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ARTICLE

Uses of ethyl benzoylacetate for the synthesis of thiophene, thiazole, pyridine, and pyran derivatives with antitumor activities

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Abstract

The reaction of ethyl benzoylacetate with malononitrile in an oil bath at 120°C gave the condensation product 3. The latter compound underwent a series of heterocyclization to give thiophene, thiazole, pyridine, and pyran derivatives. The structures of the synthesized products were established on the basis of analytical and spectral data. The antitumor evaluation of the newly synthesized products against the six cancer cell lines namely human gastric cancer (NUGC and HR), human colon cancer (DLD1), human liver cancer (HA22T and HEPG2), human breast cancer (MCF), nasopharyngeal carcinoma (HONE1), and normal fibroblast cells (WI38) indicated that many compounds expressed high inhibition against the six cancer cell lines. Compounds 3, 8a, 8c, 14b, 16b, 16c, 16d, 19a, 19b, 20a, 22a, 27b, and 28a were the most cytotoxic compounds among the tested compounds.

1 | INTRODUCTION

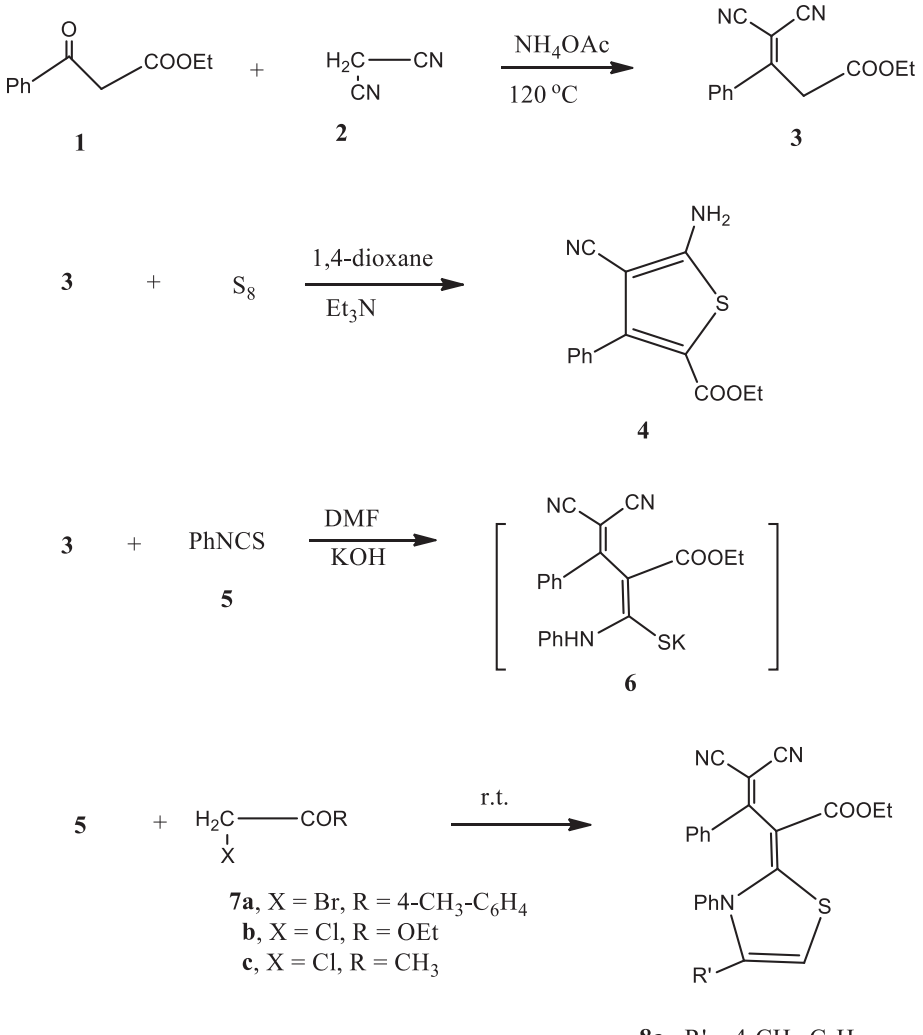
The synthesis of heterocyclic compounds attracted the attention of many researchers all over the world due to their high potentialities of biological and pharmaceutical activities. In the market, there are many drugs such as thiazole, thiophene, and pyridine derivatives. For such excessive benefits, these compounds were used in many efficient synthetic transformations and are used as intermediates in many chemical reactions.[1–10] It has been reported that many thiazole, thiophene, and pyrazole derivatives showed potent analgesic,[11,12] anticonvulsant, anti-inflammatory and antibacterial,[13,14] antipyretics,[15] antitumor,[16,17] antiparasitic,[18] antimicrobial,[19] antihistaminic,[20] anti-anexiety test in mice,[21] antiarrhythmic,[22] and serotonin antagonist.[23] In the present work, we studied the reaction of ethyl benzoylacetate with some cyanomethylene reagents followed by reaction with elemental sulfur. Moreover, studying of different heterocyclization for the reaction products together with their anti-tumor activities of towards cancer cell lines was recorded.

2 | RESULTS AND DISCUSSION

Our research group was involved in recent years through a program, which involves synthesis of new heterocyclic compounds that were evaluated as anticancer agents.[24–26] As continuation of this program, we were concentrated in this work through the synthesis of novel compounds followed by their cytotoxic evaluations toward different cancer cell lines. To achieve this goal, our strategy was to synthesize a series of thiazole, thiophene, pyridine, and pyridazine derivatives using ethyl benzoylacetate that reacted with active methylene reagents followed by heterocyclization of the product. Thus, the reaction of ethyl benzoylacetate (1) with malononitrile (2) in the presence of ammonium acetate in an oil bath at 120°C gave the Knoevenagel condensation product 3. The structure of compound 3 was elucidated on the basis of its analytical and spectral data. The reaction of compound 3 with elemental sulfur yielded the polyfunctionally substituted thiophene derivative 4.

Recently, our research group was involved through a series of reactions involving the reaction of active methylene reagents with phenylisothiocyanate in basic dimethylformamide to produce the corresponding intermediate potassium salts. Heterocyclization of the intermediate potassium salts took place through their individual reaction with any of the α-halocarbonyl derivatives. The reaction leading to the formation of either thiophene or thiazole derivatives depended on the nature of the active methylene compound that is being used.[27–29] The active methylene moiety present in compound 3 showed interesting reactivity toward the formation of potassium sulfide salts. Thus, compound 3 was reacted with phenylisothiocyanate (5) in DMF/KOH solution to give the intermediate potassium salt 6. The latter intermediate was reacted with any of the α-halocarbonyl compounds namely 2-bromo-1-(p-tolyl) ethanone (7a), ethyl chloroacetate (7b), or chloroacetone (7c) to give the thiazole derivatives 8a-c, respectively (Scheme 1). Structures of compounds 8a-c were confirmed on the basis of their respective analytical and spectral data. Thus, the ^{1}H NMR spectrum of compound 8a showed besides the expected signals, a singlet at δ 2.69 ppm equivalent to the CH_3 group, a singlet at δ 6.03 ppm due to thiazole H-5, and a multiplet at δ 7.23-7.42 ppm corresponding to the two C_6H_5 and one C_6H_4 groups. In addition, the ^{13}C NMR spectrum showed the presence of two signals at 116.3 and 117.5 equivalent to the two CN groups, signals at 120.3, 122.5, 123.1, 123.9, 124.2, 124.8, 125.0, 126.3, 127.5, 128.0, 128.5, 129.0, 139.2, 140.1 equivalent to the two C_6H_5, one C_6H_4 group, and thiazoles C-3, C-4, and a singlet at 164.8 due to the CO group.

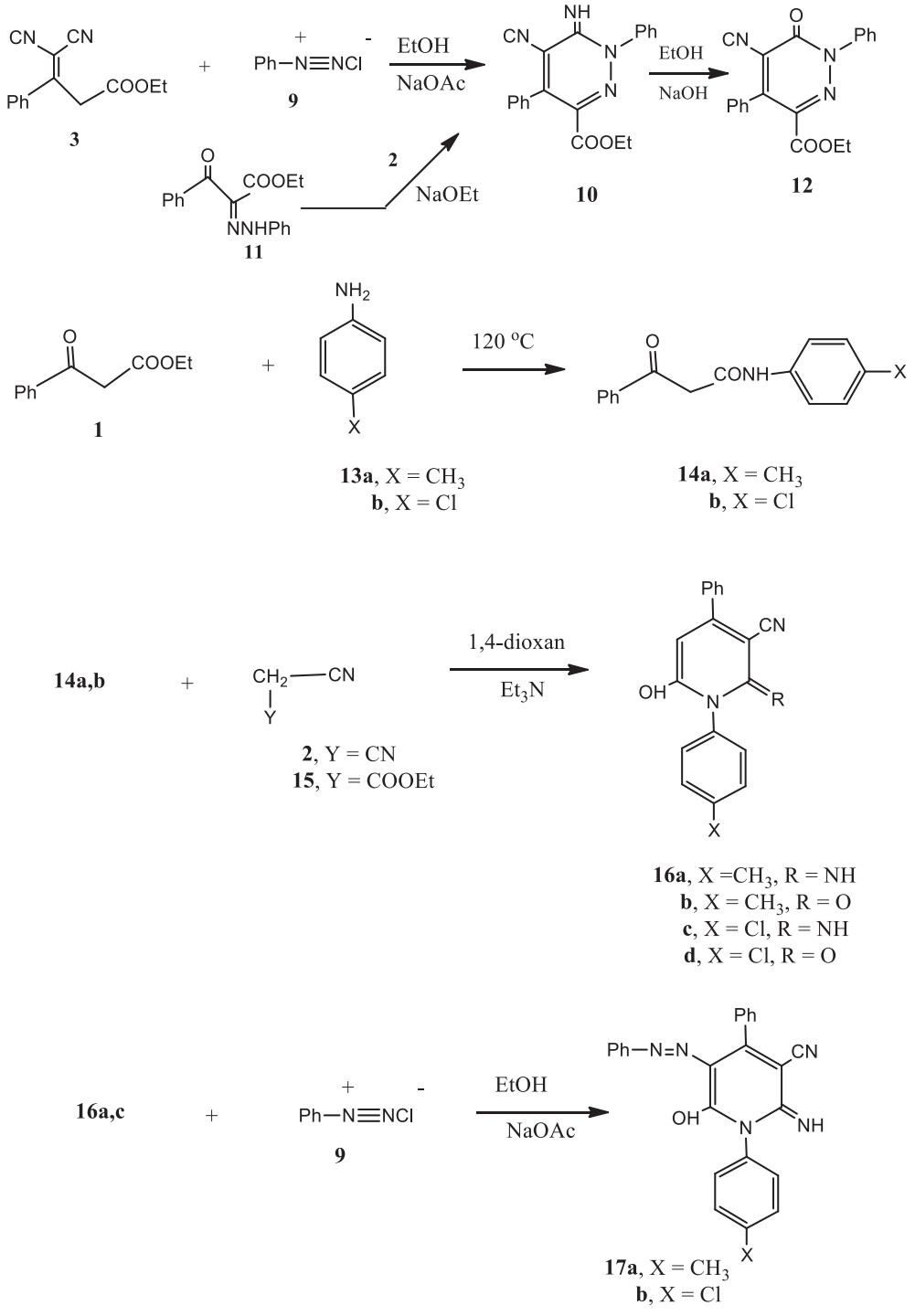
On the other hand, the reaction of compound 3 with benzenediazonium chloride (9) in ethanolic solution containing ammonium acetate gave the pyridazine derivative 10. The structure of the latter product was based on its analytical and spectral data (see experimental section)



SCHEME 1 Synthesis of compounds 3, 4 and 8a-c

besides its synthesis using another reaction route. Thus, the reaction of the ethyl 3-oxo-3-phenyl-2-(2-phenylhydrazono)propanoate (11) with malononitrile (2) in sodium ethoxide solution gave the same reaction product 10 (m.p., mixed m.p, and fingerprint IR spectrum). Moreover, compound 10, which resulted by the two reaction pathways, underwent C=NH moiety hydrolysis upon its heating in ethanol containing sodium hydroxide pellets to give the 3-oxopyridazine derivative 12 through ammonia elimination.

The anilide derivatives 14a,b were formed through the reaction of ethyl benzoyl acetate (1) with either 4-methylaniline (13a) or 4-chloroaniline (13b) according to the reported work.[30] The reaction of either compound 14a or 14b with either of malononitrile (2) or ethyl cyanoacetate (15) gave the pyridine derivatives 16a-d, respectively. The reaction took place through the first condensation of the active methylene with either 14a or 14b followed by cyclization. The reaction of either compound 16a or 16c with benzenediazonium (9) gave the polyfunctionally substituted

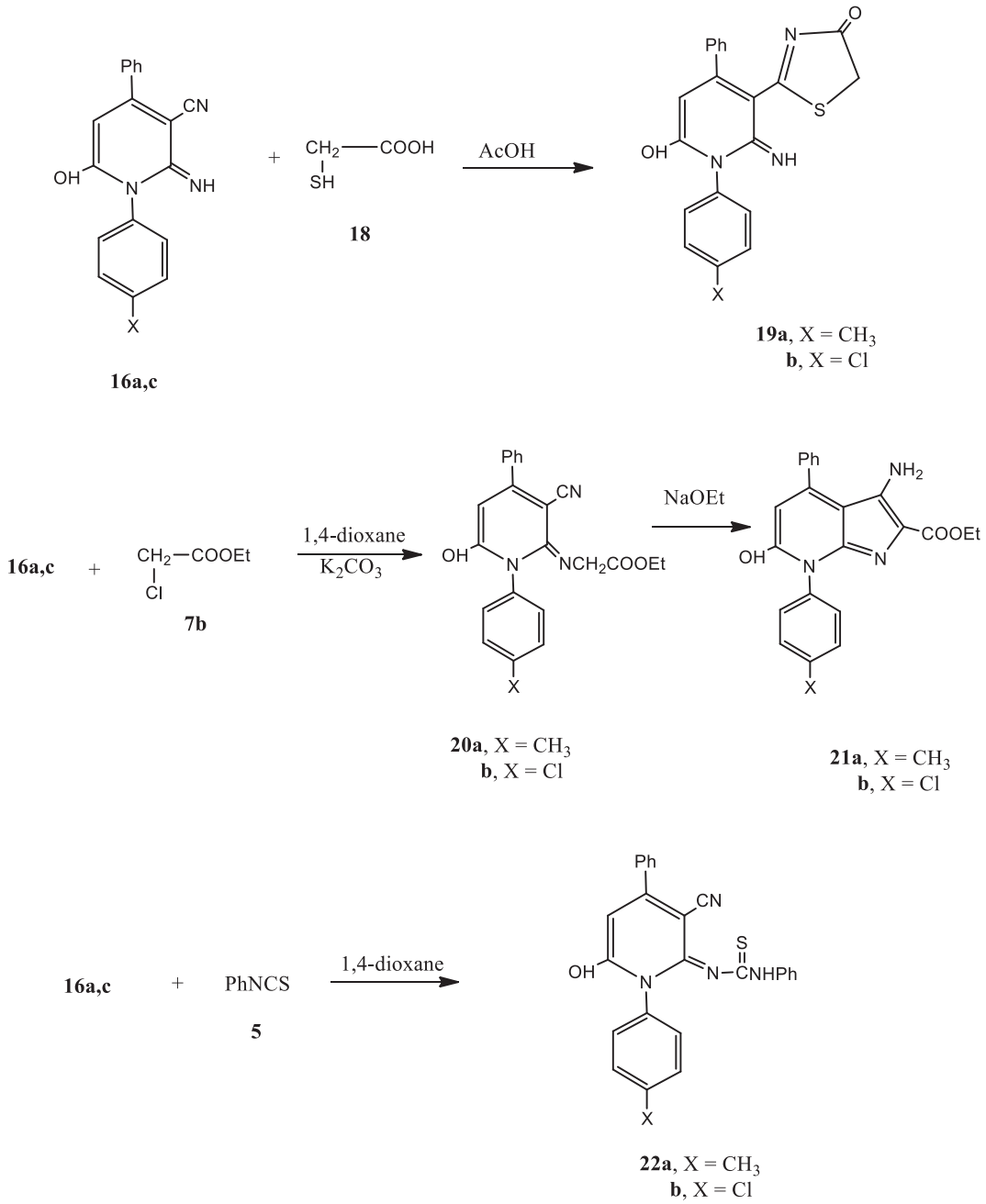


SCHEME 2 Synthesis of compounds 10, 12, 14a,b; 16a-d and 17a,b

pyridine derivatives 17a and 17b, respectively (Scheme 2). The analytical and spectral data of compounds 17a and 17b were in agreement with their respective structures.

On the other hand, the reaction of either compound 16a or 16c with thioglycolic acid (18) gave the thiazole derivatives 19a and 19b respectively. The analytical and spectral data of the latter products were consistent with their respective structures.

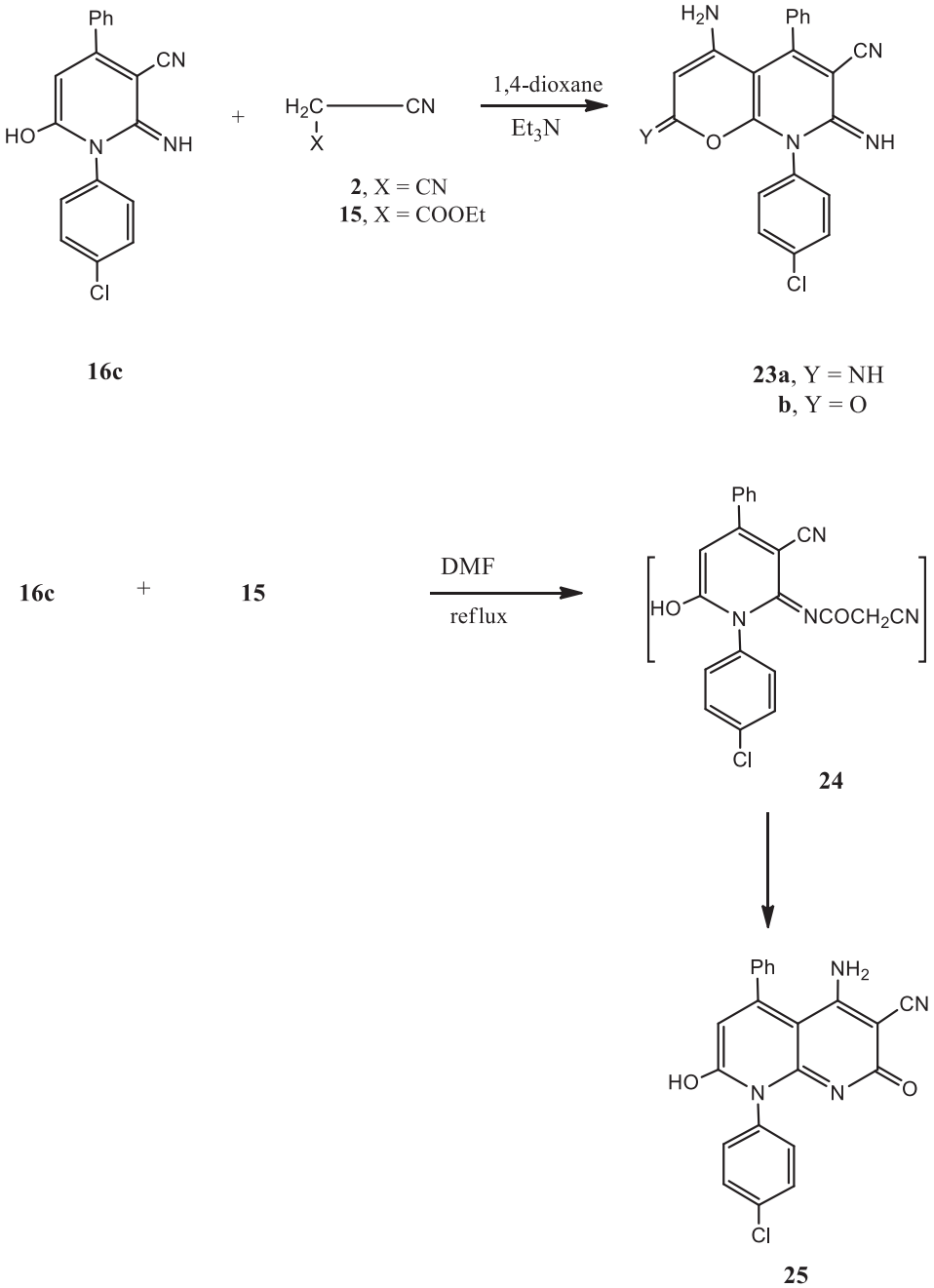
The 2-imino group present in each of the compounds 16a and 16c showed interesting reactivity toward alkylation and addition reactions. Thus, the reaction of either compound 16a or 16c with ethyl chloroacetate (7b) gave the pyridin-2(1*H*)-ylidene) amino)acetate derivatives 20a and 20b, respectively. Structures of the latter products were based on their respective analytical and spectral data (see experimental section). The existence of the $=NCH_2$-COOEt moiety in compounds 20a and 20b can be confirmed based on their further cyclization in sodium ethoxide solution to give the pyrrolo[2,3-*b*]pyridine derivatives 21a and 21b, respectively. On the other hand, the reaction of either compound 16a or 16c with phenylisothiocyanate (5) in 1,4-dioxane solution gave pyridin-2(1*H*)-ylidene)-3-phenylthiourea derivatives 22a and 22b, respectively (Scheme 3).



SCHEME 3 Synthesis of compounds 19a,b; 20a,b; 21a,b and 22a,b

Compound 16 reacted with either malononitrile (2) or ethyl cyanoacetate (15) to give the 7,8-dihydro-2*H*-pyrano [2,3-*b*]pyridine-6-carbonitrile derivatives 23a and 23b, respectively. The 2-imino moiety present in compound 16c reacted with ethyl cyanoacetate (15) in dimethylformamide to give 1,8-naphthyridine-3-carbonitrile derivative 25 (Scheme 4). The reaction took place through the intermediate formation of 24 followed by cyclization.

Recently, a major concern about the multicomponent reactions (MCRs) has been considered as through such types of reactions, three or more components are combined together in one reaction vessel to produce final products with the privilege of a short synthetic time and effort[31]; as a result, no separation of reaction intermediates occurs.[32]. In addition, these reactions were characterized by high atom economy and high selectivity products.[33] Due to such great benefits of MCRs, the synthesis of many heterocyclic compounds was carried out applying such MCRs.[34] On the other hand, many pharmaceutical drugs contained 4-*H* pyran moieties[35–37]; this encouraged us to synthesize 4-*H* pyran derivatives through the MCRs of compound 14a. Therefore, the reaction of compound 14a with either of the aromatic aldehydes 26a, 26b, or 26c and malononitrile (2) in 1,4-dioxane containing triethylamine gave the pyran derivatives 27a-c, respectively. Moreover,



SCHEME 4 Synthesis of compounds 23a,b and 25

the reaction of compound 14a with either of the aromatic aldehydes 26a, 26b, or 26c and malononitrile (2) in 1,4-dioxane containing ammonium acetate gave the pyridine derivatives 28a-c, respectively (Scheme 5).

3 | BIOLOGICAL ASSAY

3.1 | In vitro cytotoxic assay

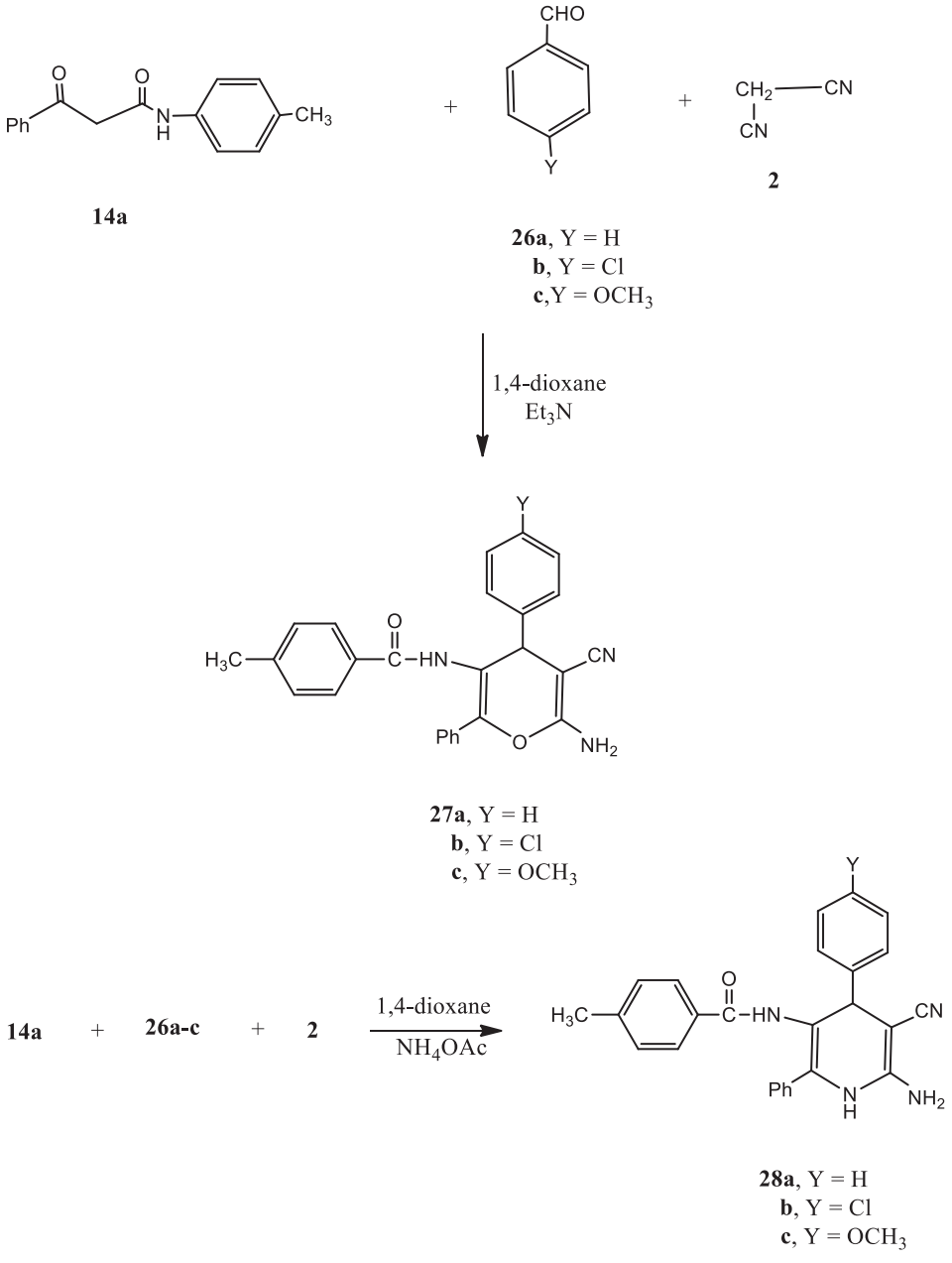
3.1.1 | Chemicals

Through this work, all chemicals that were used through screening process were purchased from international companies. Fetal bovine serum (FBS) and L-glutamine were purchased from Gibco Invitrogen Co. (Scotland, UK). RPMI-1640 medium was purchased from Cambrex (New Jersey). Dimethyl sulfoxide (DMSO), doxorubicin, penicillin, streptomycin, and sulforhodamine B (SRB) were purchased from Sigma Chemical Co. (Saint Louis).

3.1.2 | Cell cultures

The cancer cell lines NUGC, DLDI, HA22T, HEPG2, HONE1, and MCF were provided from the National Cancer Institute (NCI, Cairo, Egypt).

The newly synthesized compounds throughout this work were evaluated according to standard methods for



SCHEME 5 Synthesis of compounds 27a-c and 18a-c

their in vitro cytotoxicity against the six human cancer cell lines, which are derived from human gastric cancer (NUGC), human colon cancer (DLD1), human liver cancer (HA22T and HEPG2), human breast cancer (MCF), nasopharyngeal carcinoma (HONE1), and normal fibroblast cells (WI38). All of the IC_{50} values were listed in Table 1. Some heterocyclic compounds were observed with significant cytotoxicity against most of the cancer cell lines tested (IC_{50} = 10-1000 nM). The normal cell line fibroblast cells (WI38) were affected to a much lesser extent (IC50 > 10 000 nM). The reference compound used during measurements is CHS-828, which is a pyridyl cyanoguanidine anti-tumor agent.

3.1.3 | Structure-activity relationship

It is clear from Table 1 that compounds 3, 8a, 8c, 14b, 16b, 16c, 16d, 19a, 19b, 20a, 22a, 27b, and 28a were most cytotoxic among the tested compounds. Compound 3 showed high cytotoxicity against DLDI, HA22T, HEPG2, HONE1, and MCF cell lines. Its activity is attributed to the presence of the two CN groups together with the COOEt group. Considering the thiophene derivative 4, it showed low cytotoxicities toward NUGC, HA22T, and HEPG2 cell lines, whereas it showed moderate activities toward DLDI, HONE1, and MCF cell lines. For the thiazole derivatives 8a-c, it is obvious that compounds 8a

TABLE 1 Cytotoxicity of the selected synthesized compounds against a variety of cancer cell lines [$IC_{50}{}^{b}$ (nM)]

	Compound				Cytotoxic assay		
	NUGC	DLDI	HA22T	HEPG2	HONE1	MCF	WI38
3	1327	328	529	1160	128	427	NA
4	2160	1142	3277	2761	1265	1290	NA
8a	130	315	402	168	624	143	NA
8b	2138	1760	1410	1272	1265	265	NA
8c	452	82	116	320	160	172	NA
10	2401	1468	2153	2041	2183	2159	NA
14a	3277	2159	1273	3217	2180	2913	NA
14b	327	423	431	128	219	1265	NA
16a	1756	1088	1761	2111	2870	2258	NA
16b	284	3809	2341	1209	2196	1273	NA
16c	1463	48	213	76	683	1022	NA
16d	38	1036	272	120	417	529	NA
17a	1760	146	1630	1833	1872	1336	NA
17b	2160	2208	1272	2129	2250	1266	NA
19a	132	241	810	266	1830	320	NA
19b	742	639	130	283	1196	1620	399
20a	1020	158	542	320	168	1046	865
20b	2255	2269	1194	1672	1438	1562	NA
22a	382	213	94	62	1402	339	NA
22b	1086	2779	1429	622	1148	1241	NA
25	2120	2840	1621	2837	1643	2251	NA
27a	1820	1368	1225	329	1180	2373	NA
27b	89	96	253	238	388	220	NA
27c	2657	1878	2282	1362	1829	2422	NA
28a	265	563	1530	2677	1523	672	NA
28b	1038	2318	1172	1893	1539	1730	NA
28c	1485	2236	2793	2260	1209	2446	NA
CHS828	25	2315	2067	1245	15	18	NA

Abbreviations: DLDI, colon cancer; HA22T, liver cancer; HEPG2, liver cancer; HONEI, nasopharyngeal carcinoma; HR, gastric cancer; MCF, breast cancer; NUGC, gastric cancer; WI38, normal fibroblast cells.

(R′ = 4-CH_3-C_6H_4) and 8c (R′ = CH_3) were more cytotoxic than 8b (R′ = OH). The pyridazine derivative 10 showed low cytotoxicity toward the five cancer cell lines NUGC, HA22T, HEPG2, HONE1, and MCF while it showed moderate activity toward DLDI cell line with IC_{50} 1468 nM. For the anilide derivatives 14a,b, it is clear that compound 14b (X = Cl) revealed high cytotoxicities with IC_{50}'s 327, 423, 431, 128, and 219 nM toward NUGC, DLDI, HA22T, HEPG2, and HONE1 cell lines and these are higher than those of compound 13a (X = CH_3) although the latter exhibited moderate inhibition toward HA22T cell line with IC_{50} 1273 nM. On the other hand, for compounds 16a-d, it is clear that compounds 16b (X = CH_3, Y = O), 16c (X = Cl, Y = NH), and 16d (X = Cl, Y = O) showed high cytotoxicities. For the pyridine derivatives 17a,b, compound 17a exhibited moderate inhibitions toward the six cancer cell lines while compound 17b showed low inhibitions. Considering the 1,2-dihydropyridin-3-yl)thiazol derivatives 19a,b where compound 19a (X = CH_3) high inhibitions toward the five cancer cell lines NUGC, DLDI, HA22T, HEPG2 and MCF cell lines with IC_{50}'s 132, 241, 810, 266 and 320 nM while it showed moderate inhibition toward HONE1 cell line. On the other hand, compound 19b (X = Cl) showed high cytotoxicities toward NUGC, DLDI, HA22T, and HEPG2. Considering pyridine derivatives 20a,b and 22a,b, it is clear from Table 1 that compounds 20a (X = CH_3) and 22a (X = CH_3) were more cytotoxic than compounds 20b (X = Cl) and 22b (X = Cl). Compound 25 showed low inhibitions toward the six cancer cell line. For the pyran derivatives 27a-c, it is obvious that compound 27b (X = OCH_3) is the most cytotoxic compound among the three compounds. Although, compound 27a (X = H) showed high inhibition toward HEPG2 cell line with IC_{50} 329 nM. However, for the pyridine derivatives 28a-c, it is obvious that compound 28a (X = H) exhibited high inhibitions toward the three cancer cell lines NUGC, DLDI, MCF with IC_{50}'s 265, 563, and 672 nM while compound 28b (X = Cl) showed moderate inhibitions and compound 28c (X = OCH_3) exhibited low inhibitions.

4 | CONCLUSIONS

Through this work, we have synthesized new series of pyridine, pyran, and thiophene derivatives. The obtained compounds were screened against NUGC, DLDI, HA22T, HEPG2, HONE1, and MCF and the normal cell line WI38. The results showed that compounds 3, 8a, 8c, 14b, 16b, 16c, 16d, 19a, b, 20a, 22a, 27b, and 28 were the most active compounds toward the six cancer cell lines and no activity toward the normal cell line. In most cases, the presence of electronegative Cl or OCH_3 groups enhances the cytotoxicity of the tested compound.

5 | EXPERIMENTAL

5.1 | General

The obtained compounds showed their melting points using electrothermal digital melting point apparatus and are uncorrected. IR spectra (KBr disks) were measured on an FTIR plus 460 or Pye Unicam SP-1000 spectrophotometer (Pye Unicam, Cambridge, UK). ^{1}H NMR spectra were obtained using Varian Gemini-300 (300 MHz, Varian, UK) using DMSO-d_6 as a solvent and tetraethylsilane (TMS) as internal standard chemical shifts are expressed as δ ppm. The mass spectra were measured with Hewlett Packard 5988 A GC/MS system (Hewlett Packard, Agilent) instrument. Analytical data were obtained from Vario EL III Elemental CHNS analyzer. Compounds 12a and 12b were synthesized according to the reported literature.[27]

5.2 | Ethyl 4,4-dicyano-3-phenylbut-3-enoate (3)

To a dry solid of compound 1 (1.92 g, 0.01 mol), each of malononitrile (0.66 g) and ammonium acetate (0.50 g) were added. The reaction mixture was heated in an oil bath at 120°C for 15 minutes and then was left to cool. The formed solid was triturated with diethyl ether, and the crystallized product was collected by filtration.

Orange crystals from 1,4-dioxane yield (1.68 g, 70%), mp 120-122°C, IR (KBr) νmax 2984 (CH_2), 2225, 2220 (2CN), 1689 (C=O), 1625 (C=C); ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.28 (t, 3H, *J* = 7.28 Hz, CH_3), 4.22 (q, 2H, *J* = 7.28 Hz, CH_2), 7.29-7.37 (m, 5H, C_6H_5); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.3 ($OCH_2\underline{CH_3}$), 38.2 (CH_2), 50.6 ($O\underline{CH_2}CH_3$), 86.7, 103.5 (C=C), 116.3, 117.0 (2CN), 120.2, 122.6, 124.8, 128.0 (C_6H_5), 163.8 (CO). EIMS: *m/z* 240 $[M]^+$ (38%). Analysis calculated for $C_{14}H_{12}N_2O_2$ (240.26): C, 69.99; H, 5.03; N, 11.66%. Found: C, 70.21; H, 4.83; N, 11.80%.

5.3 | Ethyl 5-amino-4-cyano-3-phenylthiophene-2-carboxylate (4)

Elemental sulfur (0.32 g, 0.01 mol) was added to a solution of compound 3 (2.40 g, 0.01 mol) in 1,4-dioxane (30 mL) containing triethylamine (0.50 mL). The reaction mixture was heated under reflux for 1 hour and then

poured onto ice/water containing few drops of hydrochloric acid, and the formed solid product was collected by filtration.

Yellow crystals from acetic acid yield (1.57 g, 58%), mp 160-162°C, IR (KBr) νmax 3452, 3339 (NH_2), 2980 (CH_2), 2221 (CN), 1687 (C=O), 1623 (C=C); ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.25 (t, 3H, *J* = 6.59 Hz, CH_3), 4.24 (q, 2H, *J* = 6.59 Hz, CH_2), 4.79 (s, 2H, D_2O exchangeable, NH_2), 7.28-7.39 (m, 5H, C_6H_5); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.3 ($OCH_2\underline{CH_3}$), 50.3 ($O\underline{CH_2}CH_3$), 116.8 (CN), 120.8, 123.2, 126.9, 129.0 (C_6H_5), 164.5 (CO). EIMS: *m/z* 272 $[M]^+$ (42%). Analysis calculated for $C_{14}H_{12}N_2O_2S$ (272.32): C, 61.75; H, 4.44; N, 10.29; S, 11.77%. Found: C, 61.83; H, 4.53; N, 11.03; S, 11.53%.

5.4 | General procedure for the synthesis of the thiazole derivatives 8a-c

Phenylisothiocyanate (1.30 g, 0.01 mol) was added to a solution of compound 1 (1.92 g, 0.01 mol) in dimethylformamide (40 mL) containing potassium hydroxide (0.40 mL, 0.01 mol). The reaction mixture was kept at room temperature with continuous stirring for 24 hours. On the next day, either of the α-halocarbonyl compounds 7a (215 g, 0.01 mol), 7b (1.22 g, 0.01 mol), or 7c (0.92 g, 0.01 mol) was added. The whole reaction mixture was kept at room temperature for another 24 hours with continuous stirring. The solid product, formed in each case upon pouring onto ice/water mixture containing few drops of hydrochloric acid, was collected by filtration.

5.5 | Ethyl 4,4-dicyano-3-phenyl-2-(3-phenyl-4-(p-tolyl)thiazol-2(3*H*)-ylidene)but-3-enoate (8a)

Yellow crystals from 1,4-dioxane yield (3.22 g, 66%), mp 140-142°C, IR (KBr) νmax 2988, 2875 (CH_3, CH_2), 2223, 2220 (2CN), 1689 (C=O), 1626 (C=C); ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.14 (t, 3H, *J* = 7.17 Hz, CH_3), 2.69 (s, 3H, CH_3), 4.21 (q, 2H, *J* = 7.17 Hz, CH_2), 6.03 (s, 1H, thiazole H-5), 7.23-7.42 (m, 14H, $2C_6H_5$, C_6H_4); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.4 ($OCH_2\underline{CH_3}$), 24.3 (CH_3), 50.2 ($O\underline{CH_2}CH_3$), 90.3, 105.6, 108.1, 110.1 (2 C=C), 116.3, 117.5 (2CN), 120.3, 122.5, 123.1, 123.9, 124.2, 124.8, 125.0, 126.3, 127.5, 128.0, 128.5, 129.0, 139.2, 140.1 ($2C_6H_5$, C_6H_4, thiazole C-3, C-4), 164.8 (CO). EIMS: *m/z* 489 $[M]^+$ (32%). Analysis calculated for $C_{30}H_{23}N_3O_2S$ (489.59): C, 73.60; H, 4.74; N, 8.58; S, 6.55%. Found: C, 73.52; H, 4.81; N, 8.72; S, 6.73%.

5.6 | Ethyl 4,4-dicyano-2-(4-hydroxy-3-phenylthiazol-2(3*H*)-ylidene)-3-phenylbut-3-enoate (8b)

Pale yellow crystals from ethanol yield (3.23 g, 78%), mp 109-111°C, IR (KBr) νmax 3525-3323 (NH), 2989, 2876 (CH_3, CH_2), 2222, 2220 (2CN), 1688 (C=O), 1623 (C=C); ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.16 (t, 3H, *J* = 6.30 Hz, CH_3), 4.23 (q, 2H, J = 6.30 Hz, CH_2), 6.06 (s, 1H, thiazole H-5), 7.25-7.46 (m, 10H, $2C_6H_5$), 10.28 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.8 ($OCH_2\underline{CH_3}$), 50.3 ($O\underline{CH_2}CH_3$), 90.1, 105.3, 108.6, 109.4 (2 C=C), 116.8, 117.2 (2CN), 120.1, 122.3, 122.9, 123.8, 124.2, 124.8, 126.2, 127.3, 138.5, 140.3 ($2C_6H_5$, thiazole C-3, C-4), 164.4 (CO). EIMS: *m/z* 415 $[M]^+$ (38%). Analysis calculated for $C_{23}H_{17}N_3O_3S$ (415.46): C, 66.49; H, 4.12; N, 10.11; S, 7.72%. Found: C, 66.53; H, 4.29; N, 9.84; S, 7.58%.

5.7 | Ethyl 4,4-dicyano-2-(4-methyl-3-phenylthiazol-2(3*H*)-ylidene)-3-phenylbut-3-enoate (8c)

Yellow crystals from dioxane yield (2.97 g, 72%), mp 130-132°C, IR (KBr) νmax 2986, 2872 (CH_3, CH_2), 2224, 2220 (2CN), 1689 (C=O), 1623 (C=C); ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.14 (t, 3H, *J* = 7.42 Hz, CH_3), 2.67 (s, 3H, CH_3), 4.21 (q, 2H, *J* = 7.42 Hz, CH_2), 6.06 (s, 1H, thiazole H-5), 7.25-7.46 (m, 10H, $2C_6H_5$); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.2 ($OCH_2\underline{CH_3}$), 50.6 ($O\underline{CH_2}CH_3$), 90.6, 105.2, 108.3, 110.6 (2 C=C), 116.1, 117.8 (2CN), 120.1, 122.6, 123.8, 124.0, 124.6, 125.8, 125.9, 126.2, 126.9, 127.1, 128.2, 130.3, 138.6, 140.6 ($2C_6H_5$, C_6H_4, thiazole C-3, C-4), 164.5 (CO). EIMS: *m/z* 413 $[M]^+$ (28%). Analysis calculated for $C_{24}H_{19}N_3O_2S$ (413.49): C, 69.71; H, 4.63; N, 10.16; S, 7.75%. Found: C, 69.92; H, 4.72; N, 10.36; S, 7.83%.

5.8 | 3-Imino-2,5-diphenyl-2,3-dihydropyridazine-4-carbonitrile (10)

Method (A). Benzenediazonium chloride (0.01 mol) (prepared by the addition of sodium nitrite (0.70 g, 0.01 mol) dissolved in water (5 mL) to a cold solution of aniline (0.93 g, 0.01 mol) dissolved in concentrated hydrochloric acid [18 mol, 8 mL] was added with continuous stirring to a solution of compound 1 (1.92 g, 0.01 mol) in ethanol (50 mL) containing ammonium acetate (4.00 g). The reaction mixture was stirred at room temperature for 2 hours and the formed solid product formed was collected by filtration.

Method (B). To a suspension of compound 11 (2.96 g, 0.01 mol) in sodium ethoxide (prepared by the addition of metallic sodium (0.36 g, 0.02 mol) to absolute ethanol (40 mL) till all sodium is being dissolved), malononitrile (0.66 g, 0.01 mol) was added. The reaction mixture, in each case, was heated in a boiling water bath for 3 hours and then poured onto ice/water mixture containing a few drops of hydrochloric acid and the formed solid product was collected by filtration.

Orange crystals from 1,4-dioxane yield (1.90 g, 70%), mp 100-102°C, IR (KBr) νmax 3455-3328 (NH), 2986 (CH_2), 2221 (CN), 1687 (C=O), 1623 (C=C); ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.13 (t, 3H, J = 6.84 Hz, CH_3), 4.23 (q, 2H, J = 6.84 Hz, CH_2), 7.26-7.39 (m, 10H, $2C_6H_5$), 8.25 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.9 (ester CH_3), 52.1 (ester CH_2), 116.8 (CN), 120.2, 122.6, 124.8, 125.8, 126.9, 127.1, 128.2, 130.3, 132.6, 134.8 ($2C_6H_5$, pyridazine C-4, C-5), 168.5, 170.2 (2C=N). EIMS: *m/z* 344 $[M]^+$ (39%). Analysis calculated for $C_{20}H_{16}N_4O_2$ (344.37): C, 69.76; H, 4.68; N, 16.27%. Found: C, 70.19; H, 4.63; N, 16.45%.

5.9 | Ethyl 5-cyano-6-oxo-1,4-diphenyl-1,6-dihydropyridazine-3-carboxylate (12)

To a solution of compound 11 (3.29 g, 0.01 mol) in ethanol (50 mL), sodium hydroxide pellets (0.80 g, 0.02 mol) were added. The reaction mixture was heated under reflux for 4 hours and then poured onto ice/water containing hydrochloric acid (18 mol, 3 mL) till pH 6 and the formed solid product was collected by filtration.

Orange crystals from 1,4-dioxane yield (1.90 g, 70%), mp 100-102°C, IR (KBr) νmax 3482-3346 (NH), 2985 (CH_2), 2223 (CN), 1689, 1687 (2C=O), 1626 (C=C); ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.12 (t, 3H, *J* = 7.22 Hz, CH_3), 4.23 (q, 2H, *J* = 7.22 Hz, CH_2), 7.28-7.42 (m, 10H, $2C_6H_5$); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.4 (ester CH_3), 52.3 (ester CH_2), 116.9 (CN), 120.4, 121.3, 123.5, 124.6, 125.2, 126.7, 127.6, 130.1, 132.8, 136.3 ($2C_6H_5$, pyridazine C-4, C-5), 168.2, 170.6 (2C=N). EIMS: *m/z* 345 $[M]^+$ (48%). Analysis calculated for $C_{20}H_{15}N_3O_3$ (345.35): C, 69.56; H, 4.38; N, 12.17%. Found: C, 69.38; H, 4.52; N, 12.40%.

5.10 | General procedure for the synthesis of the pyridine derivatives 16a-d

Either of malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) was added to a solution of either compound 14a (2.53 g, 0.01 mol) or 14b (2.73 g, 0.01 mol) in 1,4-dioxane (40 mL) containing triethylamine (0.50 mL). The reaction mixture was heated under reflux for 3 hours and then poured onto ice/water mixture containing a few drops of hydrochloric acid and the formed solid product, in each case, was collected by filtration.

5.11 | 6-Hydroxy-2-imino-4-phenyl-1-(p-tolyl)-1,2-dihydropyridine-3-carbonitrile (16a)

Orange crystals from 1,4-dioxane yield (2.40 g, 80%), mp 133-135°C, IR (KBr) νmax: 3582-3348 (OH, NH), 3055 (CH aromatic), 2220 (CN), 1657 (exocyclic C=N), 1623 (C=C); ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.68 (s, 3H, CH_3), 6.29 (s, 1H, pyridine H-4), 7.27-7.41 (m, 9H, C_6H_5, C_6H_4), 8.28 (s, 1H, D_2O exchangeable, NH), 10.19 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 116.5 (CN), 120.8, 123.2, 124.8, 125.8, 126.9, 128.0, 129.6, 130.1, 132.6, 133.5, 138.7, 142.6 (C_6H_5, C_6H_4, pyridine C-2, C-3, C-4, C-5), 170.8 (C=N). EIMS: *m/z* 301 $[M]^+$ (28%). Analysis calculated for $C_{19}H_{15}N_3O$ (301.34): C, 75.73; H, 5.02; N, 13.94%. Found: C, 75.92; H, 4.88; N, 14.28%.

5.12 | 6-Hydroxy-2-oxo-4-phenyl-1-(p-tolyl)-1,2-dihydropyridine-3-carbonitrile (16b)

Orange crystals from 1,4-dioxane yield (2.32 g, 77%), mp 116-118°C, IR (KBr) νmax: 3542-3323 (OH), 3056 (CH aromatic), 2220 (CN), 1693 (CO), 1623 (C=C); ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.65 (s, 3H, CH_3), 6.27 (s, 1H, pyridine H-4), 7.29-7.46 (m, 9H, C_6H_5, C_6H_4), 10.25 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.6 (CH_3), 116.3 (CN), 121.2, 122.7, 123.4, 125.5, 126.3, 127.2, 128.9, 130.4, 132.8, 134.2, 136.9, 142.2 (C_6H_5, C_6H_4, pyridine C-2, C-3, C-4, C-5), 165.2 (C=O). EIMS: *m/z* 302 $[M]^+$ (42%). Analysis calculated for $C_{19}H_{14}N_2O_2$ (302.33): C, 75.48; H, 4.67; N, 9.27%. Found: C, 75.19; H, 4.72; N, 9.03%.

5.13 | 1-(4-Chlorophenyl)-6-hydroxy-2-imino-4-phenyl-1,2-dihydropyridine-3-carbonitrile (16c)

Orange crystals from 1,4-dioxane yield (2.11 g, 66%), mp 170-172°C, IR (KBr) νmax: 3568-3315 (OH, NH), 3056 (CH aromatic), 2220 (CN), 1659 (exocyclic C=N), 1621 (C=C); ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 6.26 (s, 1H, pyridine H-4), 7.22-7.46 (m, 9H, C_6H_5, C_6H_4), 8.26 (s, 1H,

D_2O exchangeable, NH), 10.22 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 116.8 (CN), 120.6, 122.8, 123.6, 124.1, 125.3, 126.8, 128.3, 130.6, 131.2, 134.8, 139.9, 142.9 (C_6H_5, C_6H_4, pyridine C-2, C-3, C-4, C-5), 170.2 (C=N). EIMS: *m/z* 321 $[M]^+$ (42%). Analysis calculated for $C_{18}H_{12}ClN_3O$ (321.76): C, 67.19; H, 3.76; N, 13.06%. Found: C, 67.42; H, 3.80; N, 12.92%.

5.14 | 1-(4-Chlorophenyl)-6-hydroxy-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (16d)

Orange crystals from 1,4-dioxane yield (2.42 g, 77%), mp 160-162°C, IR (KBr) νmax: 3562-3342 (OH), 3054 (CH aromatic), 2221 (CN), 1690 (CO), 1626 (C=C); ^1H NMR (DMSO-d_6, 200 MHz): δ = 6.28 (s, 1H, pyridine H-4), 7.22-7.48 (m, 9H, C_6H_5, C_6H_4), 10.25 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 116.8 (CN), 120.8, 123.1, 123.6, 124.3, 125.9, 128.1, 128.8, 130.6, 132.9, 136.5, 138.8, 142.9 (C_6H_5, C_6H_4, pyridine C-2, C-3, C-4, C-5), 164.8 (C=O). EIMS: *m/z* 322 $[M]^+$ (32%). Analysis calculated for $C_{18}H_{11}ClN_2O_2$ (322.75): C, 66.99; H, 3.44; N, 8.68%. Found: C, 67.26; H, 3.69; N, 8.92%.

5.15 | General procedure for the synthesis of the phenylazo derivatives 17a,b

Benzenediazonium chloride (0.01 mol) (prepared by the addition of sodium nitrite [0.70 g, 0.01 mol] dissolved in water [5 mL] to a cold solution of aniline [0.93 g, 0.01 mol] dissolved in concentrated hydrochloric acid [18 mol, 8 mL]) was added with continuous stirring to a solution of either compound 16a (3.01 g, 0.01 mol) or 16c (3.21 g, 0.01 mol) in ethanol (50 mL) containing ammonium acetate (4.00 g). The reaction mixture was stirred at room temperature for 2 hours and the formed solid product formed was collected by filtration.

5.16 | 6-Hydroxy-2-imino-4-phenyl-5-(phenyldiazenyl)-1-(p-tolyl)-1,2-dihydropyridine-3-carbonitrile (17a)

Orange crystals from 1,4-dioxane yield (2.79 g, 79%), mp 137-139°C, IR (KBr) νmax: 3463-3323 (NH), 3055 (CH aromatic), 2220 (CN), 1655 (exocyclic C=N), 1623 (C=C); ^1H NMR (DMSO-d_6, 200 MHz): δ = 2.65 (s, 3H, CH_3), 7.25-7.38 (m, 14H, $2C_6H_5$, C_6H_4), 8.25 (s, 1H, D_2O exchangeable, NH), 10.26 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.6 (CH_3), 116.7 (CN), 120.8, 123.2, 124.8, 125.8, 126.9, 127.2, 127.8, 128.0, 129.6, 129.8, 130.1, 131.2, 132.6, 133.5, 138.7, 142.6 ($2C_6H_5$, C_6H_4, pyridine C-2, C-3, C-4, C-5), 170.3 (C=N). EIMS: *m/z* 405 $[M]^+$ (33%). Analysis calculated for $C_{25}H_{19}N_5O$ (405.45): C, 74.06; H, 4.75; N, 17.27%. Found: C, 75.29; H, 4.82; N, 17.19%.

5.17 | 1-(4-Chlorophenyl)-6-hydroxy-2-imino-4-phenyl-5-(phenyldiazenyl)-1,2-dihydropyridine-3-carbonitrile (17b)

Orange crystals from 1,4-dioxane yield (2.81 g, 66%), mp 180-182°C, IR (KBr) νmax: 3480-3319 (NH), 3056 (CH aromatic), 2221 (CN), 1652 (exocyclic C=N), 1628 (C=C); ^1H NMR (DMSO-d_6, 200 MHz): δ = 2.68 (s, 3H, CH_3), 7.22-7.46 (m, 14H, $2C_6H_5$, C_6H_4), 8.27 (s, 1H, D_2O exchangeable, NH), 10.23 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 116.9 (CN), 120.3, 121.8, 123.6, 124.1, 125.2, 126.0, 126.5, 127.5, 128.4, 129.2, 130.6, 130.8, 132.8, 134.9, 136.3, 142.1 ($2C_6H_5$, C_6H_4, pyridine C-2, C-3, C-4, C-5), 170.6 (C=N). EIMS: *m/z* 425 $[M]^+$ (26%). Analysis calculated for $C_{24}H_{16}ClN_5O$ (425.87): C, 67.69; H, 3.79; N, 16.44%. Found: C, 67.48; H, 3.60; N, 16.58%.

5.18 | General procedure for the synthesis of the 1,2-dihydropyridin-3-yl) thiazole derivatives 19a,b

Thioglycolic acid (0.92 g, 0.01 mol) was added to a solution of either compound 16a (3.01 g, 0.01 mol) or 16c (3.21 g, 0.01 mol) in acetic acid (40 mL). The reaction mixture was heated under reflux for 2 hours and then evaporated in vacuum. The remaining product was triturated with ethanol and the formed solid product was collected by filtration.

5.19 | 2-(6-Hydroxy-2-imino-4-phenyl-1-(p-tolyl)-1,2-dihydropyridin-3-yl)thiazol-4(5*H*)-one (19a)

Orange crystals from 1,4-dioxane yield (2.17 g, 58%), mp 103-105°C, IR (KBr) νmax: 3580-3319 (OH, NH), 3052 (CH aromatic), 2222 (CN), 1680 (CO), 1658 (exocyclic C=N), 1626 (C=C); ^1H NMR (DMSO-d_6, 200 MHz): δ = 2.68 (s, 3H, CH_3), 5.26 (s, 2H, thiazole CH_2), 7.22-7.37 (m, 10H, C_6H_5, C_6H_4, pyridine H-5), 8.27 (s, 1H, D_2O exchangeable, NH), 10.26 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.6 (CH_3), 60.8 (thiazole CH_2), 116.8 (CN), 120.8, 123.2, 124.8, 125.8,

126.9, 127.2, 127.8, 128.0, 129.6, 129.8, 130.1, 131.2, 132.6, 133.5, 138.7, 142.6 ($2C_6H_5$, C_6H_4, pyridine C-2, C-3, C-4, C-5), 165.8 (CO), 169.3, 170.8 (2C=N). EIMS: *m/z* 375 $[M]^+$ (28%). Analysis calculated for $C_{21}H_{17}N_3O_2S$ (375.44): C, 67.18; H, 4.56; N, 11.19; S, 8.54%. Found: C, 67.24; H, 4.63; N, 11.38; S, 8.29%.

5.20 | 2-(1-(4-Chlorophenyl)-6-hydroxy-2-imino-4-phenyl-1,2-dihydropyridin-3-yl) thiazol-4(5*H*)-one (19b)

Orange crystals from 1,4-dioxane yield (2.68 g, 68%), mp 212-214°C, IR (KBr) νmax: 3573-3331 (OH, NH), 3058 (CH aromatic), 2220 (CN), 1685 (CO), 1655 (exocyclic C=N), 1628 (C=C); ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.63 (s, 3H, CH_3), 5.24 (s, 2H, thiazole CH_2), 7.23-7.45 (m, 10H, C_6H_5, C_6H_4, pyridine H-5), 8.29 (s, 1H, D_2O exchangeable, NH), 10.23 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 60.6 (thiazole CH_2), 116.4 (CN), 120.2, 122.6, 123.7, 124.3, 126.6, 127.0, 128.3, 129.2, 129.3, 132.3, 132.8, 133.8, 134.6, 136.2, 138.8, 142.2 ($2C_6H_5$, C_6H_4, pyridine C-2, C-3, C-4, C-5), 165.8 (CO), 169.1, 170.5 (2C=N). EIMS: *m/z* 395 $[M]^+$ (52%). Analysis calculated for $C_{20}H_{14}ClN_3O_2S$ (395.86): C, 60.68; H, 3.56; N, 10.61; S, 8.10%. Found: C, 60.88; H, 3.72; N, 10.42; S, 8.23%.

5.21 | General procedure for the *N*-ethyl acetate pyridine derivatives 20a,b

Ethyl chloroacetate (1.22 g, 0.01 mol) was added to a solution of either compound 16a (3.01 g, 0.01 mol) or 16c (3.21 g, 0.01 mol) in 1,4-dioxane (40 mL) containing potassium carbonate (0.80 g). The reaction mixture was heated under reflux for 4 hours and then poured onto ice/water mixture and the formed solid product, in each case, was collected by filtration.

5.22 | Ethyl 2-((3-cyano-6-hydroxy-4-phenyl-1-(p-tolyl)pyridin-2(1*H*)-ylidene) amino)-acetate (20a)

Orange crystals from 1,4-dioxane yield (3.21 g, 87%), mp 107-108°C, IR (KBr) νmax: 3563-3348 (OH), 3055 (CH aromatic), 2220 (CN), 1655 (exocyclic C=N), 1623 (C=C); ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.15 (t, 3H, *J* = 5.93 Hz, CH_3), 2.67 (s, 3H, CH_3), 4.22 (q, 2H, *J* = 5.93 Hz, CH_2), 5.78 (s, 2H, CH_2), 7.25-7.38 (m, 10H, C_6H_5, C_6H_4, pyridine H-5), 10.28 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 17.2 ($OCH_2\underline{CH_3}$), 22.6 (CH_3), 53.2 ($O\underline{CH_2}CH_3$), 58.4 (CH_2), 116.6 (CN), 120.3, 123.2, 124.80, 124.2, 125.2, 125.5, 129.3, 130.6, 132.6, 134.2, 136.7, 141.8 (C_6H_5, C_6H_4, pyridine C-2, C-3, C-4, C-5), 164.6 (CO), 170.4 (C=N). EIMS: *m/z* 387 $[M]^+$ (52%). Analysis calculated for $C_{23}H_{21}N_3O_3$ (387.43): C, 71.30; H, 5.46; N, 10.85%. Found: C, 71.58; H, 5.83; N, 11.06%.

5.23 | Ethyl 2-((1-(4-chlorophenyl)-3-cyano-6-hydroxy-4-phenylpyridin-2(1*H*)-ylidene)-amino)acetate (20b)

Orange crystals from 1,4-dioxane yield (2.40 g, 59%), mp 160-162°C, IR (KBr) νmax: 3549-3322 (OH), 3056 (CH aromatic), 2220 (CN), 1651 (exocyclic C=N), 1626 (C=C); ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.14 (t, 3H, J = 6.23 Hz, CH_3), 4.23 (q, 2H, J = 6.23 Hz, CH_2), 5.79 (s, 2H, CH_2), 7.21-7.46 (m, 10H, C_6H_5, C_6H_4, pyridine H-5), 10.24 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 17.0 ($OCH_2\underline{CH_3}$), 22.8 (CH_3), 52.9 ($O\underline{CH_2}CH_3$), 58.7 (CH_2), 116.5 (CN), 120.1, 122.8, 123.6, 124.1, 124.6, 127.3, 129.2, 130.9, 131.2, 134.6, 135.2, 142.3 (C_6H_5, C_6H_4, pyridine C-2, C-3, C-4, C-5), 164.9 (CO), 170.2 (C=N). EIMS: *m/z* 407 $[M]^+$ (36%). Analysis calculated for $C_{22}H_{18}ClN_3O_3$ (407.85): C, 64.79; H, 4.45; N, 10.30%. Found: C, 64.88; H, 4.26; N, 10.52%.

5.24 | General procedure for the synthesis of the pyrrolo[2,3-*b*]pyridin-2-yl propionate derivatives 21a,b

To a suspension of either compound 20a (3.87 g, 0.01 mol) or 20b in sodium ethoxide solution prepared by dissolving metallic sodium (0.26 g, 0.02 mol) in absolute ethanol (50 mL) was heated under reflux in a boiling water bath for 6 hours. The reaction mixture in each case was left to cool and poured onto ice/water mixture containing a few drops of hydrochloric acid (till pH 6), and the precipitated solid product was collected by filtration.

5.25 | 3-Amino-6-hydroxy-4-phenyl-7-(p-tolyl)-7H-pyrrolo[2,3-*b*]pyridin-2-yl propionate (21a)

Pale yellow crystals from 1,4-dioxane yield (2.32 g, 60%), mp 240-244°C, IR (KBr) νmax: 3548-3328 (OH), 3055 (CH aromatic), 1659 (exocyclic C=N), 1628 (C=C); ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 1.13 (t, 3H, *J* = 7.21 Hz, CH_3), 2.69 (s, 3H, CH_3), 4.21 (q, 2H, J = 7.21 Hz, CH_2), 4.52 (s, 2H, D_2O exchangeable, NH_2), 7.23-7.42 (m, 10H,

C_6H_5, C_6H_4, pyridine H-5), 10.30 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.8 ($OCH_2\underline{CH_3}$), 22.8 (CH_3), 52.7 ($O\underline{CH_2}CH_3$), 120.2, 122.6, 123.7, 124.1, 124.7, 125.2, 127.8, 128.0, 130.8, 132.6, 134.1, 136.5, 140.3, 141.6, 143.8 (C_6H_5, C_6H_4, pyridine C-2, C-3, C-4, C-5, pyrrole C-3, C-4), 164.9 (CO), 171.6 (C=N). EIMS: *m/z* 387 $[M]^+$ (100%). Analysis calculated for $C_{23}H_{21}N_3O_3$ (387.43): C, 71.30; H, 5.46; N, 10.85%. Found: C, 71.22; H, 5.36; N, 10.63%.

5.26 | 3-Amino-7-(4-chlorophenyl)-6-hydroxy-4-phenyl-7*H*-pyrrolo[2,3-*b*]pyridin-2-yl propionate (21b)

Pale yellow crystals from 1,4-dioxane yield (2.68 g, 66%), mp 288-291°C, IR (KBr) νmax: 3551-3348 (OH), 3055 (CH aromatic), 1653 (exocyclic C=N), 1628 (C=C); ^1H NMR (DMSO-d_6, 200 MHz): δ = 1.12 (t, 3H, *J* = 6.29 Hz, CH_3), 4.22 (q, 2H, *J* = 6.29 Hz, CH_2), 4.58 (s, 2H, D_2O exchangeable, NH_2), 7.23-7.49 (m, 10H, C_6H_5, C_6H_4, pyridine H-5), 10.27 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.8 ($OCH_2\underline{CH_3}$), 22.9 (CH_3), 52.9 ($O\underline{CH_2}CH_3$), 120.4, 121.8, 122.9, 124.6, 125.1, 126.7, 127.1, 128.3, 130.6, 132.3, 133.8, 135.9, 140.1, 141.4, 142.9 (C_6H_5, C_6H_4, pyridine C-2, C-3, C-4, C-5, pyrrole C-3, C-4), 164.97 (CO), 170.6 (C=N). EIMS: *m/z* 407 $[M]^+$ (80%). Analysis calculated for $C_{22}H_{18}ClN_3O_3$ (407.85): C, 64.79; H, 4.45; N, 10.30%. Found: C, 64.46; H, 4.69; N, 10.23%.

5.27 | General procedure for the synthesis of the *N*-phenylthiourea derivatives 22a,b

Phenylisothiocyanate (1.30 g, 0.01 mol) was added to a solution of either compound 16a (3.01 g, 0.01 mol) or 16c (3.21 g, 0.01 mol) in 1,4-dioxane (40 mL). The reaction mixture was heated under reflux for 2 hours and then was left to cool. The formed solid product, in each case, was collected by filtration.

5.28 | 1-(3-Cyano-6-hydroxy-4-phenyl-1-(p-tolyl)pyridin-2(1*H*)-ylidene)-3-phenylthiourea (22a)

Pale yellow crystals from ethanol yield (3.22 g, 74%), mp 105-107°C, IR (KBr) νmax: 3579-3353 (OH), 3057 (CH aromatic), 2220 (CN), 1653 (exocyclic C=N), 1622 (C=C), 1200 (C=S); ^1H NMR (DMSO-d_6, 200 MHz): δ = 2.68 (s, 3H, CH_3), 7.26-7.46 (m, 15H, $2C_6H_5$, C_6H_4, pyridine H-5), 8.29 (s, 1H, D_2O exchangeable, NH), 10.25 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 22.9 (CH_3), 116.9 (CN), 120.3, 122.1, 122.8, 124.1, 124.8, 125.7, 125.1, 127.2, 127.9, 128.3, 129.3, 130.8, 132.2, 134.2, 138.1, 142.2 ($2C_6H_5$, C_6H_4, pyridine C-2, C-3, C-4, C-5), 171.9 (C=N), 179.2 (C=S). EIMS: *m/z* 436 $[M]^+$ (68%). Analysis calculated for $C_{26}H_{20}N_4OS$ (436.53): C, 71.54; H, 4.62; N, 12.83; S, 7.35%. Found: C, 71.38; H, 4.79; N, 13.05; S, 7.66%.

5.29 | 1-(1-(4-Chlorophenyl)-3-cyano-6-hydroxy-4-phenylpyridin-2(1*H*)-ylidene)-3-phenylthiourea (22b)

Pale yellow crystals from ethanol yield (2.50 g, 55%), mp 152-154°C, IR (KBr) νmax: 3583-3326 (OH), 3054 (CH aromatic), 2220 (CN), 1652 (exocyclic C=N), 1620 (C=C), 1210 (C=S); ^1H NMR (DMSO-d_6, 200 MHz): δ = 7.23-7.49 (m, 15H, $2C_6H_5$, C_6H_4, pyridine H-5), 8.27 (s, 1H, D_2O exchangeable, NH), 10.28 (s, 1H, D_2O exchangeable, OH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 116.5 (CN), 120.1, 121.4, 123.6, 124.1, 125.1, 125.7, 126.7, 127.0, 128.2, 129.8, 130.1, 130.8, 132.9, 135.6, 139.8, 142.8 ($2C_6H_5$, C_6H_4, pyridine C-2, C-3, C-4, C-5), 171.7 (C=N), 179.6 (C=S). EIMS: *m/z* 456 $[M]^+$ (30%). Analysis calculated for $C_{25}H_{17}ClN_4OS$ (456.95): C, 65.71; H, 3.75; N, 12.26; S, 7.02%. Found: C, 65.80; H, 3.85; N, 12.41; S, 7.25%.

5.30 | General procedure for the synthesis of the pyrano[2,3-*b*]pyridin-7(8*H*)-imine derivatives 23a,b

Either of malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.0 mol) was added to a solution of compound 16c (3.21 g, 0.01 mol) in 1,4-dioxane (40 mL) containing triethylamine (0.50 mL). The reaction mixture was heated under reflux for 4 hours and then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

5.31 | 4-Amino-8-(4-chlorophenyl)-2,7-diimino-5-phenyl-7,8-dihydro-2*H*-pyrano[2,3-*b*]pyridine-6-carbonitrile (23a)

Pale brown crystals from 1,4-dioxane yield (2.78 g, 72%), mp 150-152°C, IR (KBr) νmax: 3493-3328 (NH, NH_2),

3054 (CH aromatic), 2220 (CN), 1659 (exocyclic C=N), 1623 (C=C); ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 4.80 (s, 2H, D_2O exchangeable, NH_2), 7.26-7.41 (m, 10H, C_6H_5, C_6H_4, H-6), 8.23, 8.31 (2 seconds, 2H, D_2O exchangeable, 2NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 108.6, 111.7 (C-5, C-6), 117.1 (CN), 120.5, 122.8, 124.0, 125.8, 126.5, 127.5, 128.4, 130.8, 131.8, 135.3, 138.7, 140.6 (C_6H_5, C_6H_4, pyridine C-2, C-3, C-4, C-5), 168.2, 170.6 (2 C=N). EIMS: *m/z* 387 $[M]^+$ (55%). Analysis calculated for $C_{21}H_{14}ClN_5O$ (387.82): C, 65.04; H, 3.64; N, 18.06%. Found: C, 64.88; H, 3.47; N, 18.28%.

5.32 | 4-Amino-8-(4-chlorophenyl)-7-imino-2-oxo-5-phenyl-7,8-dihydro-2*H*-pyrano[2,3-*b*]pyridine-6-carbonitrile (23b)

Pale brown crystals from 1,4-dioxane yield (3.25 g, 84%), mp 160-162°C, IR (KBr) νmax: 3474-3341 (NH, NH_2), 3055 (CH aromatic), 2220 (CN), 1656 (exocyclic C=N), 1621 (C=C); ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 4.83 (s, 2H, D_2O exchangeable, NH_2), 7.23-7.45 (m, 10H, C_6H_5, C_6H_4, H-6), 8.25 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 108.9, 111.2 (C-5, C-6), 117.3 (CN), 120.2, 123.4, 124.3, 126.0, 126.8, 127.5, 128.2, 130.5, 133.3, 136.9, 138.3, 140.9 (C_6H_5, C_6H_4, pyridine C-2, C-3, C-4, C-5), 164.8 (CO), 170.8 (C=N). EIMS: *m/z* 388 $[M]^+$ (34%). Analysis calculated for $C_{21}H_{13}ClN_4O_2$ (388.81): C, 64.87; H, 3.37; N, 14.41%. Found: C, 64.92; H, 3.29; N, 14.60%.

5.33 | 4-Amino-8-(4-chlorophenyl)-7-hydroxy-2-oxo-5-phenyl-2,8-dihydro-1,8-naphthyridine-3-carbonitrile (25)

Ethyl cyanoacetate (1.13 g, 0.01 mol) was added to a solution of compound 16c (3.21 g, 0.01 mol) in dimethylformamide (40 mL). The reaction mixture was heated under reflux for 3 hours and then poured onto ice/water mixture. The formed solid product was collected by filtration.

Pale brown crystals from 1,4-dioxane yield (2.71 g, 77%), mp 290-292°C, IR (KBr) νmax: 3564-3323 (OH, NH, NH_2), 3055 (CH aromatic), 2220 (CN), 1654 (exocyclic C=N), 1624 (C=C); ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 4.88 (s, 2H, D_2O exchangeable, NH_2), 7.26-7.49 (m, 10H, C_6H_5, C_6H_4, H-6), 10.32 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 107.3, 111.8 (C-5, C-6), 117.1 (CN), 120.8, 122.6, 123.8, 126.4, 127.2, 127.9, 128.0, 130.7, 132.9, 135.2, 137.0, 141.7 (C_6H_5, C_6H_4, pyridine C-2, C-3, C-4, C-5), 170.4 (C=N). EIMS: *m/z* 388 $[M]^+$ (32%). Analysis calculated for $C_{21}H_{13}ClN_4O_2$ (388.81): C, 64.87; H, 3.37; N, 14.41%. Found: C, 64.69; H, 3.42; N, 14.55%.

5.34 | General procedure for the synthesis of the pyran derivatives 27a-c

Any of the benzaldehyde (1.06 g, 0.01 mol), 4-chlorobenzaldehyde (1.40 g, 0.01 mol) or 4-methoxybenzaldehyde (1.83 g, 0.01 mol), and malononitrile (0.66 g, 0.01 mol) was added to a solution of compound 14a (2.53 g, 0.01 mol), in 1,4-dioxane (40 mL) containing triethylamine (0.50 mL). The whole reaction mixture was heated under reflux for 3 hours and then left to cool and the formed solid product, in each case, was collected by filtration.

5.35 | 6-Amino-5-cyano-2,4-diphenyl-*N*-(p-tolyl)-4*H*-pyran-3-carboxamide (27a)

Pale yellow crystals from ethanol yield (2.73 g, 68%), mp 110-112°C, IR (KBr) νmax: 3479-3353 (NH, NH_2), 3054 (CH aromatic), 2220 (CN), 1688 (CO), 1656 (C=C), 1622 (C=C); ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.68 (s, 3H, CH_3), 5.02 (s, 2H, D_2O exchangeable, NH_2), 6.03 (s, 1H, pyran H-4), 7.26-7.48 (m, 14H, $2C_6H_5$, C_6H_4), 8.29 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 22.7 (CH_3), 116.6 (CN), 120.1, 122.6, 123.8, 124.4, 124.8, 125.9, 126.8, 127.2, 127.9, 128.3, 129.3, 130.8, 134.7, 136.5, 138.8, 142.2 ($2C_6H_5$, C_6H_4, pyran C-2, C-3, C-5, C-6), 165.9 (CO). EIMS: *m/z* 407 $[M]^+$ (27%). Analysis calculated for $C_{26}H_{21}N_3O_2$ (407.46): C, 76.64; H, 5.19; N, 10.31%. Found: C, 76.56; H, 4.84; N, 10.25%.

5.36 | 6-Amino-4-(4-chlorophenyl)-5-cyano-2-phenyl-*N*-(p-tolyl)-4*H*-pyran-3-carboxamide (27b)

Yellow crystals from ethanol yield (2.98 g, 72%), mp 240-242°C, IR (KBr) νmax: 3442-3322 (NH, NH_2), 3056 (CH aromatic), 2222 (CN), 1688 (CO), 1656 (C=C), 1626 (C=C); ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.68 (s, 3H, CH_3), 5.16 (s, 2H, D_2O exchangeable, NH_2), 6.05 (s, 1H, pyran H-4), 7.21-7.47 (m, 14H, $2C_6H_5$, C_6H_4), 8.23 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 22.8 (CH_3), 116.8 (CN), 120.8, 123.1, 123.5, 124.2, 124.8, 125.7, 127.0, 127.8, 128.1, 128.3, 129.3, 130.4, 133.2, 135.5, 138.2, 142.8 ($2C_6H_5$, C_6H_4, pyran C-2, C-3, C-5, C-6), 165.4 (CO). EIMS: *m/z* 441 $[M]^+$ (34%). Analysis calculated for $C_{26}H_{20}ClN_3O_2$ (441.91): C, 70.67; H, 4.56; N, 9.51%. Found: C, 70.45; H, 4.78; N, 9.76%.

5.37 | 6-Amino-5-cyano-4-(4-methoxyphenyl)-2-phenyl-*N*-(p-tolyl)-4*H*-pyran-3-carboxamide (27c)

Pale yellow crystals from ethanol yield (3.34 g, 79%), mp 50-52°C, IR (KBr) νmax: 3458-3320 (NH, NH_2), 3056 (CH aromatic), 2220 (CN), 1689 (CO), 1652 (C=C), 1628 (C=C); ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.68 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 5.08 (s, 2H, D_2O exchangeable, NH_2), 6.02 (s, 1H, pyran H-4), 7.22-7.45 (m, 13H, C_6H_5, $2C_6H_4$), 8.29 (s, 1H, D_2O exchangeable, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 22.8 (CH_3), 52.3 (OCH_3), 116.68 (CN), 120.9, 123.2, 123.8, 124.1, 125.8, 125.9, 126.4, 127.0, 128.2, 129.0, 129.3, 130.6, 134.9, 136.2, 138.8, 142.6 (C_6H_5, $2C_6H_4$, pyran C-2, C-3, C-5, C-6), 165.7 (CO). EIMS: *m/z* 437 $[M]^+$ (18%). Analysis calculated for $C_{27}H_{23}N_3O_3$ (437.49): C, 74.12; H, 5.30; N, 9.60%. Found: C, 74.31; H, 5.42; N, 9.88%.

5.38 | General procedure for the synthesis of the pyridine derivatives 28a-c

Any of the benzaldehyde (1.06 g, 0.01 mol), 4-chlorobenzaldehyde (1.40 g, 0.01 mol) or 4-methoxybenzaldehyde (1.83 g, 0.01 mol), and malononitrile (0.66 g, 0.01 mol) was added to a solution of either compound 14a (2.53 g, 0.01 mol) in 1,4-dioxane (40 mL) containing ammonium acetate (0.50 mL). The whole reaction mixture was heated under reflux conditions for 3 hours and then left to cool, and the formed solid product, in each case, was collected by filtration.

5.39 | 6-Amino-5-cyano-2,4-diphenyl-*N*-(p-tolyl)-1,4-dihydropyridine-3-carboxamide (28a)

Pale yellow crystals from ethanol yield (2.96 g, 73%), mp 50-52°C, IR (KBr) νmax: 3493-3325 (NH, NH_2), 3056 (CH aromatic), 2221 (CN), 1689 (CO), 1620 (C=C); ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.69 (s, 3H, CH_3), 5.08 (s, 2H, D_2O exchangeable, NH_2), 6.13 (s, 1H, pyridine H-4), 7.28-7.43 (m, 14H, $2C_6H_5$, C_6H_4), 8.25, 8.27 (2 seconds, 2H, D_2O exchangeable, 2NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 22.9 (CH_3), 116.5 (CN), 120.6, 121.3, 122.6, 123.4, 125.6, 125.8, 126.1, 127.7, 128.0, 128.6, 129.8, 131.6, 133.9, 135.2, 137.3, 142.2 ($2C_6H_5$, C_6H_4, pyridine C-2, C-3, C-5, C-6), 165.7 (CO). EIMS: *m/z* 406 $[M]^+$ (19%). Analysis calculated for $C_{26}H_{22}N_4O$ (406.48): C, 76.83; H, 5.46; N, 13.78%. Found: C, 76.92; H, 5.29; N, 13.92%.

5.40 | 6-Amino-4-(4-chlorophenyl)-5-cyano-2-phenyl-*N*-(p-tolyl)-1,4-dihydropyridine-3-carboxamide (28b)

Yellow crystals from ethanol yield (2.72 g, 62%), mp 90-92°C, IR (KBr) νmax: 3461-3353 (NH, NH_2), 3055 (CH aromatic), 2220 (CN), 1688 (CO), 1628 (C=C); ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.66 (CH_3), 5.13 (s, 2H, D_2O exchangeable, NH_2), 6.09 (s, 1H, pyridine H-4), 7.25-7.49 (m, 13H, C_6H_5, $2C_6H_4$), 8.24, 8.29 (2 seconds, 2H, D_2O exchangeable, 2NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 22.6 (CH_3), 116.4 (CN), 120.3, 123.6, 124.2, 125.9, 126.1, 126.9, 128.3, 128.9, 129.2, 129.6, 130.3, 131.6, 132.8, 134.9, 137.4, 142.2 (C_6H_5, $2C_6H_4$, pyridine C-2, C-3, C-5, C-6), 165.4 (CO). EIMS: *m/z* 440 $[M]^+$ (62%). Analysis calculated for $C_{26}H_{21}ClN_4O$ (440.92): C, 70.82; H, 4.80; N, 12.71%. Found: C, 70.69; H, 4.53; N, 12.93%.

5.41 | 6-Amino-5-cyano-4-(4-methoxyphenyl)-2-phenyl-*N*-(p-tolyl)-1,4-dihydropyridine-3-carboxamide (28c)

Pale yellow crystals from ethanol yield (3.319 g, 73%), mp 70-72°C, IR (KBr) νmax: 3470-3355 (NH, NH_2), 30 565 (CH aromatic), 2221 (CN), 1688 (CO), 1623 (C=C); ^{1}H NMR (DMSO-d_6, 200 MHz): δ = 2.69 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 5.12 (s, 2H, D_2O exchangeable, NH_2), 6.16 (s, 1H, pyridine H-4), 7.27-7.42 (m, 13H, C_6H_5, $2C_6H_4$), 8.26, 8.31 (2 seconds, 2H, D_2O exchangeable, 2NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 22.5 (CH_3), 52.1 (OCH_3), 116.9 (CN), 120.3, 122.8, 124.1, 124.5, 126.2, 126.9, 127.1, 127.3, 128.6, 129.1, 129.5, 130.3, 134.2, 136.8, 137.2, 141.9 (C_6H_5, $2C_6H_4$, pyridine C-2, C-3, C-5, C-6), 165.5 (CO). EIMS: *m/z* 436 $[M]^+$ (22%). Analysis calculated for $C_{27}H_{24}N_4O_2$ (436.51): C, 74.29; H, 5.54; N, 12.84%. Found: C, 74.42; H, 5.63; N, 12.63%.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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