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SYNTHESES OF HETEROCYCLIC DERIVATIVES AS POTENTIAL CYTOTOXIC COMPOUNDS EVALUATED TOWARD HEPATOCELLULAR AND CERVICAL CARCINOMA CELL LINES

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ABSTRACT. Through the present work the 3-oxo-N,3-diphenylpropamide derivatives **5a,b** were used to synthesize pridine, pyrazole and thiophene derivatives. 3-Phenylisoxazol-5(4*H*)-one produced from the reaction of ethyl benzoylacetate was used as the key starting compound for different multi-component reactions. The synthesized compounds were evaluated toward Hepatocellular carcinoma HepG2 and cervical carcinoma HeLa cell lines. Compounds **3b**, **5b**, **7b**, **7d**, **9c**, **9d**, **15e**, **15f**, **16b**, **18b**, **18e**, **18f**, **19e** and **19f** were the most cytotoxic compounds against the tested cell lines. The results obtained in this work encourage further work in the future to produce new cytotoxic compounds.

KEY WORDS: Diphenylpropamide, 3-Phenylisoxazole, Pyran, Pyridine, Cytotoxicity

INTRODUCTION

The importance of 1,3-diketones in synthetic organic chemistry is difficult to overestimate. Their accessibility, stability, and often unique properties make them promising for use in various fields of human activity [1-3]. High reactivity of 1,3-diketones opens wide prospects for the design of a variety of organic compounds, including those structurally related to natural ones. Continuously, the growing interest in β-dicarbonyl compounds was observed among researchers working in various fields of medicinal chemistry and chemistry of metal complexes. Sol–gel syntheses with β-diketones afforded organic–inorganic hybrid materials used in gas sensors and molecular thermometers, as well as in the manufacture of optical fiber and light converting materials [4-6]. Over the past 10–15 years, not only selectivity parameters and overall yield of reaction products but also such factors as enhanced requirements to starting materials, reaction time, energy consumption, toxicity, etc., have acquired increasing significance in the assessment of the efficiency of chemical syntheses. 1,3-Diketones turned out to be excellent versatile intermediates in multicomponent reactions, in particular regio- and stereoselective, which is especially important in the synthesis of potentially biologically active compounds [7-12]. Moreover, 1,3-diketones (β-diketones) are ubiquitous scaffolds found in many natural products, exhibiting a wide range of biological activities. Thus, many naturally occurring 1,3-diketones shown in Scheme 1, such as dibenzoylmethane (DBM, 1) or n-tritriacontane16,18-dione (TTAD, 2), are typical examples of this type of compounds, naturally obtained from plants such as eucalyptus leaves [13,14], licorice roots [15], vanilla beans [16] or sunflower pollen [17]. These powerful natural antioxidants possess prominent anti-cancer properties with minimal toxicity; thus, the potential activity of DBM as a therapeutic option for cancer treatment (in vitro and in vivo activity inhibiting the growth and proliferation of colon, mammary, lung, prostate, neuroblastoma and skin cancers), as well as for diabetes and dementia, has been recently reviewed [18]. Thus, in the present work we are demonstrating the uses of 3-oxo-N,3-diphenylpropanamide to synthesis fused thiophene, pyran and pyrazole derivatives. Compounds obtained with varieties of functional groups that enhance the studying the effect of these groups toward Hepatocellular Carcinoma and Cervical Carcinoma Cell Lines in the aim of producing new cytotoxic compounds.

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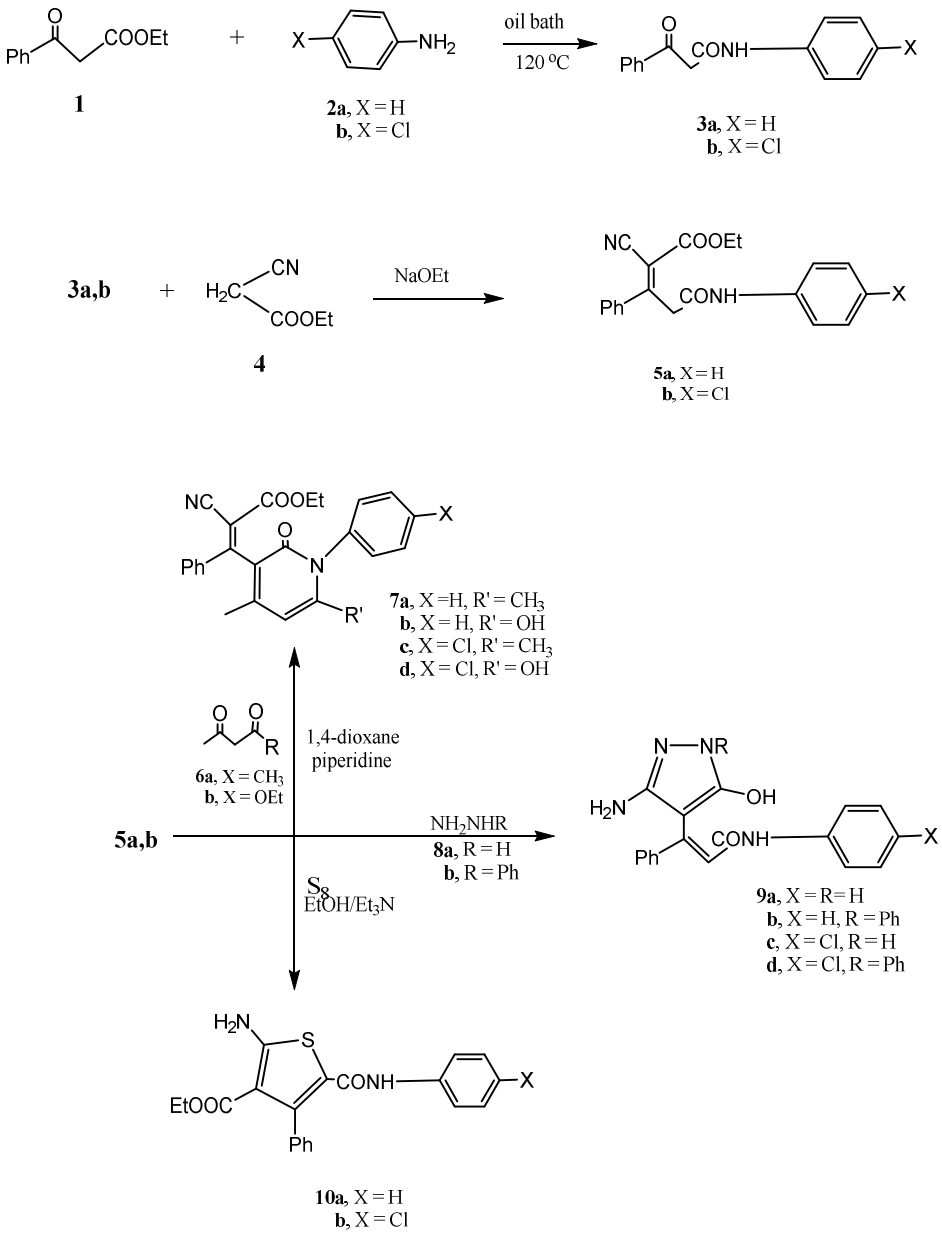
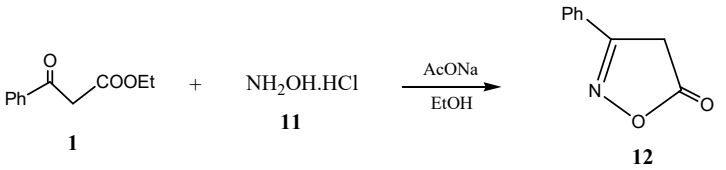
RESULTS AND DISCUSSION

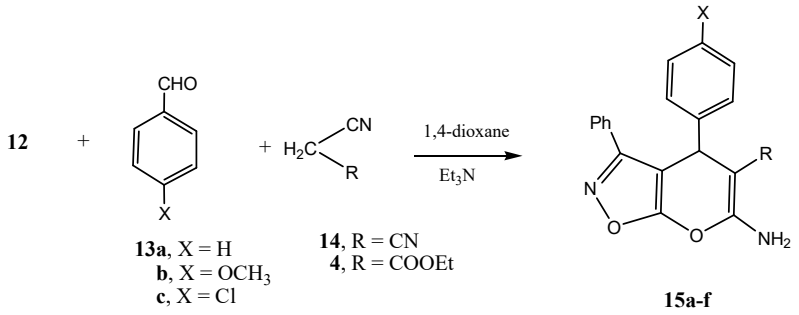
With a broad spectrum of pharmacological activities [19-22] hydrazone and its derivatives with the characteristic carboxamide –NH-CO-group are considered as important class of compounds, for that reason many of carboxamide derivatives have been synthesized with varieties of pharmacological activities. In the present work, we demonstrated the use of 3-oxo-*N*,3-diphenylpropanamide to synthesis different heterocyclic compounds and the reactions were outlined through Schemes 1-3. Throughout this work, the reaction of ethyl benzoylacetate (**1**) with aniline (**2a**) and 4-chloroaniline (**2b**) in an oil bath at 120 ºC gave the 3-oxo-propanamide derivatives **3a** and **3b**, respectively. Both of compounds **3a** and **3b** were reacted with ethyl cyanoacetate (**4**) in sodium ethoxide solution in a boiling water bath gave the Knoevenagel condensation products **5a** and **5b**, respectively. Structures of the latter products were confirmed based on the obtained analytical and spectral data. Thus, the ^{1}H NMR spectrum of **5a** (as an example) showed beside expected signals, a triplet and quartet at δ 1.16, 4.25 ppm equivalent to the ester OCH_2CH_3 group, a singlet at δ 5.46 ppm for the CH_2 group a singlet at δ 8.33 ppm (D_2O exchangeable) for the NH group. In addition, the ^{13}C NMR spectrum revealed the presence signals at δ 16.4 and 50.6 for the OCH_2CH_3 group, a signal at δ 48.6 for the CH_2 group, a signal at δ 117.0 indicating the presence of the CN group and two signals at δ 164.5, 165.8 corresponding to two C=O groups. Further confirmations of structures of compounds **5a** and **5b** were obtained through the studying of their reactivity's toward different reagents. Thus, the reaction of compound **5a** or **5b** with acetylacetone (**6a**) or ethyl acetoacetate (**6b**) in 1,4-dioxane solution containing a catalytic amount of triethylamine gave the polyfunctionally substituted pyridine derivatives **7a-d**, respectively. Moreover, the reaction of compound **5a** or **5b** with hydrazine hydrate (**8a**) or phenylhydrazine (**8b**) gave the pyrazole derivatives **9a-d**, respectively. In addition, the reaction of either **5a** or **5b** with elemental sulfur in absolute ethanol containing triethylamine afforded the thiophene derivatives **10a** and **10b**, respectively (Scheme 1). Recently our research group mentioned some reactions concerning with the Gewald's thiophene synthesis [23-25].

The reaction of ethyl benzoylacetate with hydroxylamine hydrochloride in absolute ethanol containing sodium acetate gave the 3-phenylisoxazol-5(4*H*)-one (**12**). The latter compound underwent a series of multi-component reactions to give varieties of heterocyclic compounds with potential biological activities. Thus, the multi-component reactions of compound **12** with benzaldehyde (**13a**), 4-methoxybenzaldehyde (**13b**) or 4-chlorobenzaldehyde (**13c**) and malononitrile (**14**) or ethyl cyanoacetate (**4**) in 1,4-dioxane containing triethylamine gave the 4*H*-pyrano[3,2-*d*]isoxazole derivatives **15a-f**, respectively. Structures of compounds were confirmed based on the obtained analytical and spectral data. Thus, the ^{1}H NMR spectrum of **15a** (as an example) showed beside the expected signals, a singlet (D_2O exchangeable) for the NH_2 group, a singlet at δ 6.12 equivalent to the pyran H-4. In addition, the ^{13}C NMR spectrum revealed the presence of the signals at 90.8 for the pyran C-4, a signal at 116.8 equivalent to the CN group, signals at 129.8, 130.6, 132.5, 134.6 equivalent to the pyran C-2, C-3, C-5, C-6 and a signal at 172.8 corresponding to the C=N moiety. The multi-component reaction of compound **12** with salicylaldehyde and malononitrile (**14**) or ethyl cyanoacetate (**4**) in 1,4-dioxane containing triethylamine gave the chromeno[4',3':4,5]-pyrano[3,2-*d*]isoxazole derivatives **16a** and **16b**, respectively (Scheme 2).

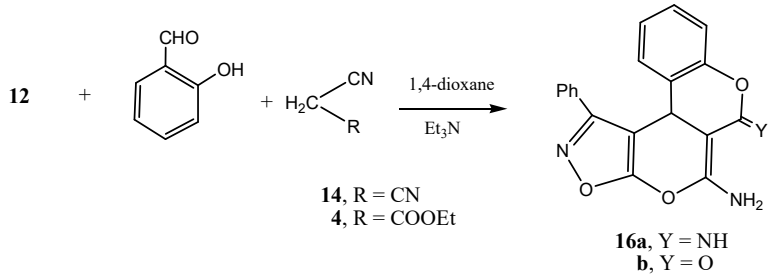


Scheme 1. Synthesis of compounds **5a**,**b**; **7a-d**; **9a-d** and **10a**,**b**.





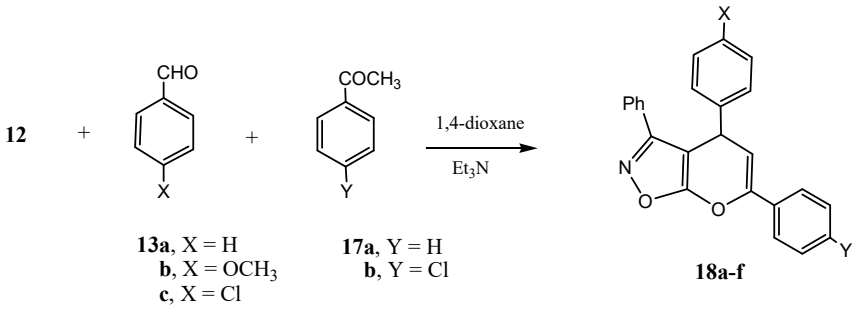
15	a	b	c	d	e	f
R	CN	COOEt	CN	COOEt	CN	COOEt
X	H	H	OCH_3	OCH_3	Cl	Cl



Scheme 2. Synthesis of compounds **12**, **15a-f** and **16a**,**b**.

The multi-component reactions of compound **12** with benzaldehyde (**13a**), 4-methoxybenzaldehyde (**13b**) or 4-chlorobenzaldehyde (**13c**) and acetophenone (**17a**) and 4-chloroacetophenone (**17b**) gave the 4*H*-pyrano[3,2-*d*]isoxazole derivatives **18a-f**, respectively. Then we moved toward the synthesis of fused pyridine derivatives from compound **12**. Thus, the multi-component reactions of compound **12** with either benzaldehyde (**13a**), 4-methoxybenzaldehyde (**13b**) or 4-chlorobenzaldehyde (**13c**) and either malononitrile (**14**) or ethyl cyanoacetate (**4**) in 1,4-dioxane containing ammonium acetate gave the 4*H*-pyrido[3,2-*d*]isoxazole derivatives **19a-f**, respectively. The analytical and spectral data of compounds **19a-f** were in agreement with their respective structures (see experimental section). Finally, the multi-

component reaction of compound **12** with salicylaldehyde and malononitrile (**14**) or ethyl cyanoacetate (**4**) in 1,4-dioxane containing ammonium acetae gave the chromeno[4',3':4,5]-pyrido[3,2-*d*]isoxazole derivatives **20a** and **20b**, respectively (Scheme 3).

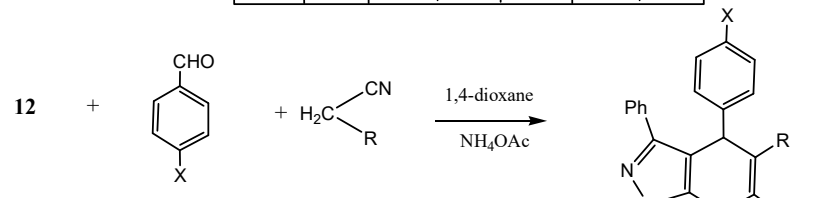


13a, X = H
b, X = OCH_3
c, X = Cl

17a, Y = H
b, Y = Cl

18a-f

18	a	b	c	d	e	f
X	H	H	OCH_3	OCH_3	Cl	Cl
Y	H	Cl	H	Cl	H	Cl

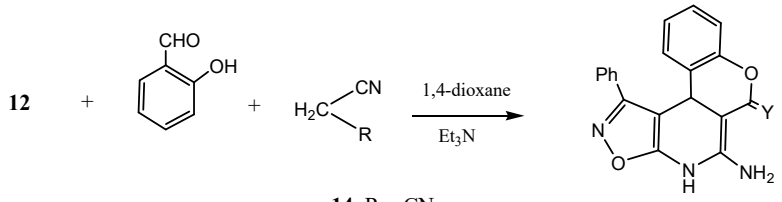


13a, X = H
b, X = OCH_3
c, X = Cl

14, R = CN
4, R = COOEt

19a-f

19	a	b	c	d	e	f
R	CN	COOEt	CN	COOEt	CN	COOEt
X	H	H	OCH_3	OCH_3	Cl	Cl



14, R = CN
4, R = COOEt

20a, Y = NH
b, Y = O

Scheme 3. Synthesis of compounds **18a-f**; **19a-f** and **20a**,**b**.

Cytotoxic activity

Hepatocellular carcinoma HepG2 and cervical carcinoma HeLa were used for screening of the newly synthesized compounds. The cytotoxicity of the compounds was determined using MTT assay and Doxorubicin as a positive control [26-30]. In general, it can be seen that all synthesized compounds exhibited cytotoxic activities against both tested cancer cell lines. Moreover, it can be seen that both cells reacted in a dose-dependent manner toward the applied concentrations. Additionally, both tested cell lines varied in their response toward different synthesized compounds.

MTT assay

The cancer cell lines were cultured in minimum essential medium (MEM) supplemented with 10% fetal bovine serum (FBS). Approximate 4 x 10^3 cells, suspended in MEM medium, were plated onto each well of a 96-well plate and incubated in 5% CO_2 at 37 ºC for 24 h. The compounds tested at the indicated final concentrations were added to the culture medium and the cell cultures were continued for 72 h. Fresh MTT was added to each well at a terminal concentration of 5 µg/mL and incubated with cells at 37 ºC for 4 h. The formazan crystals were dissolved in 100 µg/L of DMSO each well, and the absorbency at 492 nM (for absorbance of MTT formazan) and 630 nM (for the reference wavelength) was measured with an ELISA reader. All of the compounds were tested three times in each cell line. The results expressed as IC_{50} (inhibitory concentration 50%) were the averages of three determinations and calculated by using the Bacus Laboratories Incorporated Slide Scanner (Bliss) software. The mean values of three independent experiments, expressed as IC_{50} values, were presented in Table 1.

Structure activity relationship (SAR)

Based on the IC_{50} values (Table 1) obtained for the tested compounds, it can be seen that cytotoxic activities ranged from very strong to non-cytotoxic. Most of the tested compounds exhibited high cytotoxicity except compounds **3b**, **5b**, **7b**, **7d**, **9c**, **9d**, **15e**, **15f**, **16b**, **18b**, **18e**, **18f**, **19e** and **19f**. It was clear from Table 1 that all compounds exhibited higher inhibitions than doxorubicin against HepG2 cell line except compounds **5a, 9b**, **15b**, **15c**, **15d**, **19b** and **19d**. On the other hand, all compounds exhibited higher higher inhibitions than doxorubicin against Hella cell line except compounds **3a**, **9a**, **15b**, **15c**, **18a**, **19a** and **19c**. Considering the anilide derivatives **3a**, **b** and **5a**,**b** it was obvious that compounds **3b** and **5b** (X = Cl) exhibited higher inhibitions than **3a** and **5a** (X = H). For the pyridine derivatives **7a-d**, it was clear that compounds **7b** (X = H, R' = OH), **7c** (X = Cl, R' = CH_3) and **7d** (X = Cl, R' = OH) exhibited high inhibitions. In addition, compound **7d** with of the highest inhibitions toward HepG2 and Hela cell lines this was attributed to the presence of both the two electronegative groups the Cl and OH. Similarly, for the pyrazole derivatives **9a-d** where compounds **9c** (X = Cl, R = H) and **9d** (X = Cl, R = Ph) showed the highest inhibitions among the four compounds. For the thiophene derivatives **10a,b** it was clear that **10b** (X = Cl) exhibited higher inhibitions than **10a** (X = H). Although the isoxazole derivative **12** exhibited low inhibitions the pyrano[3,2-*d*]isoxazole derivatives **15a-f** exhibited higher inhibitions, especially for compounds **15e** (R = CN, X = Cl) and **15f** (R = X = Cl). It was interestingly, that both of the annulated compounds **16a** and **16b** exhibited high inhibitions. For the pyrano[3,2-*d*]isoxazole and the isoxazolo[5,4-*b*]pyridine derivatives **18a-f** and **19a-f**, it was obvious that compounds **18b** (X = H, Y = Cl)**, 18e** (X = CN, Y = Cl), **18f** (X = COOEt, Y = Cl), **19e** (R = CN, Y = Cl) and **19f** (R = COOEt, Y = Cl) exhibited the highest inhibitions. Surprisingly, the annulated compounds **20a** and **20b** showed moderate inhibitions toward the two cell lines. Among the tested compounds, compound **18f** exhibited the most cytotoxicities among the tested compounds against HepG2 and Hella cell lines with IC_{50}'s 0.19 and 0.18 µM, respectively.

Table 1. Evaluations of the newly synthesized compounds against HepG2 and Hela cell lines

Compound	IC_{50} (μM)	
	HepG2	Hela cell
3a	4.25 ± 1.83	5.28 ± 3.32
3b	0.29 ± 0.15	0.26± 0.04
5a	6.24 ± 2.38	4.26 ± 2.41
5b	0.32 ± 0.12	0.41 ± 0.26
7a	3.59 ± 1.40	4.37 ± 1.28
7b	0.58 ± 0.24	0.42 ± 0.16
7c	1.62 ± 0.61	2.37 ± 1.82
7d	0.21 ± 0.08	0.24 ± 0.15
9a	4.32 ± 2.77	6.53 ± 1.84
9b	5.62 ± 1.26	4.71 ± 1.93
9c	0.48 ± 0.15	0.33 ± 0.12
9d	0.25 ± 0.13	0.21 ± 0.07
10a	2.43 ± 1.02	4.66 ± 2.30
10b	0.23 ± 0.18	0.35 ± 0.16
12	3.47 ± 1.32	4.82 ± 1.53
15a	2.52 ± 1.79	2.42 ± 0.87
15b	6.48 ± 2.09	8.43 ± 2.46
15c	8.37 ± 2.94	6.51 ± 2.73
15d	6.48 ± 1.58	4.51 ± 1.72
15e	0.23 ± 0.19	0.38 ± 0.26
15f	0.62 ± 0.28	0.51 ± 0.32
16a	1.25 ± 0.88	1.03 ± 0.62
16b	0.38 ± 0.14	0.63 ± 0.29
18a	5.26 ± 2.27	7.19 ± 2.80
18b	0.45 ± 0.18	0.52 ± 0.22
18c	4.68 ± 1.57	5.33 ± 1.72
18d	2.08 ± 1.27	3.16 ± 1.82
18e	0.37 ± 0.23	0.26 ± 0.14
18f	0.19 ± 0.07	0.18 ± 0.05
19a	5.23 ± 2.62	6.32 ± 2.29
19b	5.31 ± 1.28	4.42 ± 1.36
19c	8.46 ± 2.31	6.62 ± 2.49
19d	6.52 ± 1.19	4.62 ± 1.15
19e	0.31 ± 0.06	0.21 ± 0.11
19f	0.36 ± 0.18	0.42 ± 0.18
20a	1.25 ± 0.89	1.62 ± 0.52
20b	2.02 ± 0.38	1.76 ± 1.13
Doxorubicin	4.50 ± 0.20	5.57 ± 0.40

EXPERIMENTAL

Chemistry

All melting points were uncorrected and were recorded using an Electrothermal digital melting point apparatus. IR spectra (KBr discs) were measured using a FTIR plus 460 or PyeUnicam SP-1000 spectrophotometer. ^{1}HNMR spectra were measured using Varian Gemini-300 (300 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 measured using 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 Centre in Cairo, Egypt where the IC_{50} values were calculated.

*General procedure of the anilide derivatives **4a,b***

Equimolecular mixed amounts of ethyl benzoylacetate (1.92 g, 0.01mol) and aniline (0.93 g, 0.01 mol) or 4-chloroaniline (1.27 g, 0.01 mol) was heated in an oil bath at 120 °C for 30 min. The remaining product was poured onto ice/water mixture containing a few drops of hydrochloric acid and the formed solid product was collected by filtration.

*3-Oxo-N,3-diphenylpropanamide (**4a**)*. Pale yellow crystals from acetic acid, yield (1.55 g, 65%), mp 70.72 °C. IR (KBr) ν_{max} cm^{-1}: 3472-3343 (NH), 3055 (CH, aromatic), 1686 (C=O), 1633 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 5.62 (s, 2H, CH_2), 7.25-7.53 (m, 10H, $2C_6H_5$), 8.32 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 48.4 (CH_2), 120.8, 121.6, 122.5, 122.8, 123.2, 123.6, 124.6, 125.2 ($2C_6H_5$), 164.5, 165.6 (2C=O). Anal. calcd. for $C_{15}H_{13}NO_2$ (239.27): C, 75.30; H, 5.48; N, 5.85%. Found: C, 75.52; H, 5.67; N, 6.17%. MS: m/z 239 (M^+, 70%).

*N-(4-Chlorophenyl)-3-oxo-3-phenylpropanamide (**4b**)*. Ple brown crystals from acetic acid, yield (1.85 g, 68%), mp 136-138 °C. IR (KBr) ν_{max} cm^{-1}: 3480-3353 (NH), 3055 (CH, aromatic), 1688 (C=O), 1632 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 5.64 (s, 2H, CH_2), 7.23-7.49 (m, 9H, C_6H_5, C_6H_4), 8.29 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 48.7 (CH_2), 120.4, 121.2, 121.6, 122.3, 123.5, 123.4, 124.1, 125.6 (C_6H_5, C_6H_4), 164.7, 165.8 (2C=O). Anal. calcd. for $C_{15}H_{12}ClNO_2$ (273.71): C, 65.82; H, 4.42; N, 5.12%. Found: C, 65.93; H, 4.60; N, 5.42%. MS: m/z 273 (M^+, 76%).

*Ethyl 2-cyano-5-oxo-3-phenyl-5-(phenylamino)pent-2-enoate (**5a**)*. Pale brown crystals from acetic acid, yield (2.33 g, 70%), mp 104-106 °C. IR (KBr) ν_{max} cm^{-1}: 3486-3351 (NH), 3055 (CH, aromatic), 2220 (CN), 1702, 1688 (2C=O), 1632 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.16 (t, 3H, *J* = 6.83 Hz, CH_3), 4.25 (q, 2H, *J* = 6.83 Hz, CH_2), 5.46 (s, 2H, CH_2), 7.24-7.52 (m, 10H, $2C_6H_5$), 8.33 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.4 ($OCH_2\underline{CH_3}$), 48.6 (CH_2), 50.6 ($O\underline{CH_2}CH_3$), 117.0 (CN), 120.2, 120.8, 121.3, 122.3, 123.6, 123.9, 124.2, 125.8 (C_6H_5, C_6H_4), 164.5, 165.8 (2C=O). Anal. calcd. for $C_{20}H_{18}N_2O_3$ (334.37): C, 71.84; H, 5.43; N, 8.38%. Found: C, 71.95; H, 5.61; N, 8.52%. MS: m/z 334 (M^+, 58%).

*Ethyl 5-((4-chlorophenyl)amino)-2-cyano-5-oxo-3-phenylpent-2-enoate (**5b**)*. Yellow crystals from ethanol, yield (2.50 g, 70%), mp 141-143°C. IR (KBr) ν_{max} cm^{-1}: 3473-3342 (NH), 3055 (CH, aromatic), 2220 (CN), 1702, 1688 (2C=O), 1634 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.15 (t, *J* = 7.27 Hz, 3H, CH_3), 4.25 (q, *J* = 7.27 Hz, CH_2), 5.48 (s, 2H, CH_2), 7.25-7.58 (m, 9H, C_6H_5, C_6H_4), 8.33 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.6 ($OCH_2\underline{CH_3}$), 48.3 (CH_2), 50.8 ($O\underline{CH_2}CH_3$), 116.9 (CN), 120.4, 120.9, 121.2, 121.6, 123.2, 123.7, 124.6, 125.9 (C_6H_5, C_6H_4), 164.3, 165.6 (2C=O). Anal. calcd. for $C_{20}H_{17}ClN_2O_3$ (368.81): C, 65.13; H, 4.65; N, 7.60%. Found: C, 65.28; H, 4.45; N, 7.84%. MS: m/z 368 (M^+, 70%).

*General procedure for the synthesis of the pyridine derivatives **7a-d***

To a solution of **5a** (3.34 g, 0.01 mol) or **5b** (3.68g, 0.01 mol) in 1,4-dioxane (40 mL) containing piperidine (1.0 mL) acetylacetone (1.0 g, 0.01 mol) or ethyl acetoacetate (1.30 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 2 h then was poured onto ice/water

containing a few drops of hydrochloric acid and the formed solid product was collected by filtration.

*Ethyl 2-cyano-3-(4,6-dimethyl-2-oxo-1-phenyl-1,2-dihydropyridin-3-yl)-3-phenylacrylate (**7a**)* White crystals from acetic acid, yield (2.38 g, 60%), mp 100-103 °C. IR (KBr) ν_{max} cm^{-1}: 3055 (CH, aromatic), 2221 (CN), 1703, 1689 (2C=O), 1632 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.16 (t, 3H, *J* = 5.96 Hz, CH_3), 2.80, 2.87 (2s, 6H, $2CH_3$), 4.22 (q, 2H, *J* = 5.95Hz, CH_2), 6.09 (s, 1H, pyridine H-5), 7.23-7.57 (m, 10H, $2C_6H_5$); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.6 ($OCH_2\underline{CH_3}$), 36.2, 38.4 ($2CH_3$), 50.8 ($O\underline{CH_2}CH_3$), 116.8 (CN), 120.3, 120.5, 121.2, 122.6, 123.1, 123.7, 124.2, 125.6 ($2C_6H_5$), 132.6, 133.2, 134.3, 135.8 (pyridine C-3, C-4, C-5, C-6), 164.3, 165.5 (2C=O). Anal. calcd. for $C_{25}H_{22}N_2O_3$ (398.45): C, 75.36; H, 5.57; N, 7.03%. Found: C, 75.46; H, 5.70; N, 7.18%. MS: m/z 398 (M^+, 70%).

*Ethyl 2-cyano-3-(6-hydroxy-4-methyl-2-oxo-1-phenyl-1,2-dihydropyridin-3-yl)-3-phenylacrylate (**7b**)*. Pale brown crystals from 1,4-dioxane, yield (2.20 g, 55 %), Mp 110-112 °C. IR (KBr) ν_{max} cm^{-1}: 3580-3353 (OH), 3055 (CH, aromatic), 2220 (CN), 1701, 1688 (2C=O), 1632 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.15 (t, 3H, *J* = 7.22 Hz, CH_3), 2.86 (s, 3H, CH_3), 4.22 (q, 2H, *J* = 7.22 Hz, CH_2), 6.12 (s, 1H, pyridine H-5), 7.26-7.48 (m, 10H, $2C_6H_5$), 10.37 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.5 ($OCH_2\underline{CH_3}$), 50.7 ($O\underline{CH_2}CH_3$), 117.0 (CN), 120.1, 120.6, 121.4, 121.3, 122.81, 123.7, 124.1, 125.7 ($2C_6H_5$), 132.3, 133.6, 134.1, 135.5 (pyridine C-3, C-4, C-5, C-6), 164.1, 165.8 (2C=O). Anal. calcd. for $C_{24}H_{20}N_2O_4$ (400.34): C, 71.99; H, 5.03; N, 7.00 %. Found: C, 72.16; H, 5.20; N, 7.18 %. MS: m/z 400 (M^+, 70%).

*Ethyl 2-cyano-3-(4,6-dimethyl-2-oxo-1-phenyl-1,2-dihydropyridin-3-yl)-3-phenylacr (**7c**)*. Pale yellow crystals from 1,4-dioxane, yield (2.59 g, 60 %), Mp 150-152 °C. IR (KBr) ν_{max} cm^{-1}: 3055 (CH, aromatic), 2220 (CN), 1701, 1688 (2C=O), 1632 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.15 (t, 3H, *J* = 6.26 Hz, CH_3), 2.83, 2.89 (2s, 6H, $2CH_3$), 4.22 (q, 2H, *J* = 6.26 Hz, CH_2), 6.09 (s, 1H, pyridine H-5), 7.23-7.57 (m, 9H, C_6H_5, C_6H_4); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.5 ($OCH_2\underline{CH_3}$), 50.7 ($O\underline{CH_2}CH_3$), 116.5 (CN), 120.1, 120.8, 121.4, 122.7, 123.0, 123.5, 124.7, 125.4 (C_6H_5, C_6H_4), 132.3, 133.6, 134.5, 135.5 (pyridine C-3, C-4, C-5, C-6), 164.6, 165.8 (2C=O). Anal. calcd. for $C_{25}H_{21}ClN_2O_3$ (432.90): C, 69.36; H, 4.89; N, 6.47%. Found: C, 69.44; H, 4.93; N, 6.58%. MS: m/z 432 (M^+, 85%).

*Ethyl 3-(1-(4-chlorophenyl)-6-hydroxy-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-2-cyano-3-phenylacrylate (**7d**)*. Pale yellow crystals from 1,4-dioxane, yield (2.82 g, 65%), mp 156-158 °C. IR (KBr) ν_{max} cm^{-1}: 3564-3351 (OH), 3055 (CH, aromatic), 2222 (CN), 1703, 1688 (2C=O), 1634 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.16 (t, 3H, *J* = 7.25 Hz, CH_3), 2.83 (s, 3H, CH_3), 4.23 (q, 2H, *J* = 7.25 Hz, CH_2), 6.12 (s, 1H, pyridine H-5), 7.22-7.56 (m, 9H, C_6H_5, C_6H_4), 10.30 (s, 1H, D_2O exchangeable, OH), ; ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.4 ($OCH_2\underline{CH_3}$), 50.9 ($O\underline{CH_2}CH_3$), 116.8 (CN), 120.3, 120.6, 121.2, 122.8, 123.0, 123.3, 124.4, 125.6 (C_6H_5, C_6H_4), 132.5, 133.5, 134.2, 135.9 (pyridine C-3, C-4, C-5, C-6), 164.8, 165.4 (2C=O). Anal. calcd. for $C_{24}H_{19}ClN_2O_3$ (434.87): C, 66.29; H, 4.40; N, 6.44%. Found: C, 66.37; H, 4.59; N, 6.62%. MS: m/z 434 (M^+, 50%).

*General procedure for the synthesis of the pyrazole derivatives **9a-d***

To a solution of **5a** (3.34 g, 0.01 mol) or **5b** (3.68g, 0.01 mol) in 1,4-dioxane (40 mL) hydrazine hydrate (0.50 mL, 0.01 mol) or phenylhydrazine (1.08 g, 0.01 mol) was added. The reaction mixture in each case was heated under reflux for 2 h then was poured onto ice/water containing a few drops of hydrochloric acid and the formed solid product was collected by filtration.

*3-(3-Amino-5-hydroxy-1H-pyrazol-4-yl)-N,3-diphenylacrylamide (**9a**)*. White crystals from acetic acid, yield (2.17 g, 68%), mp 90-93 °C. IR (KBr) ν_{max} cm^{-1}: 3538-3362 (OH, NH), 3055 (CH, aromatic), 1688 (C=O), 1635 (C=C); ^{1}H NMR (DMSO-*d*$_6$, 300 MHz): δ = 4.93 (s, 2H, D_2O exchangeable, NH_2), 5.93 (s, 1H, CH), 7.22-7.49 (m, 10H, $2C_6H_5$), 8.41, 8.33 (2s, 2H, D_2O exchangeable, 2NH), 9.80 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-*d*$_6$, 75 MHz): δ 50.8, 87.6 (C=CH), 120.4, 120.6, 121.1, 122.5, 124.1, 124.9, 125.3, 125.7 ($2C_6H_5$), 130.8, 134.9 (pyrazole C-2, C-3), 165.6 (C=O), 172.4 (C=N). Anal. calcd. for $C_{18}H_{16}N_4O_2$ (320.35): C, 67.49; H, 5.03; N, 17.49%. Found: C, 67.53; H, 5.27; N, 17.68%. MS: m/z 320 (M^+, 60%).

*3-(3-Amino-5-hydroxy-1-phenyl-1H-pyrazol-4-yl)-N,3-diphenylacrylamide (**9b**)*. Pale brown crystals from 1,4-dioxane, yield (2.61 g, 66%), mp 160-162 °C. IR (KBr) ν_{max} cm^{-1}: 3518-3322 (OH, NH), 3055 (CH, aromatic), 1689 (C=O), 1636 (C=C); ^{1}H NMR (DMSO-*d*$_6$, 300 MHz): δ = 4.96 (s, 2H, D_2O exchangeable, NH_2), 5.91 (s, 1H, CH), 7.26-7.52 (m, 15H, $3C_6H_5$), 8.43 (s, 1H, D_2O exchangeable, NH), 9.95 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-*d*$_6$, 75 MHz): δ 50.7, 87.4 (C=CH), 120.1, 120.5, 121.4, 122.8, 123.0, 123.4, 123.8, 124.1, 124.5, 124.6, 125.2, 125.5 ($3C_6H_5$), 130.5, 134.6 (pyrazole C-2, C-3), 165.8 (C=O), 172.6 (C=N). Anal. calcd. for $C_{24}H_{20}N_4O_2$ (396.44): C, 72.71; H, 5.08; N, 14.13%. Found: C, 72.68; H, 5.29; N, 14.26%. MS: m/z 396 (M^+, 80%).

*3-(3-Amino-5-hydroxy-1H-pyrazol-4-yl)-N-(4-chlorophenyl)-3-phenyl-acrylamide (**9c**)*. Pale yellow crystals from ethanol, yield (2.47 g, 70%), mp 184-186 °C. IR (KBr) ν_{max} cm^{-1}: 3525-3347 (OH, NH), 3055 (CH, aromatic), 1688 (C=O), 1633 (C=C); ^{1}H NMR (DMSO-*d*$_6$, 300 MHz): δ = 4.89 (s, 2H, D_2O exchangeable, NH_2), 5.91 (s, 1H, CH), 7.25-7.52 (m, 9H, C_6H_5, C_6H_4), 8.41, 8.31 (2s, 2H, D_2O exchangeable, 2NH), 9.84 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-*d*$_6$, 75 MHz): δ 50.5, 87.9 (C=CH), 120.3, 120.2, 121.4, 122.6, 124.3, 124.5, 125.1, 125.6 ($2C_6H_5$), 130.8, 134.7 (pyrazole C-2, C-3), 165.4 (C=O), 172.5 (C=N). Anal. calcd. for $C_{18}H_{15}ClN_4O_2$ (354.79): C, 60.94; H, 4.26; N, 15.79%. Found: C, 60.86; H, 4.37; N, 15.84%. MS: m/z 354 (M^+, 55%).

*3-(3-Amino-5-hydroxy-1-phenyl-1H-pyrazol-4-yl)-N-(4-chlorophenyl)-3-phenylacrylamide (**9d**)*. Yellow crystals from ethanol, yield (3.05 g, 71%), mp 146-148 °C. IR (KBr) ν_{max} cm^{-1}: 3497-3336 (OH, NH), 3055 (CH, aromatic), 1688 (C=O), 1633 (C=C); ^{1}H NMR (DMSO-*d*$_6$, 300 MHz): δ = 4.93 (s, 2H, D_2O exchangeable, NH_2), 5.89 (s, 1H, CH), 7.23-7.56 (m, 14H, $2C_6H_5$, C_6H_4), 8.45 (s, 1H, D_2O exchangeable, NH), 9.92 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-*d*$_6$, 75 MHz): δ 50.5, 87.2 (C=CH), 120.3, 120.8, 121.5, 121.9, 123.2, 123.6, 124.0, 124.3, 124.8, 125.3, 125.5, 126.1 ($2C_6H_5$, C_6H_4), 130.8, 134.9 (pyrazole C-2, C-3), 165.6 (C=O), 172.3 (C=N). Anal. calcd. for $C_{24}H_{19}ClN_4O_2$ (430.89): C, 66.90; H, 4.44; N, 13.00%. Found: C, 67.22; H, 4.59; N, 13.26%. MS: m/z 430 (M^+, 75%).

*General procedure for the synthesis of the thiophene derivatives **10a,b***

To a solution of **5a** (3.34 g, 0.01 mol) or **5b** (3.68g, 0.01 mol) in 1,4-dioxane (40 mL) containing triethylamine, elemental sulfur (0.32 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 2 h then was poured onto ice/water containing a few drops of hydrochloric acid and the formed solid product, in each case, was collected by filtration.

*Ethyl 2-amino-4-phenyl-5-(phenylcarbamoyl)thiophene-3-carboxylate (**10a**)*. Yellow crystals from acetic acid, yield (2.01 g, 55%), mp 94-96 °C. IR (KBr) ν_{max} cm^{-1}: 3054 (CH, aromatic), 1701, 1688 (2C=O), 1633 (C=C); ^{1}H NMR (DMSO-*d*$_6$, 300 MHz): δ = 1.15 (t, 3H, *J* = 6.28Hz, CH_3), 4.22 (q, 2H, *J* = 6.28 Hz, CH_2), 4.80 (s, 2H, D_2O exchangeable, NH_2), 7.26-7.48 (m, 10H, $2C_6H_5$), 8.29 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-*d*$_6$, 75 MHz): δ 16.8 ($OCH_2\underline{CH_3}$),

50.6 ($O\underline{CH_2}CH_3$), 120.1, 120.8, 121.6, 122.2, 122.7, 123.8, 124.5, 125.8 ($2C_6H_5$), 130.3, 131.8, 133.6, 134.2 (thiophene C-2, C-3, C-4, C-5), 164.6, 166.3 (2C=O). Anal. calcd. for $C_{20}H_{18}N_2O_3S$ (366.43): C, 65.55; H, 4.95; N, 7.64%. Found: C, 65.69; H, 5.17; N, 7.59 %. MS: m/z 366 (M^+, 68%).

*Ethyl 2-amino-5-((4-chlorophenyl)carbamoyl)-4-phenylthiophene-3-carboxylate (**10b**)*. Orange crystals from acetic acid, yield (2.60 g, 65%), mp 164-166 °C. IR (KBr) ν_{max} cm^{-1}: 3055 (CH, aromatic), 1703, 1689 (2C=O), 1631 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.16 (t, 3H, *J* = 6.42 Hz, CH_3), 4.23 (q, 2H, *J* = 6.42 Hz, CH_2), 4.83 (s, 2H, D_2O exchangeable, NH_2), 7.24-7.55 (m, 9H, C_6H_5, C_6H_4), 8.32 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.5 ($OCH_2\underline{CH_3}$), 50.4 ($O\underline{CH_2}CH_3$), 120.3, 120.7, 121.2, 121.3, 122.3, 123.4, 124.1, 125.5 ($2C_6H_5$), 130.4, 131.5, 133.3, 134.6 (thiophene C-2, C-3, C-4, C-5), 164.3, 166.8 (2C=O). Anal. calcd. for $C_{20}H_{17}ClN_2O_3S$ (400.88): C, 59.92; H, 4.27; N, 7.99; S, 8.00%. Found: C, 60.25; H, 4.38; N, 7.69; S, 7.83%. MS: m/z 400 (M^+, 80%).

*3-Phenylisoxazol-5(4H)-one (**12**)*

To a solution of ethyl benzoylacetate (1.92 g, 0.01 mol) in absolute ethanol (50 mL) containing sodium acetate (1.0 g), hydroxylamine hydrochloride (0.69 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 2 h then was poured onto ice/water and the formed solide product was collected by filtration. Yellow crystals from ethanol, yield (1.28 g, 80%), mp 154-156 °C. IR (KBr) ν_{max} cm^{-1}: 3056 (CH, aromatic), 1689 (C=O), 1649 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 4.43 (s, 2H, CH_2), 7.28-7.50 (m, 5H, C_6H_5); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 64.2 (CH_2), 120.6, 122.8, 123.8, 124.8 (C_6H_5), 166.8 (C=O), 172.3 (C=N). Anal. calcd. for $C_9H_7NO_2$ (161.16): C, 67.07; H, 4.38; N, 8.69%. Found: C, 66.96; H, 4.53; N, 8.80%. MS: m/z 161 (M^+, 90%).

*General procedure for the synthesis of the pyrano[3,2-d]isoxazole derivatives **15a-f***

To a solution of compound **12** (1.61 g, 0.01 mol) in absolute ethanol (50 mL, 0.01 mol) containing triethylamine (1.0 mL) each of malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) and benzaldehyde (1.06 g, 0.01 mol), 4-methoxybenzaldehyde (1.37 g, 0.01 mol) or 4-chlorobenzaldehyde (1.40, 0.01 mol) were added. The reaction mixture, in each case, was heated under reflux for 3 h then left to cool and the formed solid product, in each case, was collected by filtration.

*6-Amino-3,4-diphenyl-4H-pyrano[3,2-d]isoxazole-5-carbonitrile (**15a**)*. Grey crystals from ethanol, yield (2.14 g, 68%), mp 102-104 °C., IR (KBr) ν_{max} cm^{-1}: 3486-3328 (NH_2), 3055 (CH, aromatic), 2220 (CN), 1632 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 4.78 (s, 2H, D_2O exchangeable, NH_2), 6.12 (s, 1H, pyran H-4), 7.24-7.53 (m, 10H, $2C_6H_5$); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 90.8 (pyran C-4), 116.8 (CN), 120.6, 121.4, 121.8, 122.8, 123.2, 123.7, 123.4, 124.5 ($2C_6H_5$), 129.8, 130.6, 132.5, 134.6 (pyran C-2, C-3, C-5, C-6), 172.8 (C=N). Anal. calcd. for $C_{19}H_{13}N_3O_2$ (315.33): C, 72.37; H, 4.16; N, 13.33%. Found: C, 72.53; H, 4.38; N, 13.62%. MS: m/e 315 (M^+, 68%).

*Ethyl 6-amino-3,4-diphenyl-4H-pyrano[3,2-d]isoxazole-5-carboxylate (**15b**)*. Yellow crystals from ethanol, yield (1.99 g, 55%), mp 180-183°C. IR (KBr) ν_{max} cm^{-1}: 3492-3358 (NH_2), 3055 (CH, aromatic), 1687(CO), 1632 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.15 (t, 3H, *J* = 5.94 Hz, CH_3), 4.22 (q, 2H, *J* = 5.94 Hz, CH_2), 4.81 (s, 2H, D_2O exchangeable, NH_2), 6.09 (s, 1H, pyran H-4), 7.26-7.49 (m, 10H, $2C_6H_5$); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.7 ($OCH_2\underline{CH_3}$), 50.2 ($O\underline{CH_2}CH_3$), 90.7 (pyran C-4), 120.4, 121.6, 122.3, 122.7, 123.3, 123.6, 124.1, 125.6

($2C_6H_5$), 129.9, 130.8, 132.2, 134.8 (pyran C-2, C-3, C-5, C-6), 172.5 (C=N). Anal. calcd. for $C_{21}H_{18}N_2O_4$ (362.38): C, 69.60; H, 5.01; N, 7.73%. Found: C, 69.72; H, 5.28; N, 7.58%. MS: m/z 362 (M^+, 70%).

6-Amino-4-(4-methoxyphenyl)-3-phenyl-4H-pyrano[3,2-d]isoxazole-5-carbonitrile (***15c***). Brown crystals from ethanol, yield (2.24 g, 65%), mp 86-88 °C. IR (KBr) ν_{max} cm^{-1}: 3474-3336 (NH_2), 3055 (CH, aromatic), 2220 (CN), 1636 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 3.70 (s, 3H, OCH_3), 4.75 (s, 2H, D_2O exchangeable, NH_2), 6.14 (s, 1H, pyran H-4), 7.23-7.56 (m, 9H, C_6H_5, C_6H_4); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 50.4 (OCH_3), 90.8 (pyran C-4), 116.8 (CN), 120.2, 120.6, 121.5, 122.6, 123.4, 123.9, 124.2, 125.8 (C_6H_5, C_6H_4), 130.2, 130.8, 132.9, 134.4 (pyran C-2, C-3, C-5, C-6), 172.6 (C=N). Anal. calcd. for $C_{20}H_{15}N_3O_3$ (345.35): C, 69.56; H, 4.38; N, 12.17%. Found: C, 69.49; H, 4.48; N, 12.08%. MS: m/z 345 (M^+, 80%).

Ethyl 6-amino-4-(4-methoxyphenyl)-3-phenyl-4H-pyrano[3,2-d]isoxazole-5-carboxylate (***15d***). Yellow crystals from ethanol, yield (2.74 g, 70%), mp 190-192 °C. IR (KBr) ν_{max} cm^{-1}: 3485-3336 (NH_2), 3055 (CH, aromatic), 1688 (CO), 1632 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.16 (t, 3H, *J* = 6.36 Hz, CH_3), 3.68 (s, 3H, OCH_3), 4.22 (q, 2H, *J* = 6.36 Hz, CH_2), 4.84 (s, 2H, D_2O exchangeable, NH_2), 6.12 (s, 1H, pyran C-4), 7.24-7.58 (m, 9H, C_6H_5, C_6H_4); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.8 ($OCH_2\underline{CH_3}$), 50.4 ($O\underline{CH_2}CH_3$), 50.6 (OCH_3), 90.9 (pyran H-4), 120.2, 121.8, 122.1, 122.4, 123.5, 123.9, 124.4, 125.8 (C_6H_5, C_6H_4), 129.4, 130.6, 132.4, 134.7 (pyran C-2, C-3, C-5, C-6), 172.6 (C=N). Anal. calcd. for $C_{22}H_{20}N_2O_5$ (392.40): C, 67.34; H, 5.14; N, 7.14%. Found: C, 67.41; H, 5.19; N, 7.25%. MS: m/e 392 (M^+, 66%).

6-Amino-4-(4-chlorophenyl)-3-phenyl-4H-pyrano[3,2-d]isoxazole-5-carbonitrile (***15e***). Pale orange crystals from ethanol, yield (2.30 g, 66%), mp 120-122 °C. IR (KBr) ν_{max} cm^{-1}: 3483-3329 (NH_2), 3055 (CH, aromatic), 2220 (CN), 1634 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 4.74 (s, 2H, D_2O exchangeable, NH_2), 6.15 (s, 1H, pyran H-4), 7.25-7.54 (m, 9H, C_6H_5, C_6H_4); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 90.5 (pyran C-4), 116.7 (CN), 120.1, 120.4, 120.5, 121.4, 122.8, 123.7, 124.3, 125.6 (C_6H_5, C_6H_4), 130.4, 131.5, 132.8, 134.7 (pyran C-2, C-3, C-5, C-6), 172.4 (C=N). Anal. calcd. for $C_{19}H_{12}ClN_3O_2$ (349.77): C, 65.24; H, 3.46; N, 12.01%. Found: C, 65.38; H, 3.56; N, 12.24%. MS: m/z 349 (M^+, 76%).

Ethyl 6-amino-4-(4-chlorophenyl)-3-phenyl-4H-pyrano[3,2-d]isoxazole-5-carboxylate (***15f***). Orange crystals from ethanol, yield (2.09 g, 53%), mp 177-179 °C. IR (KBr) ν_{max} cm^{-1}: 3471-3335 (NH_2), 3055 (CH, aromatic), 1688 (CO), 1634 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.15 (t, 3H, *J* = 7.02 Hz, CH_3), 4.23 (q, 2H, *J* = 7.02 Hz, CH_2), 4.84 (s, 2H, D_2O exchangeable, NH_2), 6.12 (s, 1H, pyran H-4), 7.22-7.56 (m, 9H, C_6H_5, C_6H_4); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.6 ($OCH_2\underline{CH_3}$), 50.3 ($O\underline{CH_2}CH_3$), 90.9 (pyran C-4), 120.0, 120.5, 122.4, 122.7, 123.2, 123.6, 124.2, 125.5 (C_6H_5, C_6H_4), 130.3, 130.9, 131.8, 133.9 (pyran C-2, C-3, C-5, C-6), 172.8 (C=N). Anal. calcd. for $C_{21}H_{17}ClN_2O_4$ (396.82): C, 63.56; H, 4.32; N, 7.06%. Found: C, 63.69; H, 4.48; N, 7.21%. MS: m/z 396 (M^+, 40%).

General procedure for the synthesis of the chromeno[4',3':4,5]pyrano[3,2-d]isoxazole derivatives ***16a-f***

To a solution of compound **12** (1.61 g, 0.01 mol) in absolute ethanol (50 mL, 0.01 mol) containing triethylamine (1.0 mL) each of malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) and salicylaldehyde (1.22 , 0.01 mol) were added. The reaction mixture, in each case, was heated under reflux for 3 h then left to cool and the formed solid product, in each case, was collected by filtration.

6-Imino-1-phenyl-6,11b-dihydrochromeno[4',3':4,5]pyrano[3,2-d]isoxazol-5-amine ***(16a)***. Orange crystals from ethanol, yield (2.31 g, 70%), mp 110-112 °C., IR (KBr) ν_{max} cm^{-1}: 3497-3347 (NH_2, NH), 3054 (CH, aromatic), 1665 (exocyclic C=N), 1634 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 4.89 (s, 2H, D_2O exchangeable, NH_2), 6.15 (s, 1H, pyran H-4), 7.28-7.49 (m, 9H, C_6H_5, C_6H_4), 8.52 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 90.8 (pyran H-4), 120.3, 120.8, 121.6, 121.9, 122.4, 122.8, 123.5, 125.8 (C_6H_5, C_6H_4), 130.1, 131.4, 131.8, 132.8 (pyran C-2, C-3, C-5, C-6), 172.4, 172.6 (2C=N). Anal. calcd. for $C_{19}H_{13}N_3O_3$ (331.32): C, 68.88; H, 3.95; N, 12.68%. Found: C, 68.64; H, 4.17; N, 12.42%. MS: m/z 331 (M^+, 56%).

5-Amino-1-phenylchromeno[4',3':4,5]pyrano[3,2-d]isoxazol-6(11bH)-one ***(16b)***. Yellow crystals from 1,4-dioxane, yield (2.19 g, 66%), mp 130-132 °C. IR (KBr) ν_{max} cm^{-1}: 3474-3336 (NH_2), 3056 (CH, aromatic), 1688 (CO), 1634 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 4.89 (s, 2H, D_2O exchangeable, NH_2), 6.18 (s, 1H, pyran H-4), 7.26-7.52 (m, 9H, C_6H_5, C_6H_4); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 90.6 (pyran H-4), 120.6, 121.3, 121.8, 122.1, 122.4, 123.2, 123.7, 124.6 (C_6H_5, C_6H_4), 130.3, 131.7, 132.4, 133.6 (pyran C-2, C-3, C-5, C-6), 166.8 (CO), 172.2, 172.8 (2C=N). Anal. calcd. for $C_{19}H_{12}N_2O_4$ (332.32): C, 68.67; H, 3.64; N, 8.43%. Found: C, 68.59; H, 3.80; N, 8.62%. MS: m/z 332 (M^+, 70%).

General procedure for the synthesis of the pyrano[3,2-d]isoxazole derivatives ***18a-f***

To a solution of compound **12** (1.61 g, 0.01 mol) in absolute ethanol (50 mL, 0.01 mol) containing triethylamine (1.0 mL) benzaldehyde (1.06 g, 0.01 mol), 4-methoxybenzaldehyde (1.37 g, 0.01 mol) or 4-chlorobenzaldehyde (1.40, 0.01 mol) and acetophenone (1.20 g, 0.01 mol) or 4-chloroacetophenone (1.54 g, 0.01 mol) were added. The reaction mixture, in each case, was heated under reflux for 3 h then left to cool and the formed solid product, in each case, was collected by filtration.

3,4,6-Triphenyl-4H-pyrano[3,2-d]isoxazole ***(18a)***. Yellow crystals from ethanol, yield (2.52 g, 72%), mp 144-146 °C. IR (KBr) ν_{max} cm^{-1}: 3055 (CH, aromatic), 1638 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 6.18 (d, 1H, *J* = 5.31 Hz, pyran H-4), 6.59 (d, 1H, *J* = 5.31 Hz, pyran H-3), 7.26-7.58 (m, 15H, $3C_6H_5$); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 90.5, 104.3 (pyran H-4, H-3), 120.3, 120.6, 121.4, 121.7, 122.2, 122.9, 123.2, 123.7, 123.4, 124.3, 124.6, 125.2 ($3C_6H_5$), 130.2, 130.4, 131.7, 133.8 (pyran C-2, C-3, C-5, C-6), 172.5 (C=N). Anal. calcd. for $C_{24}H_{17}NO_2$ (351.40): C, 82.03; H, 4.88; N, 3.99%. Found: C, 81.89; H, 4.69; N, 4.12%. MS: m/z 351 (M^+, 75%).

6-(4-Chlorophenyl)-3,4-diphenyl-4H-pyrano[3,2-d]isoxazole ***(18b)***. Pale yellow crystals from ethanol, yield (2.31 g, 60%), mp 170-172 °C. IR (KBr) ν_{max} cm^{-1}: 3056 (CH, aromatic), 1634 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 6.21 (d, 1H, *J* = 5.72 Hz, pyran H-4), 6.62 (d, 1H, *J* = 5.72 Hz, pyran H-3), 7.22-7.55 (m, 14H, $2C_6H_5$, C_6H_4); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 90.5, 104.3 (pyran H-4, H-3), 120.2, 120.8, 121.5, 121.8, 122.0, 122.4, 122.6, 123.9, 124.4, 124.6, 125.1, 125.8 ($2C_6H_5$, C_6H_4), 130.4, 130.8, 131.5, 133.6 (pyran C-2, C-3, C-5, C-6), 172.5 (C=N). Anal. calcd. for $C_{24}H_{16}ClNO_2$ (385.84): C, 74.71; H, 4.18; N, 3.63%. Found: C, 74.85; H, 4.31; N, 3.82%. MS: m/z 385 (M^+, 60%).

6-(4-Methoxyphenyl)-3,4-diphenyl-4H-pyrano[3,2-d]isoxazole ***(18c)***. Yellow crystals from ethanol, yield (2.59 g, 68%), mp 196-198 °C. IR (KBr) ν_{max} cm^{-1}: 3054 (CH, aromatic), 1636 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 3.70 (s, 3H, OCH_3), 6.24 (d, 1H, *J* = 6.01 Hz, pyran H-4), 6.68 (d, 1H, *J* = 6.01 Hz, pyran H-3), 7.24-7.57 (m, 14H, $2C_6H_5$, C_6H_4); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 50.4 (OCH_3), 90.2, 104.6 (pyran H-4, H-3), 120.4, 120.6, 121.2, 121.5, 122.8,

122.3, 122.8, 123.5, 123.7, 124.2, 125.4, 125.6 ($2C_6H_5$, C_6H_4), 130.5, 130.3, 131.8, 133.2 (pyran C-2, C-3, C-5, C-6), 172.8 (C=N). Anal. calcd. for $C_{25}H_{19}NO_2$ (381.42): C, 78.72; H, 5.02; N, 3.67%. Found: C, 78.92; H, 4.86; N, 3.76%. MS: m/z 381 (M^+, 75%).

6-(4-Methoxyphenyl)-3,4-diphenyl-4H-pyrano[3,2-d]isoxazole ***(18d)***. Pale Orange crystals from ethanol, yield (2.49 g, 60%), mp 144-146 °C. IR (KBr) ν_{max} cm^{-1}: 3056 (CH, aromatic), 1633 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 3.70 (s, 3H, OCH_3), 6.21 (d, 1H, *J* = 6.24 Hz, pyran H-4), 6.67 (d, 1H, *J* = 6.24 Hz, pyran H-3), 7.21-7.54 (m, 13H, C_6H_5, $2C_6H_4$); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 50.6 (OCH_3), 90.4, 104.1 (pyran H-4, H-3), 120.1, 120.4, 121.5, 121.8, 122.3, 122.6, 123.1, 123.4, 123.7, 124.6, 125.1, 125.5 ($2C_6H_5$, C_6H_4), 130.3, 130.1, 131.5, 133.6 (pyran C-2, C-3, C-5, C-6), 172.6 (C=N). Anal. calcd. for $C_{25}H_{11}ClNO_3$ (415.87): C, 72.20; H, 4.36; N, 3.37%. Found: C, 72.39; H, 4.52; N, 3.50%. MS: m/z 415 (M^+, 60%).

4-(4-Chlorophenyl)-3,6-diphenyl-4H-pyrano[3,2-d]isoxazole ***(18e)***. Pale brown crystals from ethanol, yield (2.38 g, 62%), mp 167-168 °C. IR (KBr) ν_{max} cm^{-1}: 3053 (CH, aromatic), 1632 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 6.21 (d, 1H, *J* = 6.24 Hz, pyran H-4), 6.63 (d, 1H, *J* = 6.24 Hz, pyran H-3), 7.22-7.62 (m, 14H, $2C_6H_5$, C_6H_4); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 90.3, 104.6 (pyran H-4, H-3), 120.4, 120.7, 121.3, 121.6, 122.1, 122.7, 122.8, 123.9, 124.3, 124.9, 125.1, 125.4 ($2C_6H_5$, C_6H_4), 130.6, 131.6, 132.1, 133.7 (pyran C-2, C-3, C-5, C-6), 172.8 (C=N). Anal. calcd. for $C_{24}H_{16}ClNO_2$ (385.84): C, 74.71; H, 4.18; N, 3.63%. Found: C, 74.85; H, 4.31; N, 3.82%. MS: m/z 385 (M^+, 60%).

4,6-Bis(4-chlorophenyl)-3-phenyl-4H-pyrano[3,2-d]isoxazole ***(18f)***. Yellow crystals from ethanol, yield (2.43 g, 58%), mp 194-196 °C. IR (KBr) ν_{max} cm^{-1}: 3054 (CH, aromatic), 1631 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 6.20 (d, 1H, *J* = 6.24 Hz, pyran H-4), 6.69 (d, 1H, *J* = 6.24 Hz, pyran H-3), 7.22-7.56 (m, 13H, C_6H_5, $2C_6H_4$); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 90.8, 104.5 (pyran H-4, H-3), 120.0, 120.3, 121.6, 121.9, 122.0, 122.4, 123.1, 123.6, 123.9, 124.7, 125.2, 125.3 ($2C_6H_5$, C_6H_4), 130.2, 130.8, 132.5, 133.9 (pyran C-2, C-3, C-5, C-6), 172.8 (C=N). Anal. calcd. for $C_{24}H_{15}Cl_2NO_3$ (420.29): C, 68.59; H, 3.60; N, 3.33%. Found: C, 68.35; H, 3.49; N, 3.49%. MS: m/z 420 (M^+, 76%).

General procedures for the synthesis of the 4,7-dihydroisoxazolo[5,4-b]pyridine ***19a-f***

To a solution of compound **12** (1.61 g, 0.01 mol) in 1,4-dioxane (50 mL, 0.01 mol) containing triethylamine (1.0 mL) each of benzaldehyde (1.06 g, 0.01 mol), 4-methoxybenzaldehyde (1.37 g, 0.01 mol) or 4-chlorobenzaldehyde (1.40 , 0.01 mol) and malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) were added. The reaction mixture, in each case, was heated under reflux for 3 h then left to cool and the formed solid product, in each case, was collected by filtration.

6-Amino-3,4-diphenyl-4,7-dihydroisoxazolo[5,4-b]pyridine-5-carbonitrile ***(19a)***. Pale yellow crystals from 1,4-dioxane, yield (2.13 g, 68%), mp 182-184 °C. IR (KBr) ν_{max} cm^{-1}: 3469-3352 (NH, NH_2), 3057 (CH, aromatic), 2220 (CN), 1636 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 4.84 (s, 2H, D_2O exchangeable, NH_2), 6.18 (s, 1H, pyridine H-4), 7.22-7.45 (m, 10H, $2C_6H_5$), 8.72 (s, 1H, D_2O exchangeable NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 90.3 (pyridine H-4), 116.8 (CN), 120.3, 120.7, 121.5, 121.9, 122.3, 123.6, 124.1, 124.8 ($2C_6H_5$), 129.1, 131.8, 132.6, 134.5 (pyridine C-2, C-3, C-5, C-6), 172.6 (C=N). Anal. calcd. for $C_{19}H_{14}N_4O$ (314.34): C, 72.60; H, 4.49; N, 17.82%. Found: C, 72.48; H, 4.62; N, 18.02%. MS: m/z 314 (M^+, 58%).

Ethyl 6-amino-3,4-diphenyl-4,7-dihydroisoxazolo[5,4-b]pyridine-5-carboxylate ***(19b)***. Orange crystals from 1,4-dioxane, yield (2.02 g, 56%), mp 172-174 °C. IR (KBr) ν_{max} cm^{-1}: 3484-3337

(NH, NH_2), 3054 (CH, aromatic), 1688 (CO), 1634 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.15 (t, 3H, *J* =7.28 Hz, CH_3), 4.22 (q, 2H, J = 7.28 Hz, CH_2), 4.86 (s, 2H, D_2O exchangeable, NH_2), 6.26 (s, 1H, pyridine H-4), 7.24-7.48 (m, 10H, $2C_6H_5$), 8.76 (s, 1H, D_2O exchangeable NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.5 ($OCH_2\underline{CH_3}$), 50.4 ($O\underline{CH_2}CH_3$), 90.6 (pyridine H-4), 120.5, 120.9, 121.2, 121.6, 122.5, 123.8, 124.4, 125.3 ($2C_6H_5$), 129.8, 131.6, 133.2, 134.8 (pyridine C-2, C-3, C-5, C-6), 165.2 (CO), 172.5 (C=N). Anal. calcd. for $C_{21}H_{19}N_3O_3$ (361.39): C, 69.79; H, 5.30; N, 11.63%. Found: C, 69.64; H, 5.48; N, 11.74%. MS: m/z 361 (M^+, 75%).

*6-Amino-4-(4-methoxyphenyl)-3-phenyl-4,7-dihydroisoxazolo[5,4-b]pyridine-5-carbonitrile (**19c**)*. Yellow crystals from 1,4-dioxane, yield (1.92 g, 56%), mp 202-204 °C. IR (KBr) ν_{max} cm^{-1}: 3453-3341 (NH, NH_2), 3055 (CH, aromatic), 2220 (CN), 1633 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 3.72 (s, 3H, OCH_3), 4.84 (s, 2H, D_2O exchangeable, NH_2), 6.18 (s, 1H, pyridine H-4), 7.22-7.45 (m, 9H, C_6H_5, C_6H_4), 8.72 (s, 1H, D_2O exchangeable NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 50.8 (OCH_3), 90.3 (pyridine H-4), 116.8 (CN), 120.3, 120.7, 121.5, 121.9, 122.3, 123.6, 124.1, 124.8 (C_6H_5, C_6H_4), 129.1, 131.8, 132.6, 134.5 (pyridine C-2, C-3, C-5, C-6), 172.6 (C=N). Anal. calcd. for $C_{20}H_{16}N_4O_2$ (344.37): C, 69.76; H, 4.68; N, 16.27%. Found: C, 69.52; H, 4.59; N, 16.42%. MS: m/z 344 (M^+, 68%).

*Ethyl 6-amino-4-(4-methoxyphenyl)-3-phenyl-4,7-dihydroisoxazolo[5,4-b]pyridine-5-carboxylate (**19d**)*. Pale brown crystals from 1,4-dioxane, yield (2.61 g, 67%), mp 177-179 °C. IR (KBr) ν_{max} cm^{-1}: 3463-3328 (NH, NH_2), 3055 (CH, aromatic), 1689 (CO), 1632 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.16 (t, 3H, *J* = 6.52 Hz, CH_3), 3.69 (s, 3H, OCH_3), 4.22 (q, 2H, J = 6.52 Hz, CH_2), 4.88 (s, 2H, D_2O exchangeable, NH_2), 6.26 (s, 1H, pyridine H-4), 7.22-7.56 (m, 9H, C_6H_5, C_6H_4), 8.76 (s, 1H, D_2O exchangeable NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.7 ($OCH_2\underline{CH_3}$), 50.6 ($O\underline{CH_2}CH_3$), 50.8 (OCH_3), 90.8 (pyridine H-4), 120.7, 120.9, 121.4, 121.8, 122.9, 123.3, 124.5, 125.6 (C_6H_5, C_6H_4), 129.5, 132.3, 133.7, 134.4 (pyridine C-2, C-3, C-5, C-6), 165.8 (CO), 172.1(C=N). Anal. calcd. for $C_{22}H_{21}N_3O_4$ (391.42): C, 67.51; H, 5.41; N, 10.74%. Found: C, 67.62; H, 5.38; N, 10.93%. MS: m/e 391 (M^+, 80%).

*6-Amino-4-(4-chlorophenyl)-3-phenyl-4,7-dihydroisoxazolo[5,4-b]pyridine-5-carbonitrile (**19e**)*. Yellow crystals from 1,4-dioxane, yield (2.43 g, 70%), mp 210-212 °C. IR (KBr) ν_{max} cm^{-1}: 3482-3331 (NH, NH_2), 3055 (CH, aromatic), 2220 (CN), 1631 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 4.86 (s, 2H, D_2O exchangeable, NH_2), 6.18 (s, 1H, pyridine H-4), 7.22-7.54 (m, 9H, C_6H_5, C_6H_4), 8.76 (s, 1H, D_2O exchangeable NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 90.6 (pyridine H-4), 116.9 (CN), 120.1, 120.4, 121.2, 121.8, 122.0, 123.8, 124.3, 124.9 ($2C_6H_5$), 129.6, 131.4, 132.8, 134.4 (pyridine C-2, C-3, C-5, C-6), 172.3 (C=N). Anal. calcd. for $C_{19}H_{13}ClN_4O$ (348.79): C, 65.43; H, 3.76; N, 16.06%. Found: C, 65.28; H, 3.93; N, 16.25%. MS: m/z 348 (M^+, 69%).

*Ethyl 6-amino-4-(4-chlorophenyl)-3-phenyl-4,7-dihydroisoxazolo[5,4-b]-pyridine-5-carboxylate (**19f**)*. Yellowish white crystals from 1,4-dioxane, yield (2.60 g, 66%), mp 158-160 °C. IR (KBr) ν_{max} cm^{-1}: 3492-3341 (NH, NH_2), 3055 (CH, aromatic), 1687 (CO), 1631 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.17 (t, 3H, *J* = 6.80 Hz, CH_3), 4.22 (q, 2H, J = 6.80 Hz, CH_2), 4.88 (s, 2H, D_2O exchangeable, NH_2), 6.24 (s, 1H, pyridine H-4), 7.21-7.55 (m, 9H, C_6H_5, C_6H_4), 8.73 (s, 1H, D_2O exchangeable NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.6 ($OCH_2\underline{CH_3}$), 50.2 ($O\underline{CH_2}CH_3$), 90.9 (pyridine H-4), 120.1, 120.4, 121.5, 121.9, 122.1, 123.7, 124.6, 125.8 ($2C_6H_5$), 129.3, 131.2, 133.1, 134.6 (pyridine C-2, C-3, C-5, C-6), 165.4 (CO), 172.3 (C=N). Anal. calcd. for $C_{21}H_{18}ClN_3O_3$ (395.84): C, 63.72; H, 4.58; N, 10.62%. Found: C, 63.58; H, 4.70; N, 10.48%. MS: m/z 395 (M^+, 80%).

General procedure for the synthesis of the chromeno[4,3-d]isoxazolo[5,4-b]pyridine derivatives ***20a,b***

To a solution of compound **12** (1.61 g, 0.01 mol) in 1,4-dioxane (50 mL, 0.01 mol) containing triethylamine (1.0 mL) each of salicylaldehyde (1.22 g, 0.01 mol), and malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) were added. The reaction mixture, in each case, was heated under reflux for 5 h then left to cool and the formed solid product, in each case, was collected by filtration.

*6-Imino-1-phenyl-6,11b-dihydro-4H-chromeno[4,3-d]isoxazolo[5,4-b]pyridine-5-amine (**20a**)*. Pale brown crystals from 1,4-dioxane, yield (2.14 g, 65%), mp 177-119 °C. IR (KBr) ν_{max} cm^{-1}: 3474-3340 (NH, NH_2), 3055 (CH, aromatic), 1660 (exocyclic C=N)), 1634 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 4.72(s, 2H, D_2O exchangeable, NH_2), 6.21 (s, 1H, pyridine H-4), 7.25-7.52 (m, 9H, C_6H_5, C_6H_4), 8.76, 9.01 (2s, 2H, D_2O exchangeable, 2NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 90.8 (pyridine H-4), 116.7 (CN), 120.3, 120.8, 121.0, 121.4, 122.3, 123.6, 124.5, 125.2 (C_6H_5, C_6H_4), 129.8, 131.5, 132.4, 134.8 (pyridine C-2, C-3, C-5, C-6), 172.1, 174.5 (2C=N). Anal. calcd. for $C_{19}H_{14}N_4O_2$ (330.34): C, 69.08; H, 4.27; N, 16.96%. Found: C, 68.94; H, 4.38; N, 16.76%. MS: m/z 330 (M^+, 85%).

*5-Amino-1-phenyl-4H-chromeno[4,3-d]isoxazolo[5,4-b]pyridin-6(11bH)-one (**20b**)*. Yellow crystals from 1,4-dioxane, yield (1.78 g, 54%), mp 205-207 °C. IR (KBr) ν_{max} cm^{-1}: 3483-3329 (NH, NH_2), 3055 (CH, aromatic), 1668 (CO)), 1631 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 4.78 (s, 2H, D_2O exchangeable, NH_2), 6.25 (s, 1H, pyridine H-4), 7.23-7.50 (m, 9H, C_6H_5, C_6H_4), 8.78 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 90.5 (pyridine H-4), 116.9 (CN), 120.1, 121.3, 121.6, 121.8, 122.6, 123.8, 124.6, 125.8 (C_6H_5, C_6H_4), 130.4, 131.6, 133.7, 134.6 (pyridine C-2, C-3, C-5, C-6), 165.8 (CO), 172.4, (C=N). Anal. calcd. for $C_{19}H_{13}N_3O_3$ (331.32): C, 68.88; H, 3.95; N, 12.68%. Found: C, 68.71; H, 4.16; N, 12.80%. MS: m/z 331 (M^+, 70%).

CONCLUSION

The target molecules were synthesized using 3-oxo-N,3-diphenylpropamide and 3-phenylisoxazol-5(4H)-one. In addition, the newly synthesized compounds were screened for their cytotoxicity against hepatocellular carcinoma HepG2 and cervical carcinoma HeLa cell lines. The results obtained in this work encourage further work in the future since many compounds were considered as promising anticancer agents. Compounds **3b**, **5b**, **7b**, **7d**, **9c**, **9d**, **10b, 15e**, **15f**, **16b**, **18b**, **18e**, **18f**, **19e** and **19f** were the most cytotoxic compounds against the tested cell lines.

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