Received: 27 September 2019 | Revised: 13 December 2019 | Accepted: 16 December 2019

DOI: 10.1002/jhet.3881

WILEY

ARTICLE

Facile synthesis of novel heterocyclic compounds based on pyridine moiety with pharmaceutical activities

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Abstract

A novel run of fused heterocyclic derivatives containing pyridine moieties has been disclosed by allowing 2-amino-4-phenyl-6-(phenyl amino)pyridine-3,-5-dicarbonitrile **1** to undergo annulation reactions with different reagents. Most of synthesized compounds have moderate to strong antitumor activity against HePG-2 and MCF-7. Moreover, MOE 2014.09 software was used to run the computational studies to support the biological activity results. The assigned structures for all the newly prepared derivatives were ascertained on the basis of elemental analyses and spectral data.

KEYWORDS

anticancer, azepan, molecular docking, *o*-aminonitrile pyridine, pyrazolo pyrimidine

1 | INTRODUCTION

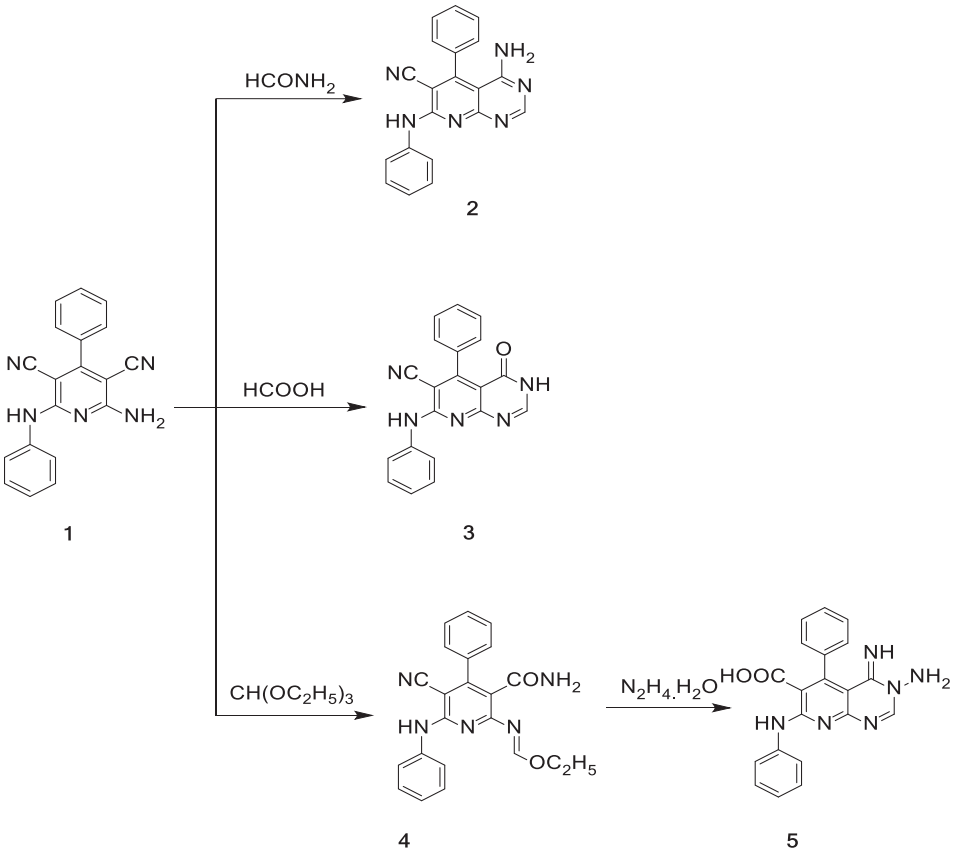
Pyridine moieties are familiar substructures in numerous natural pharmaceuticals and functional materials [1–3]. Polysubstituted pyridines possess important biological and pharmacological behavior and could be used as possible agrochemicals, for example as herbicides [4]. In addition, the molecules containing pyridine moiety are used as nonlinear optical materials [5], electrical materials [6], and chelating agents in metal ligand chemistry [7]. Among them, 2-amino-3-cyanopyridines are known as IKK-β inhibitors [8]. They have been identified to possess biological behavior such as antimicrobial [9], antiviral [10], antibacterial [11], antifungal [12], antitumor [13–18], anti-inflammatory [19], as well as antihypertensive properties [20]. Besides, they are important and useful intermediates in preparing a variety of heterocyclic compounds [12,21]. In extension of our previous work [22–27], 2-amino-4-phenyl-6-(phenylamino) pyridine-3,-5-dicarbonitrile will be utilized as a substrate for the synthesis of different heterocyclic derivatives, and their pharmaceutical behavior as anticancer agent will be studied.

2 | RESULTS AND DISCUSSION

The starting compound 2-amino-4-phenyl-6-(phenylamino) pyridine-3, 5-dicarbonitrile **1** was prepared by the reaction of benzaldehyde, malononitrile, and aniline without catalyst and solvent free [22]. A novel series of heterocyclic compounds containing pyridine moieties has been disclosed by allowing 2-amino-4-phenyl-6-(phenylamino)pyridine-3, 5-dicarbonitrile **1** to undergo annulation reactions with different reagents.

Initially, 2-amino-3-cyano pyridine derivative **1** underwent thermal cycloaddition with formamide to afford 4-imino-5-phenyl-7-(phenylamino)-3, 4-di-hydropyrido[2,3-d] pyrimidine-6-carbonitrile **2**. The structural elucidation of **2** was inferred from its IR and elemental microanalysis. In particular, its IR showed characteristic stretching bands at 3310, 3186, and 2208 cm^{-1} due to the presence of NH_2, NH, and CN, respectively. The mass spectrum exhibited the molecular ion peak at m/z 338 ($M^{+\cdot}$, 12%) **(**Scheme 1**)**.

Moreover, the cyclocondensation of 2-amino-3-cyano pyridine derivative **1** with formic acid yielded 4-oxo-5-phenyl-7-(phenylamino)-3, 4-di-hydropyrido [2,3-d]pyrimidine-6-carbonitrile **3** which showed a new



SCHEME 1
Cyclocondensation of **1** with formamide, formic acid, and triethyl orthoformate

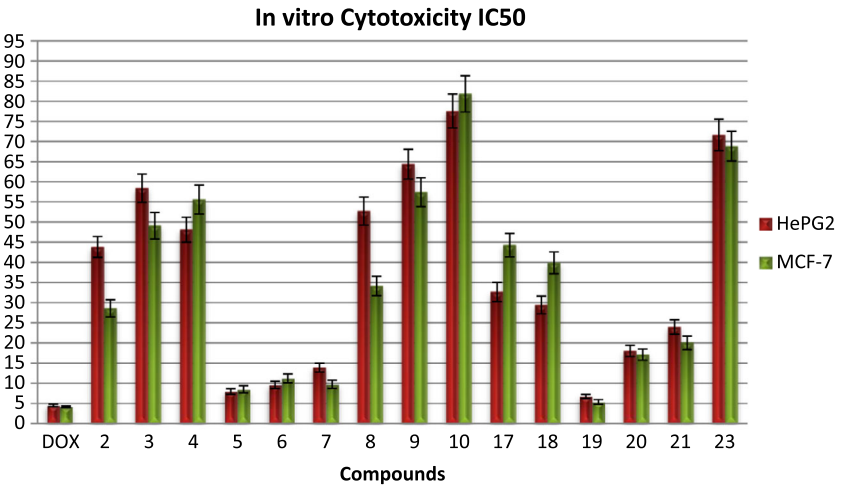


FIGURE 1 Graphical correlation between tested compounds and their IC_{50} against Hep G-2 and MCF-7

absorption band in the IR spectrum at 1676 cm^{-1} of (C═O) **(**Scheme 1**)**.

On the other hand, reaction of 2-amino-3-cyano pyridine derivative **1** with triethyl orthoformate afforded ethyl-N-(3-carbamoyl-5-cyano-4-phenyl-6-(phenylamino) pyridin-2-yl) formimidate **4** which in turn underwent refluxing with hydrazine hydrate in alcoholic solution to afford pyridopyrimidine carboxylic acid derivative **5**. The IR spectrum of compound **4** showed broad absorption bands at 3456 cm^{-1} (NH_2, NH), 2225 cm^{-1} (CN), and 1670 cm^{-1} (C═O). Mass spectrum showed the molecular in peak at m/z 385 ($M^{+\bullet}$, 1%). The IR spectrum of compound **5** showed absorption bands at 3424 cm^{-1} (OH), 3286, 3233 cm^{-1} (NH_2), 3146 cm^{-1} (NH), and 1722 cm^{-1} (C═O) and disappearance of any band related to cyano group **(**Scheme 1**)**.

Formation of pyrido pyrimidine thione and dithione derivatives by reaction of 2-amino-3-cyano pyridine derivative **1** with phenyl isothiocyanate and/or carbon disulphide was carried out to afford pyrido pyrimidine

thione derivative **6** and pyrido pyrimidine dithione derivative **7**, respectively. ^{1}H-NMR showed disappearance of NH_2 groups. Meanwhile, the IR spectrum showed new absorption bands related to (NH) groups at 3207 and 3218 cm^{-1}, respectively.

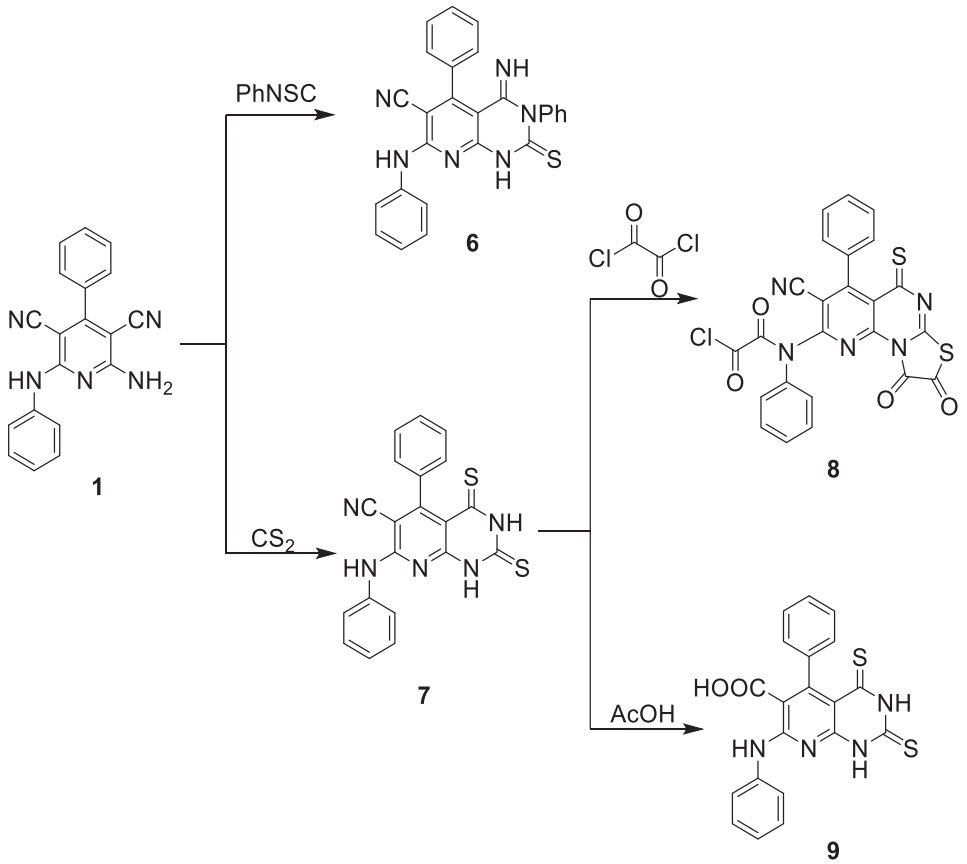
The treatment of dithioxo-pyrido pyrimidine derivative **7** with oxalyl chloride in dry benzene gave pyrido thiazolo pyrimidine oxoacetyl chloride derivative **8**. The IR spectrum of compound **8** showed new absorption bands related to (4 C═O) at 1773, 1750, 1727, and 1690 cm^{-1} while ^{1}H-NMR showed the disappearance of NH_2 and NH signals.

The acid hydrolysis of dithioxo-pyrido pyrimidine derivative **7** with acetic acid gave the di- thioxo pyrido pyrimidine carboxylic acid derivative **9** where its IR spectrum showed peaks corresponding to (OH) group at 3444 cm^{-1} and a peak at 1716 cm^{-1} corresponding to (C═O). Furthermore, mass spectrum showed the molecular ion peak at m/z 406 ($M^{+\bullet}$, 3%) **(**Scheme 2**)**.

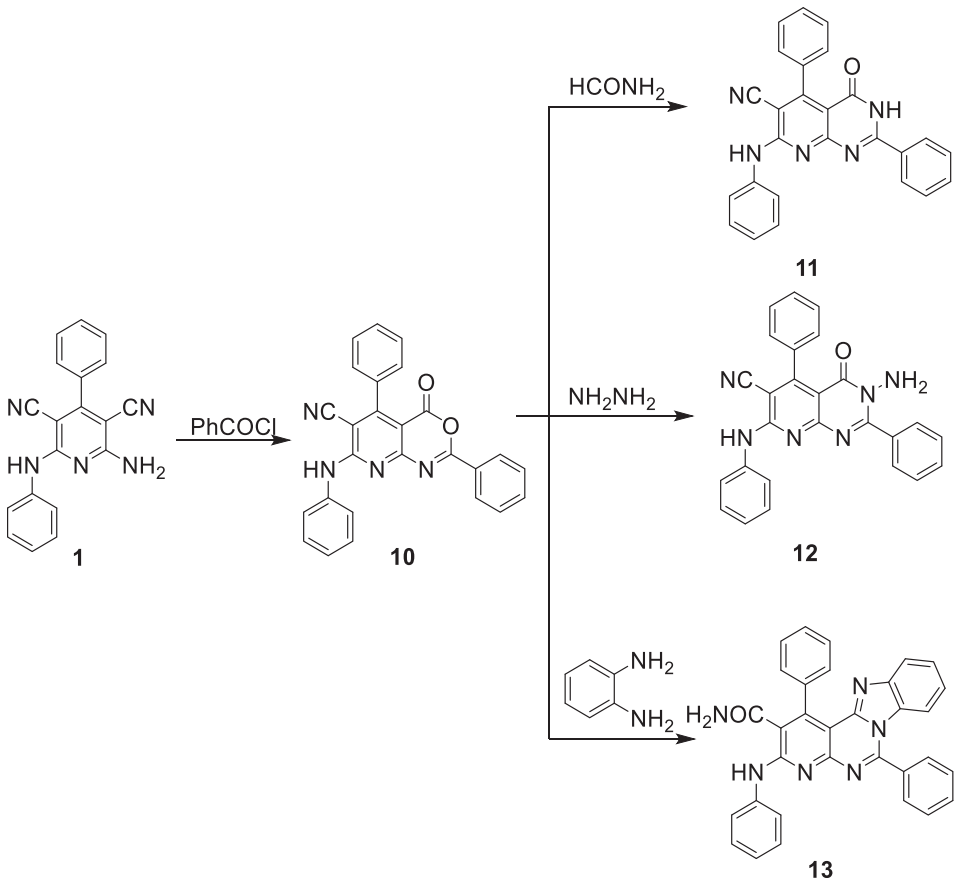
The strategy for construction for oxazinone scaffold was emanated from allowing **1** to undergo benzoylation upon treatment with benzoyl chloride to afford 4-oxo-2,5-diphenyl-7-(phenylamino)-4H-pyrido [2,3-d] [1,3] oxazine-6-carbonitrile **10**. The reaction took place *via* nucleophilic attack of the amino group on the electron deficient carbonyl group followed by releasing of a hydrogen chloride mole to produce a cyclized intermediate. Ultimate hydrolysis and elimination of ammonia afforded the anticipated pyrido oxazine derivative **10**. The IR spectrum of compound **10** showed absorptions bands at 3341 cm^{-1} (NH), 2225 cm^{-1} (CN), 1744 cm^{-1} (C═O), while its ^{1}H-NMR showed a D_2O-exchangeable signal at 10.21 ppm due to NH proton **(**Scheme 3**)**.

Ammonolysis of pyridoxazine-6-carbonitrile **10** by boiling with formamide gave 4-oxo-2,5-diphenyl-7-(phenylamino)-3,4-di-hydropyrido [2,3-d] pyrimidine-6-carbonitrile **11**. The reaction took place *via* nucleophilic attack of amino group on carbonyl carbon atom followed by amino intramolecular nucleophilic cyclization. Finally, a dehydration followed by the release of formic acid molecule was able to afford **11**. The structure of **11** was confirmed by the IR spectrum which exhibited strong absorption bands at 3305 cm^{-1} (2NH), 2220 cm^{-1} (CN), and 1667 cm^{-1} (C═O), respectively. Mass spectrum showed m/z 415 ($M^{+\bullet}$, 29%) **(**Scheme 3**)**.

Hydrazinolysis of pyridoxazine-6-carbonitrile **10** was achieved when it refluxed with hydrazine hydrate in butanol to afford, 3-amino-4-oxo-2,5-diphenyl-7-(phenylamino)-3,4-dihydro pyrido [2,3-d]pyrimidine-6-carbonitrile **12**. The IR spectrum of compound **12** showed broad absorption bands at 3415, 3178 cm^{-1} (NH_2, NH), 2228 cm^{-1} (CN), and 1673 cm^{-1} (C═O). Mass spectrum showed m/z 429 ($M^{+\bullet}$ −1, 7%) **(**Scheme 3**)**.



SCHEME 2 Formation of pyridopyrimidine thione and dithione derivatives



SCHEME 3 Reactions of derivative **10** with formamide, hydrazine hydrate, and *o*-phenylene diamine

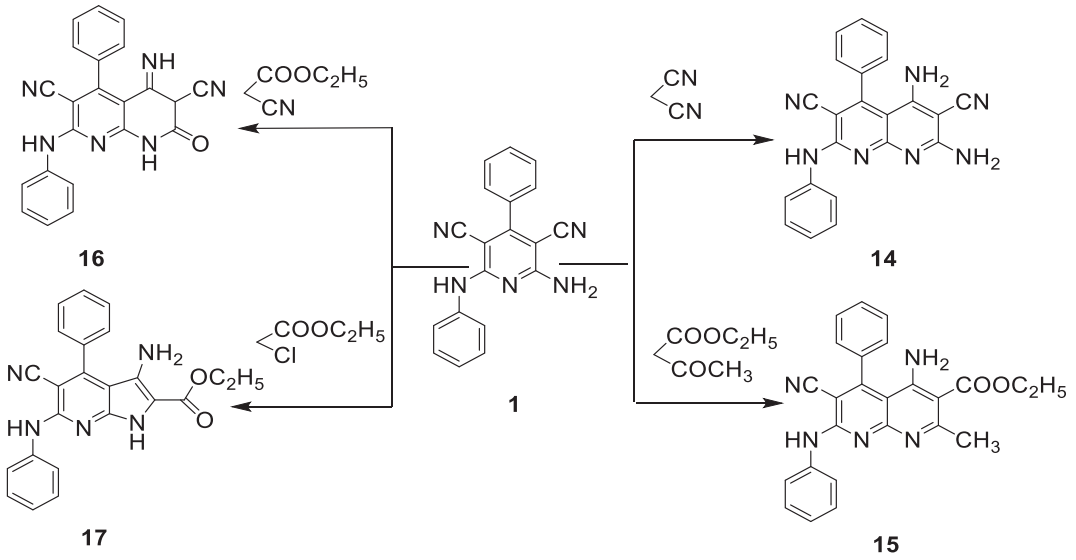
The electrophilicity of the lactonic carbonyl group of compound **10** was studied by nucleophilic reaction with *o*-phenylene diamine to yield 1,6-diphenyl-3-(phenylamino) benzo [4,5] imidazo [1,2-c] pyrido [3,2-e] pyrimidine-2-carboxamide **13**, which was formed *via* ring opening of the oxazine ring by an amino group followed by ring closure and then dehydration with the other amino group and hydrolysis of cyano group to carboxamide. The IR spectrum of compound **13** showed the appearance of strong absorption bands at 3430, 3313 cm^{-1} (NH_2), 3172 cm^{-1}(NH), and 1685 cm^{-1} (C═O) and disappearance of any bands related to cyano groups. ^{1}H-NMR of compound **13** showed D_2O-exchangeable signals at 9.17 and 3.41 ppm due to NH and NH_2 protons. Mass spectrum showed m/z 508 ($M^{+\bullet}$ +2, 6%) **(**Scheme 3**)**.

Reactions of 2-amino-3-cyano pyridine derivative **1** with active methylenes such as malononitrile, ethyl acetoacetate, ethyl cyanoacetate, and ethyl chloroacetate afforded 2,4-diamino-5-phenyl-7-(phenylamino)-1,8-naphthyridine-3,6-dicarbonitrile **14**, ethyl-4-amino-6-cyano-2-methyl-5-phenyl-7-(phenylamino)-1,8-naphthyridine-3 -carboxylate **15**, 4-imino-2-oxo-5-phenyl-7-(phenylamino)-1,2,3,4-tetrahydro-1,8-naphthyridine-3, 6-dicarbonitrile **16**, and ethyl-3-amino-5-cyano-4-phenyl-6-(phenylamino)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate **17**, respectively. The ^{1}H-NMR spectrum of compound **14** showed exchangeable broad singlet bands of NH proton at δ 9.13 ppm and NH_2 protons at δ 4.47 ppm. All IR spectra of compounds **15**, **16**, and **17** showed new absorption bands for the carbonyl group at 1719, 1690, and 1730 cm^1, respectively **(**Scheme 4**)**.

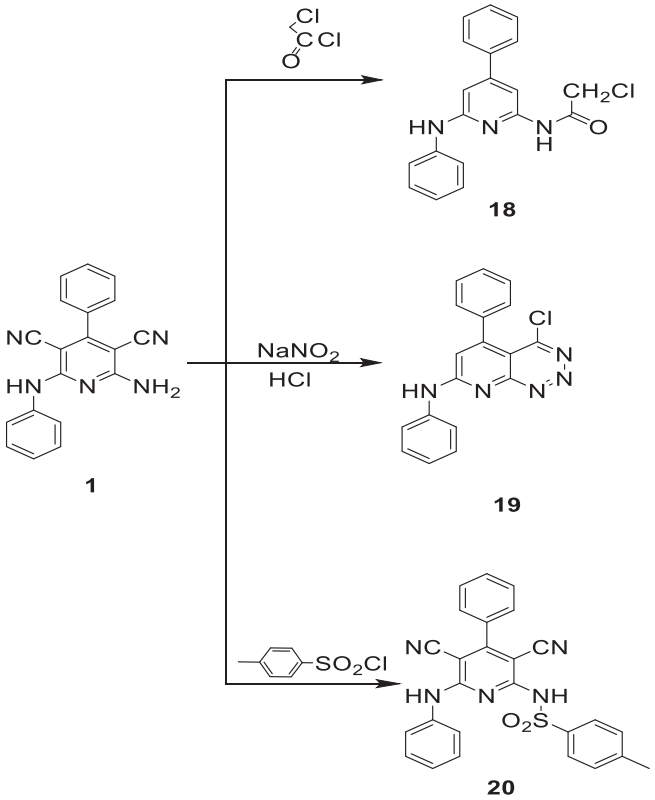
Treatment of 2-amino-3-cyano pyridine derivative **1** with chloro acetylchloride in dry benzene yielded 2-chloro-N-(4-phenyl-6-(phenylamino) pyridin-2-yl) acetamide **18**. IR of **c**ompound **18** showed strong absorption bands at 3267, 3206 cm^{-1} (NH), and 1673 cm^{-1} (C═O) and disappearance of any cyano group. The ^{1}H-NMR spectrum showed exchangeable broad singlet bands of 2NH protons at δ 10.29 and 9.10 ppm and a peak at 4.27 ppm for the methylene protons **(**Scheme 5**)**.

A new fused pyridotriazine **19** was obtained by the treatment of 2-amino-3-cyano pyridine derivative **1** with sodium nitrite in the presence of hydrochloric acid. One of the cyano groups was involved in the formation of triazine ring, while the other cyano group underwent acid-catalyzed hydrolysis functionalized into a carboxylic group followed by decarboxylation. Compound **19** was confirmed by the IR spectrum which showed the disappearance of cyano group and the absorption band at 3265 cm^{-1} of NH. The ^{1}H-NMR spectrum showed a signal at 9.68 ppm for NH proton **(**Scheme 5**)**.

2-Amino-3-cyano pyridine derivative **1** was allowed to react with *p*-toluene sulphonylchloride in pyridine/acetic



SCHEME 4 Reactions of 2-amino-3-cyano pyridine derivative **1** with different active methylenes



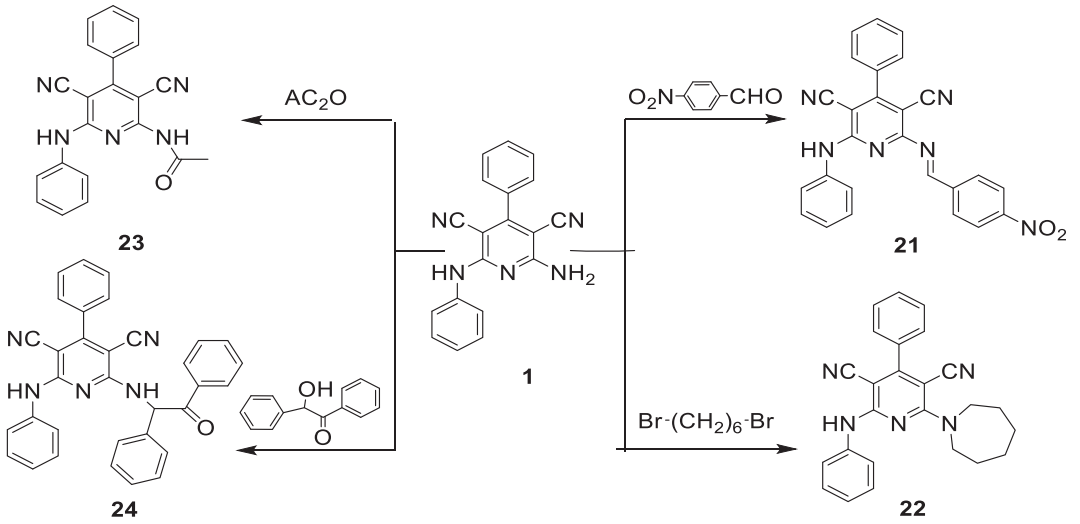
SCHEME 5 Reaction of **1** with chloro acetylchloride, sodium nitrite, and *p*-toluene sulphonylchloride

anhydride mixture to afford the corresponding N-(3, 5-dicyano-4-phenyl-6-(phenylamino) pyridin-2-yl)-4-methyl benzenesulfonamide derivative **20**. The structural feature of compound **20** was proved by the ^{1}H-NMR spectrum where it showed exchangeable broad signals at 10.92 and 9.87 corresponding to 2NH groups besides a signal at 2.26 ppm corresponding to methyl protons. The mass spectrum of **20** exhibited the molecular ion peak at m/z 465 ($M^{+\bullet}$, 6%) **(**Scheme 5**)**.

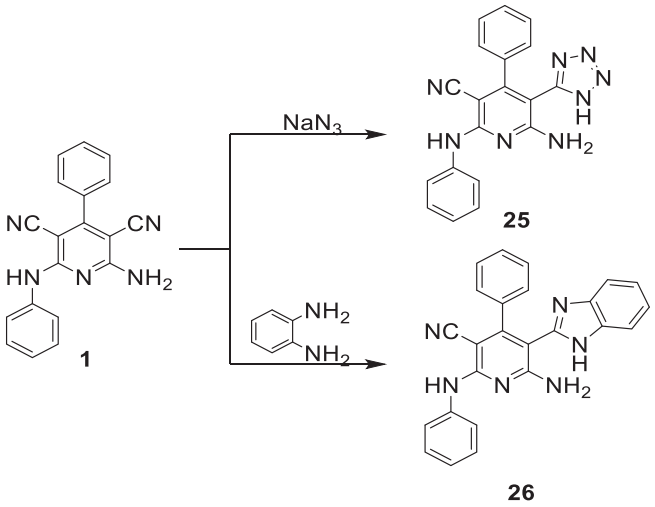
Furthermore, reaction of 2-amino-3-cyano pyridine derivative **1** with *p*-nitro benzaldehyde, 1,6-dibromohexane afforded 2-([4-nitrobenzylidene]amino)-4-phenyl-6-(phenylamino)pyridine-3,5-dicarbonitrile **21** and 2-(azepan-1-yl)-4-phenyl-6-(phenylamino)pyridine-3,5-dicarbonitrile **22**, respectively. The IR spectra of compounds **21** and **22** showed absorption bands at 3370 and 3294 cm^{-1} corresponding to NH groups in addition to two peaks at 2211 and 2216 cm^{-1} corresponding to two cyano groups. The mass spectra of compounds **21** and **22** exhibited the molecular ion peaks at m/z 444 ($M^{+\bullet}$, 3%) and 392 ($M^{+\bullet}-1$, 29%), respectively **(**Scheme 6**)**.

Reaction of 2-amino-3-cyano pyridine derivative **1** with acetic anhydride and benzoin yielded N-(3,5-dicyano-4-phenyl-6-(phenylamino) pyridin-2-yl) acetamide **23** and 2-([2-oxo-1,2-diphenylethyl]amino)-4-phenyl-6-(phenylamino) pyridine-3,5-dicarbonitrile **24**, respectively. The IR spectra of compounds **23** and **24** showed absorption bands at 1663 and 1677 cm^{-1}, respectively, corresponding to the amide carbonyl groups. The ^{1}H-NMR-spectra of compounds **23** and **24** lacked any **c**haracteristic bands for the amino groups **(**Scheme 6**)**.

Finally, nucleophilic addition on 2-amino-3-cyano pyridine derivative **1** utilizing sodium azide and *o*-phenylene diamine afforded 6-amino-4-phenyl-2-(phenylamino)-5-(1H-tetrazol-5-yl)nicotinonitrile **25** and 6-amino-5-(1H-benzo[d]imidazol-2-yl)-4-phenyl-2-(phenylamino)nicotinonitrile **26**, respectively. The mass spectra of **25** and **26** exhibited the molecular ion peaks at



SCHEME 6 Reactions of **1** with *p*-nitro benzaldehyde, dibromohexane, acetic anhydride, and benzoin



SCHEME 7 Nucleophilic addition of sodium azide and *o*-phenylene diamine on **1**

peak m/z 354 ($M^{+\bullet}$, 25%) and 402 ($M^{\cdot+}$, 20%), respectively **(**Scheme 7**)**.

2.1 | Anticancer studies

Most of the synthesized derivatives were tested for their anticancer action against two human anticancer cell lines hepatocellular carcinoma HePG-2 and mammary gland MCF-7 cell lines. Doxorubicin was used as a standard anticancer drug for comparison, where IC_{50} (μM): 1 to 10 (very strong). 11 to 20 (strong). 21 to 50 (moderate). 51 to 100 (weak) and above 100 (noncytotoxic) (Table 1).

The results showed in Table 1 that derivatives **5**, **6**, and **19** have very strong cytotoxicity, while derivatives **7** and **20** possess strong cytotoxicities; however, compounds **2**, **4**, **17**, **18**, and **21** exerted moderate cytotoxicities. Furthermore, derivatives **3**, **8**, **9**, **10**, and **23** showed weak cytotoxicities against HePG-2.

The derivatives **5**, **7**, and **19** have very strong cytotoxicities, while derivatives **6** and **20** possess strong cytotoxicities; however, derivatives **2**, **3**, **8**, **17**, **18**, and **21** exerted

TABLE 1 Antiproliferative activities of prepared derivatives against human tumor cells

	In Vitro Cytotoxicity IC_{50} (μM)	
Compounds	**HePG-2**	**MCF-7**
DOX	4.50 ± 0.3	4.17 ± 0.2
2	43.81 ± 2.6	28.58 ± 2.1
3	58.43 ± 3.5	49.11 ± 3.3
4	48.10 ± 3.1	55.60 ± 3.6
5	7.94 ± 0.7	8.49 ± 0.9
6	9.58 ± 0.9	11.23 ± 1.1
7	13.89 ± 1.1	9.72 ± 1.0
8	52.71 ± 3.5	34.15 ± 2.4
9	64.38 ± 3.7	57.42 ± 3.6
10	77.54 ± 4.2	81.83 ± 4.5
17	32.65 ± 2.4	44.26 ± 2.9
18	29.42 ± 2.2	39.87 ± 2.7
19	6.73 ± 0.5	5.36 ± 0.6
20	18.02 ± 1.4	17.10 ± 1.4
21	23.93 ± 1.8	20.04 ± 1.7
23	71.66 ± 3.9	68.85 ± 3.7

Note: IC_{50} (μM): 1-10 (very-strong), 11-20 (strong), and 21-50 (moderate).
51-100 (weak) and above-100 (non-cytotoxic). DOX, doxorubicin

moderate cytotoxicities. Furthermore, derivatives **4**, **9**, **10**, and **23** showed weak cytotoxicities against MCF-7.

Graphical correlation between tested compounds and their IC_{50} against Hep G-2 and MCF-7 is depicted in **(Figure 1**).

2.2 | Molecular docking studies

Molecular docking study of *o*-amino nitrile pyridine derivatives was performed by Molecular Operating Environment (MOE) 2014.09 [28–30]. serine/threonine-protein kinasechk1 (2YEX) was downloaded from protein data bank (http://www. rcsb. org/pdb) and prepared for docking process. The cocrystalline ligands were re-docked in the active pockets to validate the docking protocol. The structures of the target compounds were drawn in Chem Draw Ultra 14.0 (ChemOffice package), and the energy was minimized using the MMFF94x force field until a root mean-square deviation (RMSD) of atomic position gradient of (0.01) Kcal mol-1A-1. MMFF94x was reported as the efficient force field for minimizing ligand-protein complexes. The docking algorithm was done by MOE-DOCK default which uses a flexible, rigid technique for posing the molecule inside the cavity. All rotatable bonds of ligands are allowed to undergo free rotation to explore the conformational space inside the rigid receptor binding site.

The MOE 2014.09 package software was used to analyze all binding energies and docking poses between compounds **5** and **19** and the enzyme serine/threonine-protein kinasechk1(2Yex) to evaluate the affinity of compounds according to its binding energy with the enzyme. The total binding energy of compound **5** equals −6.11 E (kcal/mol) showed good affinity with the enzyme by forming two hydrogen donor interaction with Glu (91) and Asn (135) and one Pi-H interaction with Gly (16) amino acids of the target enzyme **(**Figures 2 and 3), and compound **19** equals −6.44 E (kcal/mol), showed good affinity with the enzyme by forming one hydrogen acceptor interaction with Cys (87) and one Pi-H interaction with Leu (15) amino acids of the target enzyme **(**Figures 4 and 5).

3 | EXPERIMENTAL

All melting points were measured on a Gallenkamp electric melting point apparatus uncorrected. The infrared spectra were recorded in potassium bromide disks on a Pye-Unicam SP-3-300 and Shimdazu FT IR 8101 PC infrared spectrophotometers. The ^{1}H-NMR spectrum was recorded at a Varian Mercury VX-300 MHz and ^{13}C-NMR (75 MHz), using TMS as internal standard in deuterated chloroform ($CDCl_3$) or deuterated dimethylsulphoxide (DMSO-d6). Chemical shifts are measured in ppm. The mass spectra were recorded on a Shimadzu GCMS-QP-1000EX mass spectrometer at 70 eV. Elemental analysis was carried out at the Micro analytical center of Ain Shams University. All the reactions and the purity of the new compounds were followed and checked by TLC.

3.1 | 2-Amino-4-phenyl-6-(phenylamino) pyridine-3,5-dicarbonitrile (1)

Fusion of benzaldehyde (0.01 mol, 1.06 mL), malononitrile (0.02 mol, 1.32 mL), and aniline (0.01 mol, 0.93 mL) in sand bath for 3 hours at 160°C to 200°C. After cooling, the product was recrystallized from ethanol to give **1**. Yield (90%); yellow powder; mp. 250°C to 252°C. Anal. calcd,: $C_{19}H_{13}N_5$

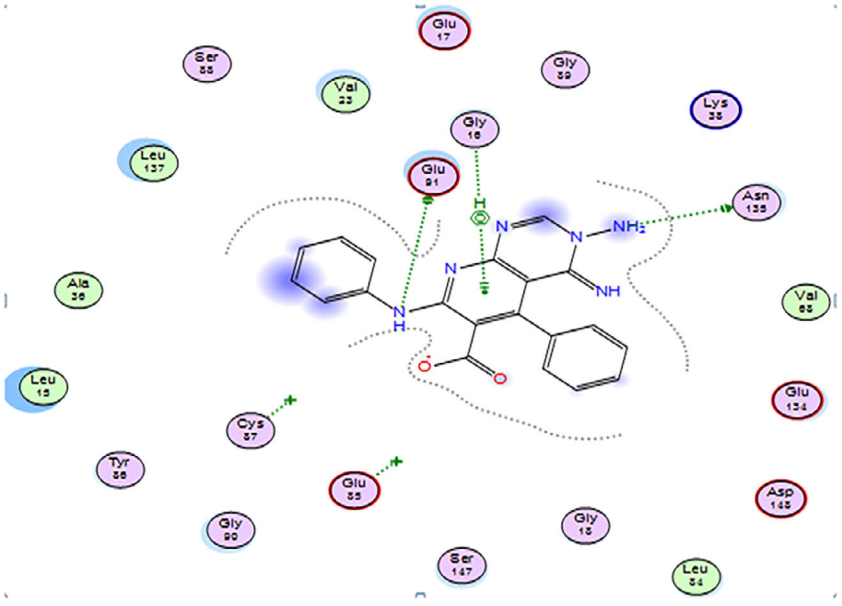


FIGURE 2 Two-dimensional representations for the interactions between compound **5** and enzyme pocket amino acids

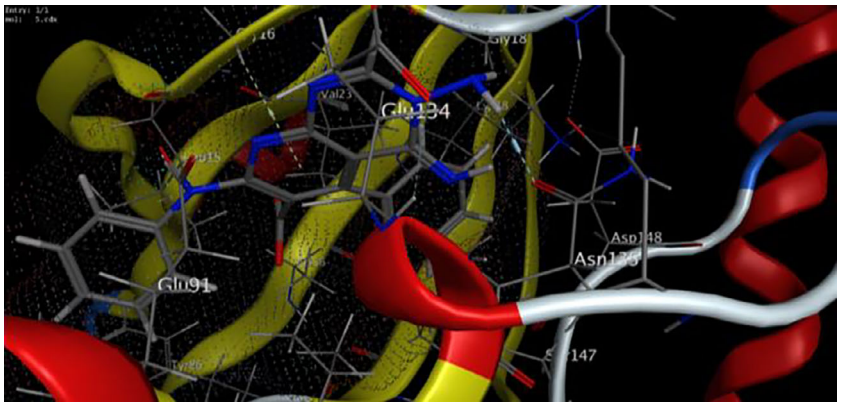
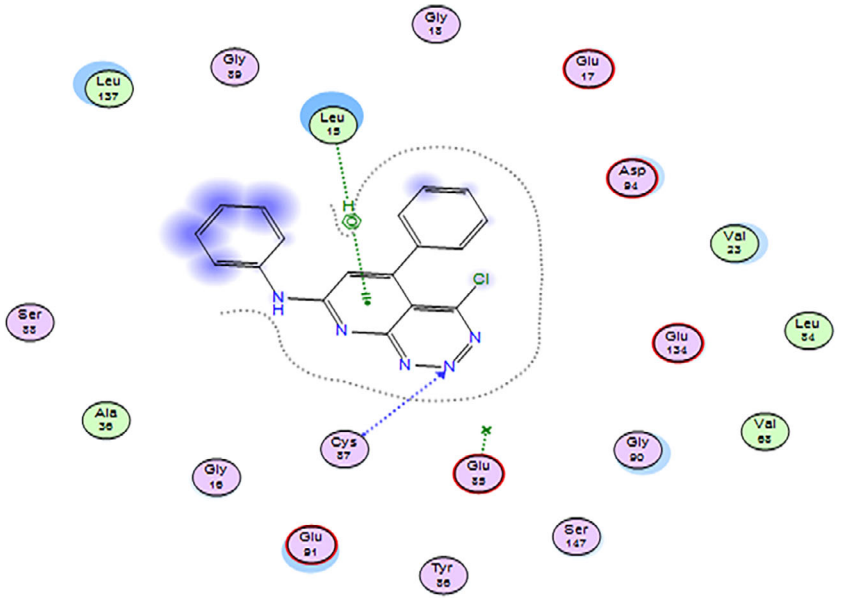


FIGURE 3 Three-dimensional representations for the interactions between compound **5** and enzyme pocket amino acids



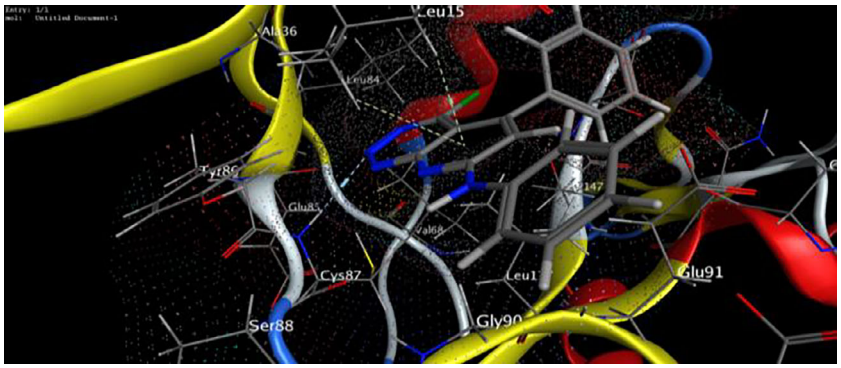


FIGURE 5 Three-dimensional representations for the interactions between compound **19** and enzyme pocket amino acids

(311.1): C, 73.30; H, 4.21; N, 22.49. Found: C, 73.35; H, 4.14; N, 22.51. FT-IR (KBr) (cm^{-1}): 3314, 3225 (NH_2), 3055 (NH), 2208 (CN), 1630 (C═N). ^{13}C-NMR (DMSO-d_6), δ ppm, 165.3, 161.2, 155.6, 138.0, 136.3, 129.7 (2), 129.4 (3), 127.3 (2), 117.8 (2), 122.5, 113.4 (2), 87.7 (2). ^{1}H-NMR (DMSO-d_6): δ_H (ppm): 9.10 (br.s., 1H, NH, D_2O exchangeable), 7.64 (br.s., 2H, NH_2, D_2O exchangeable), 7.63 to 7.05 (m, 10H, ArH). MS, m/z (%): 310 ($M^{+\cdot}$−1, 100%), 207 (20%), 77(10%).

3.2 | 4-Imino-5-phenyl-7-(phenylamino)-3,4-dihydropyrido[2,3-d]pyrimidine-6-carbonitrile (2)

A mixture of pyridine derivative **1** (0.01 mol, 3.11 g) and formamide (20 mL) was heated under refluxed for 3 hours. The solid that deposited after distilling the excess solvent was collected, washed, dried, and

recrystallized from petroleum ether 80°C to 100°C to give **2**. Yield (45%), mp > 300°C. Anal. calcd. for $C_{20}H_{14}N_6$ (338): C, 70.99; H, 4.17; N, 24.84. Found: C, 71.24; H, 4.56; N, 24.20. FT-IR (KBr) (cm^{-1}): 3310, 3186 (NH_2, NH), 2208 (CN), 1631 (C═N), 1602 (C═C). ^{13}C-NMR (DMSO-d_6), δ ppm, 157.3, 157.0, 152.6, 152.2, 151.0, 136.3, 133.0, 129.7 (2), 129.4 (3), 127.3 (2), 117.8 (2), 122.5, 113.4, 105.2, 87.7. ^{1}H-NMR (DMSO-d_6): δ_H (ppm): 10.10 (br.s., 1H, NH, D_2O exchangeable), 8.41(s, 1H, N═CH-N), 7.01 (br.s., 2H, NH_2, D_2O exchangeable), 7.75 to 7.02 (m, 10H, ArH). MS, m/z (%): 338 ($M^{+\bullet}$, 12%), 268.85(15%), 233.2 (61.7%), 231.54 (22%), 44.16 (100%).

3.3 | 4-Oxo-5-phenyl-7-(phenylamino)-3,4-dihydropyrido[2,3-d]pyrimidine-6-carbonitrile (3)

A mixture of pyridine derivative **1** (0.01 mol, 3.11 g) and formic acid (20 mL) was heated under reflux for 6 hours. The precipitate was filtered off after cooling, and formic acid was evaporated, washed, dried, and then recrystallized from benzene to give **3**. Yield (20%), mp 120°C to 122°C. Anal. calcd. for $C_{20}H_{13}N_5O$ (339): C, 70.79; H, 3.86; N, 20.64. Found: C, 70.37; H, 3.28; N, 20.99. FT-IR (KBr) (cm^{-1}): 3322, 3205 (2NH), 2215 (CN), 1676 (C═O), 1635 (C═N), 1606 (C═C). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 12.18 (br.s., 1H, NH, D_2O exchangeable), 9.44 (br.s., 1H, NH, D_2O exchangeable), 8.94 (s, 1H, CH), 8.27 to 7.12 (m, 10H, Ar-H).

3.4 | Ethyl-N-(3-carbamoyl-5-cyano-4-phenyl-6-(phenylamino)pyridin-2-yl) formimidate (4)

A mixture of pyridine derivative **1** (0.01 mol, 3.11 g) in (10 mL) triethyl orthoformate was heated under reflux for 2 hours. The solid that deposited after concentration of the reaction mixture was collected and recrystallized from benzene to give **4**. Yield (30%), mp 60°C to 62°C. Anal. calcd. for $C_{22}H_{19}N_5O_2$ (385): C, 68.56; H, 4.97; N, 18.17. Found: C, 68.17; H, 4.49; N, 18.66. FT-IR (KBr) (cm^{-1}): broad band centered at 3456 (NH_2, NH), 2225 (CN), 1670 (C═O), and 1600 (C═C). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 10.14 (br.s., 1H, NH, D_2O exchangeable), 8.77 (s, 1H, N═CH), 8.24 to 7.03 (m, 10H, Ar-H), 7.17 (br.s., 2H, NH_2, D_2O exchangeable), 3.42 (q, 2H, CH_2CH_3), 1.27 (t, 3H, CH_2CH_3). MS, m/z (%): 385 ($M^{+\bullet}$, 1%), 310 (12%), 295 (100%), 238 (15%), and 165 (4%).

3.5 | (3-Amino-4-imino-5-phenyl-7-(phenylamino)-3,4-dihydropyrido[2,3-d] pyrimidin-6-yl)(l1-oxidanyl)methanone (5)

To a solution of **4** (0.01 mol, 3.85 g) in (20 mL) ethanol, hydrazine hydrate (0.02 mol, 1 mL) was added, and the reaction mixture was heated under reflux for 30 minutes. A solid product was formed, filtered, and recrystallized from ethanol to give **5**. Yield (20%), mp 100°C to 102°C. Anal. calcd. for $C_{20}H_{15}N_6O_2$ (371): C, 64.68; H, 4.07; N, 22.63. Found: C, 65.08; H, 4.46; N, 22.24. FT-IR (KBr) (cm^{-1}): broad band centered at 3424 (OH), 3286, 3233, and 3146 (NH_2, NH), 1722 (C═O), and 1609 (C═C). ^{1}H-NMR (DMSO-d_6): δ_H (ppm): 12.56 (br.s., 1H, OH, D_2O exchangeable), 10.57 (br.s., 1H, NH, D_2O exchangeable), 10.10 (br.s., 1H, NH, D_2O exchangeable), 8.41(s, 1H, N═CH-N), 5.41 (br.s., 2H, NH_2, D_2O exchangeable), 7.75 to 7.02 (m, 10H, ArH). MS, m/z (%): 355 ($M^{+\bullet}$ -NH_2, 12%), 310 (100%), 272 (40%), 244 (11%), and 216 (22%).

3.6 | 4-Imino-3,5-diphenyl-7-(phenylamino)-2-thioxo-1,2,3,4-tetrahydropyrido [2,3-d]pyrimidine-6-carbonitrile (6)

An equimolar mixture of pyridine derivative **1** (0.01 mol, 3.11 g) and phenyl isothiocyanate (0.01 mol, 1.19 mL) in pyridine (30 mL) was heated under reflux for 5 hours. The resulting precipitate was formed after distilling the excess pyridine, dried, and recrystallized from benzene to give **6**. Yield (35%), mp 108°C to 110°C. Anal. calcd. for $C_{26}H_{18}N_6S$ (446): C, 69.94; H, 4.06; N, 18.82. Found: C, 69.56; H, 4.55; N, 18.43. FT-IR (KBr) (cm^{-1}): 3321, 3207 (NH), 2210 (CN), 1624 (C═N), and 1597 (C═C). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 12.18 (br.s., 1H, NH, D_2O exchangeable), 10.57 (br.s., 1H, NH, D_2O exchangeable), 9.77 (br.s., 1H, NH, D_2O exchangeable), and 7.55 to 7.08 (m, 15H, Ar-H). MS, m/z (%): 369 ($M^{+\bullet}$−ph, 7%), 264 (100%), 236(100%), 208(37%), and 235(27%).

3.7 | 5-Phenyl-7-(phenylamino)-2,4-dithioxo-1,2,3,4-tetrahydropyrido[2,3-d] pyrimidine-6-carbo nitrile (7)

A mixture of pyridine derivative **1** (0.01 mol, 3.11 g) and excess of carbon disulphide was added dropwise, and alcoholic sodium hydroxide (20 mL) was heated in water bath for 6 hours. The solid that deposited after distilling the excess solvent was collected and

recrystallized from benzene to give **7**. Yield (60%), mp 160°C to 162°C. Anal. calcd. for $C_{20}H_{13}N_5S_2$ (387): C, 62.00; H, 3.38; N, 18.07. Found: C, 62.42; H, 3.01; N, 18.58. FT-IR (KBr) (cm^{-1}): 3321, 3218, 3120 (NH), 2225 (CN), 1623 (C═N), 1585 (C═C). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 13.31 (br.s.,1H, NH, D_2O exchangeable), 10.24 (br.s.,1H, NH, D_2O exchangeable), 9.75 (br.s., 1H, NH, D_2O exchangeable), 7.55 to 7.08 (m, 10H, Ar-H). MS, m/z (%): 355 ($M^{+\bullet}$ -S, 16%), 264(60%), 236(100%), 207 (33%), and 180(21%).

3.8 | 2-((3-Cyano-8,9-dioxo-4-phenyl-5-thioxo-8,9-dihydro-5H-pyrido[3,2-e] thiazolo[3,2-a]pyrimi din-2-yl)(phenyl) amino)-2-oxoacetyl chloride (8)

An equimolar mixture of **7** (0.01 mol, 3.87 g) and oxalyl chloride (0.01 mol, 1.26 mL) in (30 mL) dry benzene was heated under reflux for 6 hours. Most of the solvent was distilled off and left to cool. The solid product that deposited was collected, washed, dried, and recrystallized from petroleum ether 100°C to 120°C to give **8**. Yield (40%), mp 120°C to 122°C. Anal. calcd. for $C_{24}H_{10}N_5O_4S_2Cl$ (531.5): C, 54.19; H, 1.89; N, 13.17.FT-IR (KBr) (cm^{-1}): 2226 (CN), 1773, 1750, 1727, 1690 (4 C═O), 1647 (C═N), and 1591 (C═C). ^{13}C-NMR (DMSO-d_6), δ ppm, 221.3, 178.2, 172.6, 166.2, 162.4158.7, 158.1, 157.8, 153.1, 138.6, 136.3, 129.7(2), 129.4(3), 128.9(2), 127.3 (2), 113.4, 110.7, and 87.7. ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 7.57 to 7.40 (m, 10H, Ar-H). MS, m/z (%): 282 (67%), 194 (42%), 136 (100%), 119 (27%), and 77 (50%).

3.9 | 5-Phenyl-7-(phenylamino)-2,4-dithioxo-1,2,3,4-tetrahydropyrido[2,3-d] pyrimidine-6-carboxylic acid (9)

A solution of **7** (0.01 mol, 3.87 g) in acetic acid (20 mL) was heated under reflux for 3 hours. The precipitated solid product formed after cooling was collected by filtration, washed, dried, and recrystallized from acetic acid to give **9**. Yield (70%), mp 133°C to 135°C. Anal. calcd. for $C_{20}H_{14}N_4O_2S_2$ (406): C, 59.10; H, 3.47; N, 13.78. Found: C, 59.49; H, 3.05; N, 13.39. FT-IR (KBr) (cm^{-1}): 3449 (OH), 3216, 3172, 3126 (3NH), 1716 (C═O), 1649 (C═N). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 14.34 (br.s.,1H, NH, D_2O exchangeable), 13.31 (br.s.,1H, NH, D_2O exchangeable), 12.74 (br.s.,1H, OH, D_2O exchangeable), 10.51 (br.s., 1H, NH, D_2O exchangeable), 7.75 to 7.08 (m, 10H, Ar-H). MS, m/z (%): 406 ($M^{+\bullet}$, 3%), 369 (100%), 271 (19%), 207 (13%), and 127 (88%).

3.10 | 4-Oxo-2,5-diphenyl-7-(phenylamino)-4H-pyrido [2,3-d] [1,3] oxazine-6-carbonitrile (10)

A solution of pyridine derivative **1** (0.01 mol, 3.11 g) in (20 mL) benzoyl chloride was stirred and heated under reflux for 3 hours. The solid product that separated out after cooling, washed, dried, and recrystallized from petroleum 80°C to 100°C to give **10**. Yield (40%), mp 138°C to 140°C. Anal. calcd. for $C_{26}H_{16}N_4O_2$ (416): C, 74.99; H, 3.90; N, 13.45. Found: C, 74.42; H, 4.23; N, 13.04. FT-IR (KBr) (cm^{-1}): 3341 (NH), 2225(CN), 1744 (C═O), and 1655 (C═N). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 10.21 (br.s., 1H, NH, D_2O exchangeable), 7.94 to 7.06 (m, 15H, Ar-H). MS, m/z (%): 264 ($M^{+\bullet}$ −2 ph, 68%), 236 (100%), 208 (21%), 180 (15%), and 165 (12%).

3.11 | 4-Oxo-2,5-diphenyl-7-(phenylamino)-3,4-dihydropyrido[2,3-d] pyrimidine-6-carbonitrile (11)

A solution of **10** (0.01 mol, 4.16 g) in formamide (15 mL) was heated under reflux for 4 hours. Most of the solvent was distilled off and left to cool. The solid product that deposited was collected, washed, dried, and recrystallized from ethanol to give **11**. Yield (35%), mp 172°C to 174°C. Anal. calcd. for $C_{26}H_{17}N_5O$ (415): C, 75.17; H, 4.12; N, 16.86. Found: C, 75.59; H, 4.53; N, 16.35. FT-IR (KBr) (cm^{-1}): 3305 (2NH), 2220 (CN), 1667 (C═O). MS, m/z (%): 415 ($M^{+\bullet}$, 29%), 338 (74%), 316 (24%), 281 (23%), and 207 (22%).

3.12 | 3-Amino-4-oxo-2,5-diphenyl-7-(phenylamino)-3,4-dihydropyrido [2,3-d] pyrimidine-6-carbonitrile (12)

A solution of **10** (0.01 mol, 4.16 g) in butanol (20 mL) was heated under reflux with hydrazine hydrate (0.02 mol, 1 mL) for 6 hours. The reaction mixture was allowed to cool, and the precipitated product was filtered, dried, and recrystallized from ethanol to give **12**. Yield (20%), mp 80°C to 82°C. Anal. calcd. for $C_{26}H_{18}N_6O$ (430): C, 72.55; H, 4.21; N, 19.52. Found: C, 71.93; H, 4.60; N, 19.75. FT-IR (KBr) (cm^{-1}): broad band centered at 3415 (NH_2), 3178 (NH), 2228 (CN), 1673(C═O). MS,

m/z (%): 429 ($M^{+\bullet}$ −1, 7%), 338 (100%), 324 (18%), 316 (40%), and 299 (12%).

3.13 | 1,6-Diphenyl-3-(phenylamino) benzo[4,5]imidazo[1,2-c]pyrido[3,2-e] pyrimidine-2-carboxamide (13)

A mixture of compound **10** (0.01 mol, 4.16 g) and *o*-phenylenediamine (0.01 mol, 1.08 g) was fused at 120°C for 20 minutes. A white solid was obtained, then washed and recrystallized from benzene to give **13**. Yield (25%), mp 98°C to 100°C. Anal. calcd. for $C_{32}H_{22}N_6O$ (506): C, 75.87; H, 4.38; N, 16.59. Found: C, 76.42; H, 3.96; N, 16.46.FT-IR (KBr) (cm^{-1}): broad band centered at 3430, 3313 (NH_2), 3172 (NH), 1685 (C═O), 1653 (C═N), and 1621 (C═C). ^{13}C-NMR (DMSO-d_6), δ ppm, 166.3, 165.2, 164.6, 156.2, 151.4, 149.7, 148.1, 143.8, 141.1, 138.6, 135.3, 131.1, 129.7(2), 129.4(5), 127.9 (2), 127.7 (2), 123.0 (2), 122.5, 120.2, 118.4, 117.5 (2), 112.4, and 112.0. ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 9.17 (br.s., 1H, NH, D_2O exchangeable), 7.94 to 6.33 (m, 19H, Ar-H), 3.41 (br.s., 2H, NH_2, D_2O exchangeable). MS, m/z (%): 508 ($M^{+\bullet}$ +2, 6%), 295 (14%), 223 (90%), 194 (46%), and 179 (100%).

3.14 | 2,4-Diamino-5-phenyl-7-(phenylamino)-1,8-naphthyridine-3,6-dicarbonitrile (14)

A mixture of pyridine derivative **1** (0.01 mol, 3.11 g) and malononitrile (0.01 mol, 0.66 g) in ethanol (20 mL) was heated under reflux in the presence of few drops of triethylamine. For 48 hours, the reaction mixture was concentrated, allowed to cool, and then poured onto ice/water. The formed precipitate was filtered, dried, and recrystallized from petroleum ether 60°C to 80°C to give **14**. Yield (20%), mp 206°C to 208°C. Anal. calcd. for $C_{22}H_{15}N_7$ (377): C, 70.01; H, 4.01; N, 25.98. Found: C, 69.78; H, 4.62; N, 25.60. FT-IR (KBr) (cm^{-1}): band centered at 3465, 3323 (NH_2), 3220 (NH), 2226 (CN), 1623 (C═N), and 1585 (C═C). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 9.13 (br.s., 1H, NH, D_2O exchangeable), 7.08 to 7.95 (m, 10H, Ar-H), 4.47 (br.s., 2H, NH_2, D_2O exchangeable).

3.15 | Ethyl-4-amino-6-cyano-2-methyl-5-phenyl-7-(phenylamino)1,8naphthyridine −3-carboxylate (15)

A mixture of pyridine derivative **1** (0.01 mol, 3.11 g) and ethyl acetoacetate (10 mL) was heated under reflux for 6 hours. The reaction mixture was concentrated, allowed to cool, and then poured onto ice/water. The formed precipitate was filtered, dried, and recrystallized from petroleum ether 60°C to 80°C to give **15**. A solid formed was washed by ethanol. Yield (30%), mp > 300°C. Anal. calcd. for $C_{25}H_{21}N_5O_2$ (423): C, 70.91; H, 5.00; N, 16.54. Found: C, 70.44; H, 4.52; N, 16.09. FT-IR (KBr) (cm^{-1}): band centered at 3417 (NH_2, NH), 2212 (CN), 1719 (C═O), 1632 (C═N), 1591 (C═C). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 9.10 (s, 1H, NH, D_2O exchangeable), 7.05 to 7.65 (m, 10, Ar-H, br.s., 2H, NH_2, D_2O exchangeable), 4.39 to 4.44 (q, 2H, $\underline{CH_2}CH_3$), 2.27 (s, 3H, CH_3), 1.31 to 1.34 (t, 3H, $CH_2\underline{CH_3}$). MS, m/z (%): 389 ($M^{+\bullet}$-C_2H_5, 4%), 341 (28%), 264 (71%), 198 (87%), 184 (40%), and 77 (100%).

3.16 | 4-Imino-2-oxo-5-phenyl-7-(phenylamino)-1,2,3,4-tetrahydro-1,8-naphthyridine-3,6-dicarbonitrile (16)

A mixture of pyridine derivative **1** (0.01 mol, 3.11 g) and ethyl cyanoacetate (10 mL) was heated under reflux for 6 hours. The reaction mixture was concentrated, allowed to cool, and then poured onto ice/water. The formed precipitate was filtered, dried, and recrystallized from ethanol to give **16**. Yield (20%), mp 138°C to 144°C. Anal. calcd. for $C_{22}H_{14}N_6O$ (378): C, 69.83; H, 3.73; N, 22.21. Found: C, 69.51; H, 4.02; N, 22.53. FT-IR (KBr) (cm^{-1}): broad band centered at 3347, 3216 (3NH), 2207 (CN), 1690 (C═O), and 1632 (C═N). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 10.21 (br.s., 1H, NH, D_2O exchangeable), 9.10 (br. s., 1H, NH, D_2O exchangeable), 8.81 (br.s., 1H, NH, D_2O exchangeable), 7.70 to 7.03 (m, 10H, Ar-H), 3.72 (s, 1H, CH). MS, m/z (%): 379 ($M^{+\bullet}$ + 1, 4%), 342 (61%), 310 (100%), 281 (20%), and 207 (22%).

3.17 | Ethyl-3-amino-5-cyano-4-phenyl-6-(phenylamino)-1H-pyrrolo [2,3-b] pyridine-2-carboxylate (17)

A solution of pyridine derivative **1** (0.01 mol, 3.11 g) in pyridine (20 mL) was heated under reflux with ethyl chloroacetate (0.01 mol, 1.22 mL) for 6 hours. The reaction mixture was poured on ice/water. The precipitated solid was collected, washed, and recrystallized from benzene to give **17**. Yield (60%), mp 210°C to 212°C. Anal. calcd. for $C_{23}H_{19}N_5O_2$ (397): C, 69.51; H, 4.82; N, 17.62. Found: C, 69.99; H, 5.25; N, 18.00. FT-IR (KBr) (cm^{-1}): band centered at 3463, 3322 (NH_2), 3218 (NH), 2226 (CN), 1730 (C═O), 1624 (C═N), and 1586 (C═C). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 9.10 (br.s, 1H, NH, D_2O exchangeable), 7.93 (br.s, 1H, NH, D_2O exchangeable),

7.55 to 7.47 (m, 12H, Ar-H), 7.34 (br.s, 1H, NH_2, D_2O exchangeable), 4.45 to 4.39 (q, 2H, $\underline{CH_2}CH_3$), 1.35 to 1.31 (t, 3H, $CH_2\underline{CH_3}$). MS, m/z (%):397 ($M^{+\bullet}$, 6%), 369.1 (7%), 264 (100%), 208 (21%), and 77 (11%).

3.18 | 2-Chloro-N-(4-phenyl-6-(phenylamino)pyridin-2-yl) acetamide (18)

A mixture of pyridine derivative **1** (0.01 mol, 3.11 g) and chloro acetyl chloride (0.01 mol, 1.36 g) was refluxed for 3 hours with stirring. The solid that deposited and recrystallized from petroleum ether 60°C to 80°C. Yield (40%), mp 118°C to 120°C. Anal. calcd. for $C_{19}H_{16}ClN_3O$ (337.81): C, 67.56; H, 4.77; N, 12.44. Found: C, 67.09; H, 4.32; N, 12.95.FT-IR (KBr) 3267, 3206 (NH), 1673 (C═O). (cm^{-1}): ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 10.29 (br.s, 1H, NH, D_2O exchangeable), 9.10 (br.s, 1H, NH, D_2O exchangeable), 7.61 to 7.09 (m, 12H, Ar-H), and 4.27 (s, 2H, $\underline{CH_2}Cl$).

3.19 | 4-Chloro-N, 5-diphenylpyrido[2, 3-d][1,2,3]triazin-7-amine (19)

A solution of pyridine derivative **1** (0.01 mol, 3.11 g) in hydrochloric acid (10 mL) was cooled to 0°C in an ice bath, and an aqueous solution of sodium nitrite (0.8 g) in 10 mL water was added simultaneously with stirring. The precipitated solid formed was collected by filtration, washed, and recrystallized from petroleum 60°C to 80°C to give **19**. Yield (70%), mp 100°C to 102°C. Anal. calcd. for $C_{18}H_{12}ClN_5$ (333.5): C, 64.77; H, 3.62; N, 20.98. Found: C, 64.35; H, 3.98; N, 20.54. FT-IR (KBr) (cm^{-1}): broad band centered at 3265 (NH), 1630 (C═N). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 9.68 (br.s, 1H, NH, D_2O exchangeable), 7.74 to 7.04 (m, 11H, Ar-H).

3.20 | N-(3,5-dicyano-4-phenyl-6-(phenylamino)pyridin-2-yl)-4-methylbenzene sulfonamide (20)

A mixture of pyridine derivative **1** (0.01 mol, 3.11 g) and *p*-toluene sulphonylchloride (0.01 mol, 1.89 g) in a mixture of pyridine and acetic anhydride (4:20 mL), respectively, was heated under reflux for 6 h. The reaction mixture was concentrated, filtered off, dried, and recrystallized from benzene to give **20**. Yield (20%), mp 190°C to 192°C. Anal. calcd. for $C_{26}H_{19}N_5O_2S$ (465.53): C, 67.08; H, 4.11; N, 15.04. Found: C, 67.46; H, 4.40; N, 14.65. FT-IR (KBr) (cm^{-1}): broad band centered at 3443 (NH), 2221(CN), 1631(C═N). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 10.92 (br.s., 1H, NH, D_2O exchangeable), 9.87 (br. s., 1H, NH, D_2O exchangeable), 7.61 to 6.99 (m, 14H, Ar-H), 2.26 (s, 3H, CH_3). MS, m/z (%):465 ($M^{+\bullet}$, 6%), 295 (29%), 247 (21%), 91 (70%), and 77 (15%).

3.21 | 2-([4-Nitrobenzylidene]amino)-4-phenyl-6-(phenylamino)pyridine-3,5-dicarbonitrile (21)

To a solution of pyridine derivative **1** (0.01 mol, 3.11 g) in (10 mL) butanol, *p*-nitro benzaldehyde (0.01 mol, 1.5 g) was added, and the reaction mixture was heated under reflux for 18 hours. The reaction mixture was concentrated and left to cool. The solid product that separated out was filtered off, dried, and recrystallized from benzene: ethanol to give **21**. Yield (30%), mp 180°C to 182°C. Anal. calcd. for $C_{26}H_{16}N_6O_2$ (444): C, 70.26; H, 3.63; N, 18.91. Found: C, 70.72; H, 3.10; N, 19.32. FT-IR (KBr) (cm^{-1}): 3370 (NH), 2211(CN), 1605 (C═C). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 9.82 (br.s., 1H, NH, D_2O exchangeable), 8.17 to 6.44 (m, 15H, 14Ar-H and 1H, N═CH). MS, m/z (%):444 ($M^{+\bullet}$, 3%), 290 (100%), 233 (%), 207 (%), and 94 (%).

3.22 | 2-(Azepan-1-yl)-4-phenyl-6-(phenylamino)pyridine-3,5-dicarbonitrile (22)

To a solution pyridine derivative **1** (0.01 mol, 3.11 g) in (10 mL) butanol, dibromo hexane (0.01 mol, 2.41 g) was added, and the reaction mixture was heated under reflux for 20 hours. The reaction mixture was concentrated and left to cool. The solid product that separated out was filtered off, dried, and recrystallized from petroleum ether 80°C to 100°C to give **22**. Yield (40%), mp 112°C to 114°C. Anal. calcd. for $C_{25}H_{23}N_5$ (393): C, 76.31; H, 5.89; N, 17.80. Found: C, 75.82; H, 6.14; N, 18.04. FT-IR (KBr) (cm^{-1}): broad band centered at 3294 (NH), 2216 (CN). ^{13}C-NMR (DMSO-d_6), δ ppm, 167.3, 161.2, 155.6, 138.0, 136.3, 129.7 (2), 129.4 (3), 127.3 (2), 117.8 (2), 122.5, 113.4 (2), 87.7 (2), 54.5(2), 29.1(2), 26.3(2). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 10.21 (br.s., 1H, NH, D_2O exchangeable), 7.70 to 7.03 (m, 10H, Ar-H), 3.45 to 1.51 (m, 12H, hexane- H). MS, m/z (%):392 ($M^{+\bullet}$−1, 29%), 299 (64.5%), 207 (14%), 93 (4%), and 77 (26%).

3.23 | N-(3,5-dicyano-4-phenyl-6-(phenylamino)pyridin-2-yl) acetamide (23)

A mixture of pyridine derivative **1** (0.01 mol, 3.11 g) and freshly distilled acetic anhydride (10 mL) was heated

under reflux for 3 hours. The solid that deposited after distilling the excess solvent and poured on ice/water was collected and recrystallized from benzene to give **23**. Yield (60%), mp 100°C to 102°C. FT-IR (KBr) (cm^{-1}): broad band centered at 3295, 3260 (NH), 2211(CN), 1663 (C═O), 1622 (C═N). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 9.87 (br.s, 2H, 2NH, D_2O exchangeable), 7.55 to 6.97 (m, 10H, Ar-H), 2.01 (s, 3H, $COCH_3$).

3.24 | 2-([2-Oxo-1,2-diphenylethyl] amino)-4-phenyl-6-(phenylamino)pyridine-3,5-dicarbonitrile (24)

A mixture of pyridine derivative **1** (0.01 mol, 3.11 g) and benzoin (0.01 mol, 2.12 g) in dry benzene (20 mL) was heated under reflux for 15 hours. The solid that deposited after concentration of the reaction mixture was collected and recrystallized from petroleum ether 60°C to 80°C to give **24**. Yield (40%), mp 78°C to 80°C. Anal. calcd. for $C_{33}H_{22}N_5O$ (505): C, 78.40; H, 4.59; N, 13.85. Found: C, 78.82; H, 5.10; N, 13.27. FT-IR (KBr) (cm^{-1}): 3316, 3186 (NH), 2213(CN), 1677(C═O), 1659 (C═N), 1593(C═C). MS, m/z (%):506 ($M^{+\bullet}$ +1, 43%), 505 ($M^{\bullet}$+,13%), 310 (100%), 207 (20%), 93 (4%), and 77 (52%).

3.25 | 6-Amino-4-phenyl-2-(phenylamino)-5-(1H-tetrazol-5-yl) nicotinonitrile (25)

A solution of pyridine derivative **1** (0.01 mol, 3.11 g) in DMF (10 mL), sodium azide (0.01 mol, 0.65 g), and ammonium chloride (0.01 mol, 0.53 g) was added. The reaction mixture was heated under reflux for 7 hours and let to cool, and DMF was evaporated. The precipitated solid formed recrystallized from petroleum 60°C to 80°C to give **25**. Yield (40%), mp 120°C to 122°C. Anal. calcd. for $C_{19}H_{14}N_8$ (354): C, 64.40; H, 3.98; N, 31.62. Found: C, 64.02; H, 4.56; N, 31.42. FT-IR (KBr) (cm^{-1}): 3463 to 3319 (NH_2, NH), 2226 (CN), 1624 (C═N), 1586 (C═C). MS, m/z (%): 354 ($M^{+\bullet}$, 25%), 310 (100%), 207 (22%), 93 (4%), and 77 (62%).

3.26 | 6-Amino-5-(1H-benzo[d]imidazol-2-yl)-4-phenyl(phenylamino) nicotinonitrile (26)

A mixture of pyridine derivative **1** (0.01 mol, 3.11 g) and *o*-phenylenediamine (0.01 mol, 3.11 g) was fused for 20 minutes. The formed solid was crystallized from Petroleum ether 60°C to 80°C to give **26**. Yield (20%), mp 84°C to 86°C. Anal. calcd. for $C_{25}H_{18}N_6$ (402): C, 74.61; H, 4.51; N, 20.88. Found: C, 74.30; H, 4.66; N, 21.04. FT-IR (KBr) (cm^{-1}): 3385, 3363 (NH_2), 3289, 3193 (2NH), 2207 (CN), 1632 (C═N), 1591 (C═C). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 11.79 (br.s., 1H, NH, D_2O exchangeable), 10.18 (br. s., 1H, NH, D_2O exchangeable), 7.54 to 6.33 (m, 14H, Ar-H), 4.95 (br.s., 2H, NH_2). MS, m/z (%): 402 ($M^{\bullet}$+, 20%), 269 (17%), 213 (24%), 157 (96%), and 77 (4%).

4 | CONCLUSION

2-Amino-3-cyano pyridine derivative was utilized as a scaffold to synthesize different heterocyclic systems. In addition, the molecular docking study of those 2-amino-3-cyanopyridine derivatives was performed by the MOE 2014.09. Finally, in vitro growth inhibitory activity of the newly synthesized compounds was investigated against two carcinoma cell lines, a mammary gland carcinome cell line (MCF-7) and a human hepatocellular carcinoma cell line (HePG-2) using doxorubicin as an anticancer standard drug under the same condition. Some of the tested showed remarkable activities as antitumor agents.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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How to cite this article: Mahmoud NFH, El-Sewedy A. Facile synthesis of novel heterocyclic compounds based on pyridine moiety with pharmaceutical activities. *J Heterocycl Chem*. 2019; 1–14. https://doi.org/10.1002/jhet.3881