75 MHz): δ = 19.4 , 24.6 ($CH_3$, $OCH_3$), 80.4 (pyran C-4), 116.8, 117.0 (2CN), 119.6, 119.9, 120.4, 120.5, 122.0, 125.8, 126.0, 128.9, 129.6, 130.0, 132.9, 132.6 (2 C6H4, pyran C).

Compound **4c**: Yellow crystals from ethanol, yield 72 % (2.61 g), m.p> 300 °C. *Anal*. Calculated for $C_{20}H_{15}ClN_4O$ (362.81): C, 66.21; H, 4.17; N, 15.44. Found: C, 66.40; H, 4.38; N; 15.60. MS: m/e 362 (M+, 18 %), IR, υ: 3481-3319 ($NH_2$, NH), 3056 (CH, aromatic), 2224, 2220 (2CN), 1634 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): 3.12 (s, 3H, $CH_3$), 4.89 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.13 (s, 1H, pyran H-4), 7.28-7.39 (m, 8H, $C_6H_4$, $C_6H_4$), 8.29 (s, 1H, $D_2O$ exchangeable, NH).

*2-Hydroxy-4-phenyl-6-(p-tolylamino)-4H-pyran-3,5-dicarbonitrile **(6a)**, 2-hydroxy-4-(4-methoxyphenyl)-6-(p-tolylamino)-4H-pyran-3,5-dicarbonitrile **(6b)** and 2-hydroxy-4-(4-chlorophenyl)-6-(p-tolylamino)-4H-pyran-3,5-dicarbonitrile **(6c)***

**General procedure:** To a solution of compound **1** (1.74 g, 0.01 mol) in ethanol (50 mL) containing triethylamine (0.50 mL), ethyl cyanoacetate (1.13 g, 0.01 mol ), any of benzaldehyde (1.06 g, 0.01 mol), 4-methoxybenzaldehyde (1.36 g, 0.01 mol) or 4-chlorobenzaldehyde (1.41 g, 0.01 mol) was added. The reaction mixture in each case was heated under reflux for 4 h then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

Compound **6a**: Brown crystals from ethanol, yield 63 % (2.08 g), m.p 287 °C. *Anal*. Calculated for $C_{20}H_{15}N_3O_2$ (329.35): C, 72.94; H, 4.59; N, 12.76. Found: C, 73.13; H, 4.55; N; 12.46. MS: m/e 329 ($M^+$, 16 %), IR, υ: 3523-3318 (OH, NH), 3056 (CH, aromatic), 2228, 2220 (2CN), 1638 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): δ = 3.13 (s, 3H, $CH_3$), 6.12 (s, 1H, pyran H-4), 7.28-7.39 (m, 9H, $C_6H_5$, $C_6H_4$), 8.32 (s, 1H, $D_2O$ exchangeable, NH), 10.28 (s, $_1$H, $D_2O$ exchangeable, OH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ = 19.8 ($CH_3$), 80.6 (pyran C-4), 116.4, 116.7 (2CN), 120.3, 120.5, 121.4, 122.5, 123.8, 124.9, 126.1, 127.4, 128.5, 129.6, 130.0, 132.6 ($C_6H_5$, $C_6H_4$, pyran C).

Compound **6b**: Yellow crystals from ethanol, yield 67 % (2.40 g), m.p172 °C. *Anal*. Calculated for $C_{21}H_{17}N_3O_3$ (359.38): C, 70.18; H, 4.77; N, 11.69. Found: C, 70.23; H, 4.80; N; 11.72. MS: m/e 359 ($M^+$, 28 %), IR, υ: 3520-3321 (OH, NH), 3056 (CH, aromatic), 2228, 2220 (2CN), 1632 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): δ = 3.16 (s, 3H, $CH_3$), 3.14 (s, 3H, $OCH_3$), 6.13 (s, 1H, pyran H-4), 7.28-7.36 (m, 8H, 2$C_6H_4$), 8.28 (s, 1H, $D_2O$ exchangeable, NH), 10.20 (s, 1H, $D_2O$ exchangeable, OH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ = 19.6, 24.1 ($CH_3$, $OCH_3$), 80.4 (pyran C-4), 116.6, 117.2 (2CN), 120.1, 120.2, 121.6, 122.5, 124.0, 124.5, 126.1, 127.8, 129.0, 129.4, 130.3, 131.9 (2 $C_6H_4$, pyran C).

Compound **6c:** Yellow crystals from ethanol, yield 63 % (2.27 g), m.p> 300°C. *Anal*. Calculated for $C_{20}H_{14}ClN_3O_2$ (363.80): C, 66.03; H, 3.88; N, 11.55. Found: C, 66.18; H, 4.02; N; 11.63. MS: m/e 363 ($M^+$, 22 %), IR, υ: 3520-3308 (OH, NH), 3056 (CH, aromatic), 2224, 2220 (2CN), 1633(C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): 3.09 (s, 3H, $CH_3$), 6.11 (s, 1H, pyran H-4),

7.26-7.37 (m, 8H, $C_6H_4$, $C_6H_4$), 8.13 (s, 1H, $D_2O$ exchangeable, NH), 9.88 (s, $^1$H, $D_2O$ exchangeable, OH).

*2-Amino-4-phenyl-6-(p-tolylamino)-1,4-dihydropyridine-3,5-dicarbonitrile **(7a)**, 2-hydroxy-4-phenyl-6-(p-tolylamino)-1,4-dihydropyridine-3,5-dicarbonitrile **(7b)**, 2-amino-4-(4-methoxyphenyl)-6-(p-tolylamino)-1,4-dihydropyridine-3,5-dicarbonitrile **(7c)**, 2-hydroxy-4-(4-methoxyphenyl)-6-(p-tolylamino)-1,4-dihydropyridine-3,5-dicarbonitrile **(7d)**, 2-amino-4-(4-chlorophenyl)-6-(p-tolylamino)-1,4-dihydropyridine-3,5-dicarbonitrile **(7e)**,and4-(4-chlorophenyl)-2-hydroxy-6-(p-tolylamino)-1,4-dihydropyridine-3,5-dicarbonitrile **(7f)***

**General procedure:** To a solution of compound **1** (1.74 g, 0.01 mol) in ethanol (50 mL) containing ammonium acetate (0.50 g), either of malononitrile (0.66 g, 0.01 mol ) or ethyl cyanoacetate (1.13 g, 0.01 mol ), and any of benzaldehyde ( 1.06 g, 0.01 mol), 4-methoxybenzaldehyde (1.36 g, 0.01 mol) or 4-chlorobenzaldehyde (1.41 g, 0.01 mol) was added. The reaction mixture in each case was heated under reflux for 4 h then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

Compound **7a**: white crystals from ethanol, yield 64 % (2.09 g), m.p> 300 °C. *Anal*. Calculated for $C_{20}H_{17}N_5$ (327.38): C, 73.37; H, 5.23; N, 21.39. Found: C, 73.41; H, 5.08; N; 21.44. MS: m/e 327 ($M^+$, 31 %), IR, υ: 3438-3315 ($NH_2$, 2NH), 3056 (CH, aromatic), 2226, 2220 (2CN), 1634 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): δ = 3.16 (s, 3H, $CH_3$), 4.89 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.14 (s, 1H, pyridine H-4), 7.26-7.35 (m, 9H, C6H5, C6H4), 8.33, 8.38 (2s, 2H, $D_2O$ exchangeable, 2NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ = 19.8 ($CH_3$), 80.6 (pyridine C-4), 116.8, 117.0 (2CN), 120.3, 120.8, 121.3, 122.6, 123.3, 123.8, 124.8, 126.6, 127.8, 128.2, 128.9, 130.5 ($C_6H_5$, $C_6H_4$, pyridine C),.

Compound **7b**: Yellow crystals from ethanol, yield 55 % (1.81 g), m.p 134 °C. *Anal*. Calculated for $C_{20}H_{16}N_4O$ (328.37): C, 73.15; H, 4.91; N, 17.06. Found: C, 73.08; H, 4.88; N; 16.93. MS: m/e 328 ($M^+$, 22 %), IR, υ: 3538-3341 (OH, 2NH), 3057 (CH, aromatic), 2226, 2220 (2CN), 1634 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): δ = 3.14 (s, 3H, $CH_3$), 6.15 (s, 1H, pyridine H-4), 7.25-7.39 (m, 9H, $C_6H_5$, $C_6H_4$), 8.26, 8.32 (2s, 2H, $D_2O$ exchangeable, 2NH), 10.19 (s, $^1$H, $D_2O$ exchangeable, OH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ = 19.6 ($CH_3$), 80.4 (pyridine C-4), 116.6, 116.9 (2CN), 120.2, 120.6, 121.1, 122.8, 123.6, 123.8, 124.3, 126.4, 127.7, 128.2, 128.5, 130.2 ($C_6H_5$, $C_6H_4$, puridine C).

Compound **7c**: Yellow crystals from ethanol, yield 88 % (3.13 g), m.p 157 °C. *Anal*. Calculated for $C_{21}H_{19}N_5O$ (357.41): C, 70.57; H, 5.36; N, 19.59. Found: C, 70.62; H, 5.41; N; 19.77. MS: m/e 357 ($M^+$, 16 %), IR, υ: 3484-3323 ($NH_2$, 2NH), 3053 (CH, aromatic), 2226, 2221 (2CN), 1636 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): 2.99 (s, 3H, $CH_3$), 3.14 (s, 3H, $OCH_3$), 4.82 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.13 (s, 1H, pyridine H-4), 7.23-7.39 (m, 8H, $2C_6H_4$), 8.16, 8.20 (2s, 2H, $D_2O$ exchangeable, 2NH).

Compound **7d**: Yellow crystals from ethanol, yield 77 % (2.75 g), m.p179 °C. *Anal*. Calculated for $C_{21}H_{18}N_4O_2$ (358.39): C, 70.38; H, 5.06; N, 15.63. Found: C, 70.44; H, 5.28; N; 15.52. MS: m/e 358 ($M^+$, 18 %), IR, υ: 3553-3338 (OH, 2NH), 3056 (CH, aromatic), 2228, 2220 (2CN), 1638 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): δ = 3.08, 3.12 (2s, 6H, $2CH_3$), 6.11 (s, $^1$H, pyridine H-4), 7.26-7.41 (m, 8H, $2C_6H_4$), 8.13, 8.22 (2s, 2H, D2O exchangeable, 2NH), 10.09 (s, 1H, $D_2O$ exchangeable, OH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ = 19.6, 24.0 ($CH_3$, $OCH_3$), 80.6 (pyridine C-4), 116.6, 117.1 (2CN), 120.2, 120.4, 121.6, 122.5, 124.0, 124.8, 126.3, 127.8, 129.0, 129.6, 130.3, 131.9 (2 $C_6H_4$, pyridine C).

Compound **7e**: White crystals from ethanol, yield 60 % (2.17 g), m.p> 300 °C. *Anal*. Calculated for $C_{20}H_{16}ClN_5$ (361.83): C, 66.39; H, 4.46; N, 19.36. Found: C, 66.59; H, 4.28; N; 19.04. MS: m/e 361 ($M^+$, 22 %), IR, υ: 3484-3313 ($NH_2$, 2NH), 3056 (CH, aromatic), 2225, 2221 (2CN), 1632 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): 3.11 (s, 3H, $CH_3$), 4.83 (s, 2H, $D_2O$ exchangeable, NH2), 6.11 (s, 1H, pyridine H-4), 7.26-7.41 (m, 8H, $2C_6H_4$), 8.11, 8.28 (2s, 2H, $D_2O$ exchangeable, 2NH).

Compound **7f**: White crystals from ethanol, yield 64 % (2.33 g), m.p 159 °C. *Anal*. Calculated for $C_{20}H_{15}ClN_4O$ (362.81): C, 70.38; H, 5.06; N, 15.63. Found: C, 70.21; H, 5.17; N; 15.44. MS: m/e 362 ($M^+$, 23 %), IR, υ: 3529-3314 (OH, 2NH), 3052 (CH, aromatic), 2223, 2220 (2CN), 1632 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): 3.16 (s, 3H, $CH_3$), 6.13 (s, 1H, pyridine H-4), 7.27-7.39 (m, 8H, $2C_6H_4$), 8.16, 8.24 (2s, 2H, $D_2O$ exchangeable, 2NH), 10.24 (s, 1H, $D_2O$ exchangeable, OH).

*2-Amino-4-(furan-2-yl)-6-(p-tolylamino)-4H-pyran-3,5-dicarbonitrile **(9a)** and 4-(furan-2-yl)-2-hydroxy-6-(p-tolylamino)-4H-pyran-3,5-dicarbonitrile **(9b)***

**General procedure:** To a solution of compound **1** (1.74 g, 0.01 mol) in ethanol (50 mL) containing triethylamine (0.50 mL), furfural (0.96 g, 0.01 mol), either of malononitrile (0.66 g, 0.01 mol ) or ethyl cyanoacetate (1.13g, 0.01 mol ) was added. The reaction mixture in each case was heated under reflux for 4 h then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

Compound **9a**: Reddish brown crystals from ethanol, yield 60 % (1.92 g), m.p 187 °C. *Anal*. Calculated for $C_{18}H_{14}N_4O_2$ (318.33): C, 67.91; H, 4.43; N, 17.60. Found: C, 67.62; H, 4.60; N; 17.49. MS: m/e 318 ($M^+$, 28 %), IR, υ: 3489-3342 ($NH_2$, NH), 3059 (CH, aromatic), 2222, 2220 (2CN), 1636 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): δ = 3.13 (s, 3H, $CH_3$), 4.22 (s, 2H, $D_2O$-exchangeable, $NH_2$), 6.18 (s, 1H, pyran H-4), 7.22-7.45 (m, 7H, $C_6H_4$, furfuryl H), 8.16 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ = 19.6 ($CH_3$), 80.6 (pyran C-4), 116.4, 117.0 (2CN), 120.3, 121.8, 121.9, 122.4, 124.3, 127.4, 128.5, 129.8, 130.3, 138.2, 138.6, 140.3 ($C_6H_4$, furan, pyran C).

Compound **9b**: Brown crystals from ethanol, yield 60 % (1.93 g), m.p 90°C. *Anal*. Calculated for $C_{18}H_{13}N_3O_3$ (319.31): C, 67.71; H, 4.10; N, 13.16. Found: C, 67.88; H, 4.28; N; 13.39. MS: m/e 319 ($M^+$, 20 %), IR, υ: 3520-3322 (OH, NH), 3055 (CH, aromatic), 2225, 2220 (2CN), 1638 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): 3.12 (s, 3H, $CH_3$), 6.17 (s, 1H, pyran H-4), 7.26-7.41(m, 7H, $C_6H_4$, furfuryl H), 8.13 (s, 1H, $D_2O$ exchangeable, NH), 10.25 (s, $^1$H, $D_2O$ exchangeable, OH).

*2-Amino-4-(furan-2-yl)-6-(p-tolylamino)-4H-pyridine-3,5-dicarbonitrile* ***(10a)*** *and 4-(furan-2-yl)-2-hydroxy-6-(p-tolylamino)-4H-pyridine-3,5-dicarbonitrile* ***(10b)***

**General procedure:** To a solution of compound **1** (1.74 g, 0.01 mol) in ethanol (50 mL) containing ammonium acetate (0.50 mL) furfural (0.96 g, 0.01 mol), either of malononitrile (0.66 g, 0.01 mol ) or ethyl cyanoacetate (1.13g, 0.01 mol ) was added. The reaction mixture in each case was heated under reflux for 3 h then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

Compound **10a**: Reddish brown crystals from ethanol, yield 64 % (2.04 g), m.p 183 °C. *Anal*. Calculated for $C_{18}H_{15}N_5O$ (317.34): C, 68.13; H, 4.76; N, 22.07. Found: C, 67.93; H, 4.82; N; 21.99. MS: m/e 317 ($M^+$, 32 %), IR, υ: 3449-3312 ($NH_2$, 2NH), 3054 (CH, aromatic), 2226, 2222 (2CN), 1631 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): δ = 3.13 3.16 (s, 3H, $CH_3$), 4.24 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.15 (s, 1H, pyridineH-4), 7.26-7.38 (m, 7H,$C_6H_4$, furfuryl H), 8.14, 8.29 (2s, 2H, $D_2O$ exchangeable, 2NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ = 19.8 ($CH_3$), 80.3 (pyridine C-4), 116.1, 117.0 (2CN), 119.4, 121.8, 121.9, 124.8, 126.9, 130.4, 132.5, 133.1, 134.7, 136.8, 138.6, 140.4 ($C_6H_4$, furan, pyridine C).

Compound **10b**: Yellow crystals from ethanol, yield 88 % (2.78 g), m.p 150 °C. *Anal*. Calculated for $C_{18}H_{14}N_4O_2$ (318.33): C, 67.91; H, 4.43; N, 17.60. Found: C, 67.79; H, 4.36; N; 17.42. MS: m/e 318 ($M^+$, 14 %), IR, υ: 3593-3338 (OH, 2NH), 3053 (CH, aromatic), 2228, 2222 (2CN), 1633 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz), δ: 3.15 (s, 3H, $CH_3$), 6.19 (s, 1H, pyridine H-4), 7.22-7.39 (m, 7H, $C_6H_4$, furfuryl H), 8.16, 8.27 (2s, 2H, $D_2O$ exchangeable, 2NH), 10.34 (s, 1H, $D_2O$ exchangeable, OH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ = 19.6 ($CH_3$), 80.2 (pyridine C-4), 116.6, 116.9 (2CN), 119.4, 120.3, 121.9, 125.0, 126.9, 130.4, 131.8, 133.1, 134.7, 136.8, 138.8, 140.4 ($C_6H_4$, furan, pyridine C).

*2-Amino-N-(p-tolyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide* ***(12)***

To a solution of compound **1** (1.74 g, 0.01 mol) in ethanol (50 mL) containing triethylamine (0.50 mL) elemental sulfur (0.32 g, 0.01 mol) and cyclohexanone (0.98 g, 0.01 mol) were added. The reaction mixture was heated under reflux for 1 h then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

Compound **12**: Greenish yellow crystals from ethanol, yield 67 % (1.91 g), m.p 261 °C. *Anal*. Calculated for $C_{16}H_{18}N_2OS$ (286.39): C, 67.10; H, 6.33; N, 9.78; S, 11.20. Found: C, 67.22; H, 6.19; N, 9.83; S, 11.04. MS: m/e 286 ($M^+$, 19 %), IR, υ: 3477-3321 ($NH_2$, NH), 2981, 2859 ($CH_3$, $CH_2$), 1689 (CO), 3055 (CH, aromatic),1634 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): δ = 1.62-1.84 (m, 4H, $2CH_2$), 2.21-2.38 (m, 4H, $2CH_2$), 3.02 (s, 3H, $CH_3$), 5.83 (s, 2H, $D_2O$ exchangeable, $NH_2$), 7.26-7.36 (2d, 4H, $C_6H_4$), 8.26 (s, $^1$H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ = 19.6 ($CH_3$), 22.8, 26.4, 28.2, 29.6 ($4CH_2$), 118.3, 120.4, 122.7, 126.9, 130.3, 133.2, 134.6, 138.2 ($C_6H_4$, thiophene C), 164.8 (CO).

*2-(Benzylideneamino)-N-(p-tolyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide* **(13a)** *and 2-((4-methoxybenzylidene)amino)-N-(p-tolyl)-4,5,6,7- tetrahydrobenzo [b]thiophene-3-carboxamide* ***(13b)***

To a solution of compound **12** (2.86 g, 0.01 mol) in 1,4-dioxane (50 mL) containing piperidine (0.50 mL) any of benzaldehyde (1.06 g, 0.01 mol) or 4-methoxybenzaldehyde (1.36 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 3 h then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

Compound **13a**: Orange crystals from 1,4-dioxane, yield 76 % (2.86 g), m.p 184 °C. *Anal*. Calculated for $C_{23}H_{22}N_2OS$ (374.50): C, 73.76; H, 5.92; N, 7.48; S, 8.56. Found: C, 73.56; H, 6.03; N; 7.59; S, 8.67. MS: m/e 374 ($M^+$, 28 %), IR, υ: 3433, 3339 (NH), 3056 (CH, aromatic), 1688 (CO), 1631 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz) (DMSO-$d_6$, 200 MHz): δ = 1.60-1.86 (m, 4H, $2CH_2$), 2.23-2.39 (m, 4H, $2CH_2$), 3.11 (s, 3H, $CH_3$), 6.22 (s, 1H, N=CH), 7.28- 7.39 (m, 9H, $C_6H_5$, $C_6H_4$), 8.24 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ = 19.9 ($CH_3$), 22.6, 26.6, 28.4, 29.2 (4CH2), 120.3, 120.8, 121.4, 124.3, 126.7, 128.0, 129.3, 129.5, 133.5, 134.4, 138.6 ($C_6H_5$, $C_6H_4$, thiophene C), 164.8 (CO), 168.9 (C=N).

Compound **13b**: Orange crystals from 1,4-dioxane, yield 82 % (3.318 g), m.p 228 °C. *Anal*. Calculated for $C_{24}H_{24}N_2O_2S$ (404.52): C, 71.26; H, 5.98; N, 6.93; S, 7.93. Found: C, 71.36; H, 6.11; N; 6.82; S, 8.04. MS: m/e 404 ($M^+$, 17 %), IR, υ: 3463, 3316 (NH), 3053 (CH, aromatic), 1689 (CO), 1636 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): δ = 1.63-1.86 (m, 4H, $2CH_2$), 2.23-2.41 (m, 4H, $2CH_2$), 3.08, 3.24 (2s, 6H, $2CH_3$), 6.24 (s, 1H, N=CH), 7.29-7.42 (m, 8H, $2C_6H_4$), 8.26 (s, 1H, $D_2O$ exchangeable, NH). 13C NMR (DMSO-$d_6$, 75 MHz): δ = 19.8, 24.3 ($CH_3$, $OCH_3$), 22.5, 26.6, 28.4, 29.4 ($4CH_2$), 120.8, 121.2, 121.4, 124.2, 126.7, 128.3, 129.3, 129.5, 133.7, 134.4, 138.9 ($C_6H_5$, $C_6H_4$, thiophene C), 164.5 (CO), 168.6 (C=N).

*2-(2-Chloroacetamido)-N-(p-tolyl)-4,5,6,7-tetrahydrobenzo[b] thiophene-3-carboxamide* ***(15)***

To a solution of compound **12** (2.86 g, 0.01 mol) in 1,4-dioxane (50 mL) containing chloroacetylchloride (1.12 g, 0.01 mol) was added. The whole reaction mixture was heated under reflux for 6 h then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

Compound **15**: Brown crystals from 1,4-dioxane, yield 63 % (2.29 g), m.p 212 °C. *Anal*. Calculated for $C_{18}H_{19}ClN_2O_2S$ (362.87): C, 59.66; H, 5.28; N, 7.72; S, 8.8. Found: C, 59.36; H, 5.51; N; 7.82; S, 8.04. MS: m/e 362 ($M^+$, 16 %), IR, υ: 3454-3326 (2NH), 3058 (CH, aromatic), 1702, 1686 (2CO), 1630 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): δ = 1.60-1.84 (m, 4H, $2CH_2$), 2.22-2.40 (m, 4H, $2CH_2$), 3.15 (s, 3H, $CH_3$), 5.24 (s, 2H, $CH_2$), 7.25-7.39 (2d, 4H, $C_6H_4$), 8.24, 8.30 (2s, 2H, $D_2O$ exchangeable, 2NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ = 19.6 ($CH_3$), 22.4, 26.7, 28.4, 29.1 ($4CH_2$), 64.3 ($CH_2$), 120.8, 121.4, 124.3, 126.7, 128.0, 133.5, 134.4, 138.6 ($C_6H_4$, thiophene C), 164.3, 165.2 (2CO).

*2-(3-Phenylthioureido)-N-(p-tolyl)-4,5,6,7-tetrahydrobenzo[b] thiophene-3-carboxamide* ***(17)***

To a solution of compound **12** (2.86 g, 0.01 mol) in 1,4-dioxane (50 mL) phenylisothiocyanate (1.35 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 4 h then evaporated under vacuum and the remaining product was triturated with ethanol and the formed solid product was collected by filtration.

Compound **17**: Brown crystals from 1,4-dioxane, yield 61 % (2.567 g), m. p 245 °C. *Anal*. Calculated for $C_{23}H_{23}N_3OS_2$ (421.58): C, 65.53; H, 5.50; N, 9.97; S, 15.21. Found: C, 65.72; H, 5.82; N; 10.13; S, 15.35. MS: m/e 421 ($M^+$, 38 %), IR, υ: 3450-3329 (3NH), 3058 (CH, aromatic), 1686 (CO), 1642 (C=C), 1205 (C=S). $^1$H NMR (DMSO-$d_6$, 200 MHz): δ = 1.62-1.84 (m, 4H, $2CH_2$), 2.20-2.37 (m, 4H, $2CH_2$), 3.12 (s, 3H, $CH_3$), 7.26-7.39 (m, 9H, $C_6H_5$, $C_6H_4$), 8.26, 8.32, 8.36 (3s, 3H, $D_2O$ exchangeable, 3NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ = 19.4 ($CH_3$), 22.5, 26.4, 28.4, 29.2 ($4CH_2$), 120.3, 120.9, 124.3, 125.4, 126.7, 127.0, 127.9, 128.0, 129.4, 133.5, 136.7, 138.9 ($C_6H_5$, $C_6H_4$, thiophene C), 164.2, (CO), 173.6 (C=S).

*2-(4,6-Dimethyl-2-thioxopyrimidin-1(2H)-yl)-N-(p-tolyl)-4,5,6,7- tetrahydrobenzo[b] thiophene-3-carboxamide* ***(19)***

To a solution of compound **17** (4.21 g, 0.01 mol) in ethanol (50 mL) containing piperidine (0.50 mL), acetylacetone (1.0 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 3 h then evaporated under vacuum and the remaining product was triturated with ethanol and the formed solid product was collected by filtration.

Compound **19**: Reddish brown crystals from ethanol, yield 65 % (3.158 g), m.p> 300 °C. *Anal*. Calculated for $C_{28}H_{29}N_3OS_2$ (487.68): C, 68.96; H, 5.99; N, 8.62; S, 13.15. Found: C, 68.80; H, 5.73; N; 8.47; S, 12.83. MS: m/e 503 ($M^+$, 26 %), IR, υ: 3463-3316 (NH), 3056 (CH, aromatic), 1688 (CO), 1643 (C=C), 1212 (C=S). $^1$H NMR (DMSO-$d_6$, 200 MHz): δ = 1.60-1.84 (m, 4H, $2CH_2$), 2.20-2.38 (m, 4H, $2CH_2$), 2.87, 3.05, 3.13 (3s, 9H, $3CH_3$), 6.22 (m,2H, pyrimidine H-4, H-5), 7.28-7.36 (m, 9H, $C_6H_5$, C6H4), 8.28 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ = 16.8, 17.3, 19.6 ($3CH_3$), 22.4, 26.8, 28.3, 29.5 ($4CH_2$), 120.3, 121.2, 121.4, 124.6, 126.4, 128.2, 129.0, 129.7, 130.8, 134.4, 138.8 140.2, 141.8, 142.4 ($C_6H_5$, $C_6H_4$, pyridine, thiophene C), 164.5 (CO), 168.6 (C=N).

*2-((4-Methyl-3-phenylthiazol-2(3H)-ylidene)amino)-N-(p-tolyl)-4,5,6,7- tetrahydrobenzo [b]thiophene-3-carboxamide* ***(21a)*** *and 2-((4-hydroxy-3-phenylthiazol-2(3H)-ylidene)amino)-N-(p-tolyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide* ***(21b)***

**General procedure:** To a solution of compound **17** (4.21 g, 0.01 mol) in ethanol (50 mL), either of α-chloroacetone (0.92 g, 0.01 mol) or α -chloroethyl acetate (1.22 g, 0.01 mol) was added. The reaction mixture, in each case, was heated under reflux for 2 h then left to cool and the formed solid product was collected by filtration.

Compound **21a:** Greenish yellow crystals from ethanol, yield 55 % (2.53 g), m.p 151 °C. *Anal*. Calculated for $C_{26}H_{25}N_3OS_2$ (459.63): C, 67.94; H, 5.48; N, 9.14; S, 13.95. Found: C, 67.85; H, 5.62; N; 9.05; S, 14.18. MS: m/e 459 ($M^+$, 22 %), IR, υ: 3474-3329 (NH), 3053 (CH, aromatic), 1687 (CO), 1632 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): δ = 1.62-1.86 (m, 4H, $2CH_2$), 2.21-2.39 (m, 4H, $2CH_2$), 3.02, 3.14 (2s, 6H, $2CH_3$), 6.02 (s, 1H, thiazole H-5), 7.26-7.39 (m, 9H, $C_6H_5$, $C_6H_4$) , 8.25 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ = 18.8, 19.3 ($2CH_3$), 22.8, 26.3, 28.2, 29.5 ($4CH_2$), 120.6, 122.7, 123.8, 126.2, 126.9, 127.0, 127.8, 128.5, 129.2, 133.5, 134.2, 135.6, 136.8, 140.2 ($C_6H_5$, $C_6H_4$, thiazole, thiophene C), 164.4 (CO), 172.8 (C=N).

Compound **21b**: Gray crystals from ethanol, yield 56 % (2.6 g), m.p 217 °C. *Anal*. Calculated for $C_{25}H_{23}N_3O_2S_2$ (461.60): C, 65.05; H, 5.02; N, 9.10; S, 13.89. Found: C, 64.82; H, 5.14; N; 9.24; S, 14.04. MS: m/e 461 ($M^+$, 15 %), IR, υ: 3523-3320 (OH, NH), 3056 (CH, aromatic), 1688 (CO), 1630 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): δ = 1.62-1.86 (m, 4H, $2CH_2$), 2.21-2.39 (m, 4H, $2CH_2$), 3.14 (s, 3H, $CH_3$), 6.02 (s, 1H, thiazole H-5), 7.26-7.39 (m, 9H, $C_6H_5$, $C_6H_4$), 8.28 (s, 1H, $D_2O$ exchangeable, NH), 10.08 (s, 1H, $D_2O$ exchangeable, OH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ = 19.5 ($2CH_3$), 22.8, 26.3, 28.2, 29.3 ($4CH_2$), 120.3, 122.9, 123.5, 126.4, 126.9, 127.0, 127.3, 128.8, 129.6, 133.8, 134.5, 135.6, 136.8, 140.5 ($C_6H_5$, $C_6H_4$, thiazole, thiophene C), 164.3 (CO), 172.6 (C=N).

*2-((4-(4-Chlorophenyl)-3-phenylthiazol-2(3H)-ylidene)ami-*

*no)-N-(p-tolyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide* ***(23)***

To a solution of compound **17** (4.21 g, 0.01 mol) in ethanol (50 mL), ω-bromo-4-chloroacetophenone (2.33 g, 0.01 mol) was added. The reaction mixture, in each case, was heated under reflux for 4 h then left to cool and the formed solid product was collected by filtration.

Compound **23**: Yellow crystals from ethanol, yield 57 % (3.16 g), m.p 174 °C. *Anal*. Calculated for $C_{31}H_{26}ClN_3OS_2$ (556.14): C, 66.95; H, 4.71; N, 7.56; S, 11.53. Found: C, 67.16; H, 4.52; N; 7.69; S, 11.72. MS: m/e 556 ($M^+$, 38 %), IR, υ: 3482-3320 (NH), 3056 (CH, aromatic), 1690 (CO), 1631 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): δ = 1.63-1.88 (m, 4H, $2CH_2$), 2.20-2.37 (m, 4H, $2CH_2$), 3.11 (s, 3H, $CH_3$), 6.08 (s, 1H, thiazole H-5), 7.28-7.37 ( m, 13H, $C_6H_5$, $2C_6H_4$), 8.26 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ = 19.2 ($CH_3$), 22.6, 26.3, 28.2, 29.6 ($4CH_2$), 120.3, 121.9, 123.6, 124.8, 125.6, 126.8, 127.8, 128.2, 128.6, 129.2, 130.4, 130.3, 131.8, 132.8, 135.3, 136.3, 140.6 ($C_6H_5$, $2C_6H_4$, thiazole, thiophene C), 164.3 (CO), 172.3 (C=N).

*2-((2-Aminothiazol-4-yl)amino)-N-(p-tolyl)-4,5,6,7-tetrahydrobenzo-[b]thiophene-3-carboxamide* ***(25)***

To a solution of compound **15** (3.62 g, 0.01 mol) in ethanol (50 mL), thiourea (0.76 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 2 h then left to cool and the formed solid product was collected by filtration.

Compound **25**: Brown crystals from ethanol, yield 66 % (2.53 g), m.p 204 °C. *Anal*. Calculated for $C_{19}H_{20}N_4OS_2$ (384.52): C, 59.35; H, 5.24; N, 14.57; S, 16.68. Found: C, 59.27; H, 5.05; N; 14.29; S, 16.83. MS: m/e 384 ($M^+$, 100 %), IR, υ: 3487-3340 ($NH_2$, 2NH), 3056 (CH, aromatic), 1688 (CO), 1630 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): δ = 1.61-1.88 (m, 4H, $2CH_2$), 2.20-2.37 (m, 4H, $2CH_2$), 3.13 (s, 3H, $CH_3$), 4.28 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.09 (s, 1H, thiazole H-5), 7.26-7.39 (2d, 4H, $C_6H_4$), 8.23, 8.29 (2s, 2H, $D_2O$ exchangeable, 2NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ = 19.4 ($CH_3$), 22.6, 26.3, 28.2, 29.5 ($4CH_2$), 120.3, 122.4, 123.8, 126.2, 126.5, 128.8, 129.2, 133.6, 135.4, 140.8 ($C_6H_4$, thiazole, thiophene C), 164.2 (CO), 173.5 (C=N).

*2-Oxo-N'-phenyl-2-((3-(p-tolylcarbamoyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)acetohydrazonoyl chloride* ***(26)***

To a cold solution of compound **15** (3.62 g, 0.01 mol) in ethanol (60 mL) containing sodium acetate (0.99 g in 10 mL water) at 0-5 oC a cold solution of benzenediazonium chloride [prepared by the addition of sodium nitrite solution (0.70 g, 0.01 mol) to a cold solution of aniline (0.93 g, 0.01 mol) in concentrated hydrochloric acid (12 mL) with contineous stirring] was added with contineous stirring. The whole reaction mixture was stirred at room temperature for an additional 2 hours and the formed solid product was collected by filtration.

Compound **26**: Yellow crystals from ethanol, yield 97 % (4.52 g), m.p> 300 °C. *Anal*. Calculated for $C_{24}H_{23}ClN_4O_2S$ (466.98): C, 61.73; H, 4.96; N, 12.00; S, 6.87. Found: C, 61.92; H, 5.25; N; 11.83; S, 6.92. MS: m/e 466 ($M^+$, 20 %), IR, υ: 3473-3322 (3 NH), 3054 (CH, aromatic), 1689, 1703 (2CO), 1632 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): δ = 1.59-1.84 (m, 4H, $2CH_2$), 2.20-2.39 (m, 4H, $2CH_2$), 3.11 (s, 3H, $CH_3$), 7.22-7.40 (m, 9H, $C_6H_5$, $C_6H_4$), 8.21, 8.26, 8.32 (3s, 3H, $D_2O$ exchangeable, 3NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ = 19.5 ($CH_3$), 22.4, 26.3, 28.0, 29.5 (4CH2), 120.4, 121.9, 123.6, 124.2, 125.4, 126.8, 127.3, 128.6, 129.2, 131.8, 132.8, 135.3, ($C_6H_5$, $C_6H_4$, thiophene C), 162.3, 164.3 (2CO), 172.3 (C=N).

*2-(2-Chloro-3-(2-hydroxyphenyl)acrylamido)-N-(p-tolyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide* **(28)**

To a solution of compound **15** (3.62 g, 0.01 mol) in ethanol (50 mL) containing piperidine (0.50 mL), salicylaldehyde (1.22 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 3 h and the solid product, so formed, upon pouring onto ice/water mixture containing few drops of hydrochloric acid was collected by filtration.

Compound **28**: Yellow crystals from ethanol, yield 97 % (4.52 g), m.p 200 °C. *Anal*. Calculated for $C_{25}H_{23}ClN_2O_3S$ (466.98): C, 64.30; H, 4.96; N, 6.00; S, 6.87. Found: C, 64.55; H, 4.86; N; 5.83; S, 6.59. MS: m/e 466 ($M^+$, 12 %), IR, υ: 3532-3314 (OH, 2NH), 3053 (CH, aromatic), 1690 , 1702 (2CO), 1632 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): δ = 1.62-1.82 (m, 4H, $2CH_2$), 2.23-2.37 (m, 4H, $2CH_2$), 3.09 (s, 3H, $CH_3$), 5.93 (s, 1H, CH=C), 7.25-7.36 (m, 8H, $2C_6H_4$ ), 8.23, 8.30 (2s, 2H, $D_2O$ exchangeable, 2NH), 10.25 (s, 1H, $D_2O$ exchangeable, OH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ = 19.4 ($CH_3$), 22.6, 26.3, 28.0, 29.5 ($4CH_2$), 86.8, 89.3 (C=CH), 120.2, 120.6, 124.2, 125.4, 126.8, 127.3, 131.8, 132.8, 135.3 (2 $C_6H_4$, thiophene C), 162.2, 164.5 (2CO).

*2-((6-Amino-3-chloro-5-cyano-4-phenyl-4H-pyran-2-yl)amino)-N-(p-tolyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide(29a),2-((6-amino-3-chrolo-5-cyano-4-(p-tolyl)-4H-pyran-2-yl)amino-N-(p-tolyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide(29b)and2-((6-amino-3-chloro-4-(4-chlorophenyl)-5-cyano-4H-pyran-2-yl)amino)-N-(p-tolyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide* **(29c)**

**General procedure:** To a solution of compound **15** (3.62 g, 0.01 mol) in ethanol (50 mL) containing triethylamine (0.50 mL), malononitrile (0.66 g, 0.01 mol) and any of benzaldehyde (1.06 g, 0.01 mol), 4-methoxybenzaldehyde (1.36 g, 0.01 mol) or 4-chlorobenzaldehyde (1.41 g, 0.01 mol) were added. The reaction mixture was heated under reflux for 4 h then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

Compound **29a**: Reddish brown crystals from ethanol, yield 70 % (3.62 g), m.p 181 °C. *Anal*. Calculated for $C_{28}H_{25}ClN_4O_2S$ (517.04): C, 65.04; H, 4.87; N, 10.84; S, 6.20. Found: C, 65.32; H, 4.93; N; 11.05; S, 6.36. MS: m/e 517 ($M^+$, 28 %), IR, υ: 3488-3342 ($NH_2$, 2NH), 3056 (CH, aromatic), 2220 (CN), 1688 (CO), 1630 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): 1.60-1.82 (m, 4H, $2CH_2$), 2.21-2.39 (m, 4H, $2CH_2$), 3.12 (s, 3H, $CH_3$), 4.87 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.21 (s, 1H, pyran H-4), 7.26-7.42 (m, 9H, $C_6H_5$, $C_6H_4$), 8.24, 8.29 (2s, 2H, $D_2O$ exchangeable, 2NH).

Compound **29b**: Brown crystals from ethanol, yield 66 % (3.62 g), m.p 162 °C. *Anal*. Calculated for $C_{29}H_{27}ClN_4O_3S$ (547.07): C, 63.67; H, 4.97; N, 10.24; S, 5.86. Found: C, 63.77; H, 5.03; N; 10.29; S, 5.93. MS: m/e 547 ($M^+$, 17 %), IR, υ: 3469-3331 ($NH_2$, 2NH), 3058 (CH, aromatic), 2222 (CN), 1688 (CO), 1630 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): 1.63-1.82 (m, 4H, $2CH_2$), 2.24-2.37 (m, 4H, $2CH_2$), 3.11, 3.28 (2s, 6H, $2CH_3$), 4.83 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.23 (s, 1H, pyran H-4), 7.29-7.39 (m, 8H, $2C_6H_4$), 8.23, 8.26 (2s, 2H, $D_2O$ exchangeable, 2NH).

Compound **29c**: Brown crystals from ethanol, yield 66 % (3.62 g), m.p180 °C. *Anal*. Calculated for $C_{28}H_{24}Cl_2N_4O_2S$ (551.49): C, 60.98; H, 4.39; N, 10.16; S, 5.81. Found: C, 61.28; H, 4.28; N; 10.22; S, 5.79. MS: m/e 551 ($M^+$, 38 %), IR, υ: 3473-3326 ($NH_2$, 2NH), 3056 (CH, aromatic), 2220 (CN), 1685 (CO), 1632 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): 1.61-1.82 (m, 4H, $2CH_2$), 2.22-2.39 (m, 4H, $2CH_2$), 3.08 (s, 3H, $CH_3$), 4.85 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.22 (s, 1H, pyran H-4), 7.31-7.42 (m, 8H, $2C_6H_4$), 8.22, 8.28 (2s, 2H, $D_2O$ exchangeable, 2NH).

*2-((4-amino-1-chloro-5-oxo-5,10b-dihydropyrano[3,4-c] chromen-2-yl)amino)-N-(p-tolyl)-4,5,6,7-tetrahydrobenzo[b] thiophene-3-carboxamide* **(30)**

To a solution of compound **15** (3.62 g, 0.01 mol) in ethanol (50 mL) containing triethylamine (0.50 mL), malononitrile (0.66 g, 0.01 mol) and salicylaldehyde (1.22 g, 0.01 mol) were added. The reaction mixture was heated under reflux for 4 h then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

Compound **30**: Reddish brown crystals from ethanol, yield 85 % (4.52 g), m.p> 300 °C. *Anal*. Calculated for $C_{28}H_{24}ClN_3O_4S$ (534.03): C, 62.97; H, 4.53; N, 7.87; S, 6.00. Found: C, 62.77; H, 4.38; N; 7.83; S, 6.28. MS: m/e 534 ($M^+$, 22 %), IR, υ: 3483-3313 ($NH_2$, 2NH), 3053 (CH, aromatic), 1703, 1688 (2CO), 1630 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): 1.58-1.82 (m, 4H, $2CH_2$), 2.20-2.38 (m, 4H, $2CH_2$), 3.12 (s, 3H, $CH_3$), 4.89 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.24 (s, 1H, pyran H-4), 7.28-7.40 (m, 8H, $2C_6H_4$), 8.23, 8.30 (2s, 2H, $D_2O$ exchangeable, 2NH).

*Ethyl N-(3-(p-tolylcarbamoyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)formimidate* **(32)**

To a solution of compound **12** (2.86 g, 0.01 mol) in acetic acid (50 mL) triethylorthoformate (1.48 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 3 h then evaporated under vacuum and the remaining product was triturated with ethanol and the formed solid product was collected by filtration.

Compound **32**: Brown crystals from acetic acid, yield 85 % (2.89 g), m.p 203 °C. *Anal*. Calculated for $C_{19}H_{22}N_2O_2S$ (342.46): C, 66.64; H, 6.48; N, 8.18; S, 9.36. Found: C, 66.39; H, 6.61; N; 8.09; S, 9.22. MS: m/e 342 ($M^+$, 20 %), IR, υ: 3470-3310 (NH), 3050 (CH, aromatic), 1688 (CO), 1630 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): 1.13 (t, 3H, J = 7.02 Hz, $CH_3$), 1.54-1.80 (m, 4H, $2CH_2$), 2.21-2.39 (m, 4H, $2CH_2$), 3.10 (s, 3H, $CH_3$), 3.80 (q, 2H, J = 7.02 Hz, $CH_2$), 6.30 (s, 1H, CH=N), 7.23-7.43 (2d, 4H, $C_6H_4$), 8.26 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ = 16.8, 19.6 ($2CH_3$), 22.8, 26.4, 28.2, 29.6 ($4CH_2$), 28.9 ($OCH_2$), 118.6, 120.4, 122.7, 126.9, 130.3, 133.2, 134.6, 138.8 ($C_6H_4$, thiophene C), 164.6 (CO),170.2 (C=N).

*2-(((Phenylamino)methylene)amino)-N-(p-tolyl)-4,5,6,7-tetrahydrobenzo-[b]thiophene-3-carboxamide* ***(34)***

To a solution of compound **32** (3.42 g, 0.01 mol) in acetic acid (50 mL) aniline oil (0.93 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 3 h then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

Compound **34**: Brown crystals from acetic acid, yield 74 % (2.89 g), m.p150 °C. *Anal*. Calculated for $C_{23}H_{23}N_3OS$ (389.51): C, 70.92; H, 5.95; N, 10.79; S, 8.23. Found: C, 71.11; H, 6.01; N; 10.48; S, 8.04. MS:m/e 389 ($M^+$, 16 %), IR, υ: 3472-3328 (2NH), 3053 (CH, aromatic), 1686 (CO), 1630 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): 1.54-1.82 (m, 4H, $2CH_2$), 2.21-2.37 (m, 4H, $2CH_2$), 3.12 (s, 3H, $CH_3$), 6.28 (s, 1H, CH=N), 7.25-7.40 (m, 9H, $C_6H_5$, $C_6H_4$), 8.28, 8.31 (2s, 2H, $D_2O$ exchangeable, 2NH).$^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ = 19.5 ($2CH_3$), 22.6, 26.4, 28.2, 29.4 ($4CH_2$), 118.6, 119.8, 120.4, 122.7, 126.9, 128.7, 129.3, 130.3, 133.2, 134.6, 138.8 ($C_6H_5$, $C_6H_4$, thiophene C), 164.3 (CO), 170.6 (C=N).

## Conclusion

In the current investigation, we have developed new and efficient methods for the synthesis of a variety of pyran, pyridine, thiophene, pyrimidine and thiazole derivatives. The antitumor activities of the newly synthesized product were evaluated against different tumor namely (MCF-7), (NCI-H460), (SF-268) where compounds **4b**, **4c** and **34** showed the highest inhibitory effect among the tested compounds through the cancer cell lines.

## Acknowledgements

Ensaf Alwan would like to thank the Yemen Drug Company for

industry and Commerce (YEDCO) in cooperation with the Ministry of Higher Education on the continued support.

## References

1. Dömling A, Wang W, Wang K. Chemistry and biology of multicomponent reactions. Chem Rev. 2012, 112(6): 3083-3135.

2. Dömling A. Recent developments in isocyanide based multicomponent in applied chemistry. Chem Rev. 2006, 106(1): 17-89.

3. Moghaddam FM, Boinee HZ. An efficient and facile one-step synthesis of highly substituted thiophenes. Tetrahedron. 2004, 60(29): 6085-6089.

4. Molvi KI, Mansuri M, Sudarsanam V, Patel MM, Andrabi SM et al. Synthesis anti-inflammatory analgesic and antioxidant activities of some tetrasubstituted thiophenes. J En-zyme Inhib Med Chem. 2008, 23(6): 829-838.

5. Parai MK, Panda G, Chaturvedi V, Manju YK, Sinha S. Thiophene Containing Triarylmethanes as antitubercular agents. Bioorg Med Chem Lett. 2008, 18(1): 289-292.

6. Wardakhan WW, Abdel-Salam OM, Elmegeed GA. Screening for antidepressant, sedative and analgesic activities of novel fused thiophene derivatives. Acta Pharm. 2008, 58(1): 1-14.

7. Sharma S, Athar F, Maurya MR, Azam A. Copper(II) complexes with substituted thiosemicarbazones of thiophene-2-carboxaldehyde: synthesis, characterization and antiamoebic activity against E. histolytica. Eur J Med Chem. 2005, 40(12): 1414-1419.

8. William OF. Principles of Medicinal Chemistry. 3rd ed. Lippincott Williams & Wilkins Publication, Philadelphia, 1989.

9. Sagardoy AA, Gil MJ, Villar R, Viñas MJ, Arrazola A et al. Benzo[b]thiophene-6-carboxamide 1,1- dioxides: inhibitors of human cancer cell growth at nanomolar concentrations. Bioorg Med Chem. 2010, 18(15): 5701-5707.

10. Fadda AA, Abdel-Latif E, El-Mekawy RE. Synthesis and molluscicidal activity of some new thiophene, thiadiazole and pyrazole derivatives. Eur J Med Chem. 2009, 44(3): 1250-1256.