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Synthesis and in vitro evaluation of novel tetralin-pyrazolo[3,4-*b*]pyridine hybrids as potential anticancer agents

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Abstract

New hybrids of tetralin-pyrazolo[3,4-*b*]pyridine were synthesized in good yields. The structures of newly synthesized compounds were confirmed by IR, NMR, MS, and elemental analyses. Some of the new compounds were in vitro evaluated as antiproliferative candidates against two human cancer cell lines (HCT116 and MCF-7). Most of the examined derivatives showed promising anticancer activity.

1 | INTRODUCTION

Cancer is a medical term used to identify an abnormal growth of cells that *underwent uncontrolled* cell *division* to form a mass of *cancer cells*. Cancer cells are capable to invade and destroy nearby normal *tissues*. They can travel to other areas of the body through either the blood stream or the lymph system. The burden of cancer is increasing across the world[1] and it is considered as the leading cause of mortality worldwide and may affect any individual at any age, even fetuses, but the risk increases with age.[2,3] The World Health Organization (WHO) estimates around 9.6 million deaths in 2018.[4] The increasing incidence rate and uncontrolled mortality of cancer have alarmed researchers worldwide to search for better cancer chemotherapeutics. The major challenge for medicinal chemistry researchers is to design new anticancer agents with high efficacy, fewer side effects,[5] and to avoid cancer resistance to drugs which makes them ineffective.[6] The optimum goal would be achieved when scientists bring oral pills to markets that are able to treat cancer with minimum toxicity. Therefore, more novel researches are needed for further improvement in cancer therapies.

The chemistry and biological study of heterocyclic compounds especially those containing nitrogen atom has attracted much attention in the last decades, especially in medicinal chemistry. Pyridine and its derivatives represent the most important class of heterocyclic containing nitrogen. Pyridine scaffold is found in many natural products as vitamin B12 (niacin and pyridoxal) and alkaloids (nicotine), and it plays an important role in

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synthetic organic chemistry due to its therapeutic and pharmacological properties.[7–10]

In this respect, cyanopyridines attracted attention as many of their derivatives were found to have a wide range of pharmacological activities. 3-Cyanopyridines with different alkyl or aryl/heteroaryl groups were found to possess anticancer activities.[11] Also, literature survey revealed that some 2-pyridone derivatives exhibited *potent anticancer* activity via Pim *kinase* inhibition.[12–15] It was also reported that fused cyanopyridines have a wide range of pharmacological activities and revealed potent PIM-1 inhibitions.[16,17]

Moreover, pyrazolo[3,4-*b*]pyridine system is considered as the main component in many medicinally important compounds. Some pyrazolo[3,4-*b*]pyridine derivatives are currently used as drugs like etazolate **I** and tracazolate **II**[18,19] (Figure 1).

It has been reported that fused heterocyclic compounds containing pyrazolopyridine ring system are associated with several biological and medicinal activities.[20–23] They have various chemotherapeutic potentials as protein kinase inhibitors,[24] hypotensive,[25] antiallergic,[26] HIV reverse transcriptase inhibitors,[27] antioxidant,[28] antimicrobial,[29,30] antiviral,[31] fungicide,[32] antiinflammatory,[33] potent antitumor agents,[34–36] inhibitors of pan-Pim protein kinases,[37] and inhibitors of glycogen synthase kinase-3 (GSK-3)[38] as a treatment of Alzheimer's disease.[39] In addition, some arylazo heterocycles incorporating pyrazolopyridine moiety can be utilized as disperse dyes.[40]

Furthermore, the 4-thiazolidinone ring system is a core structure in medicinal chemistry, owing to its broad spectrum of biological activities such as anticancer,[41] antitubercular,[42] anti-inflammatory,[43–45] antibacterial,[46] antimycobacterial,[47] anti-HIV,[48] anticonvulsant,[49] antiprotozoan,[50] antihistaminic,[51] and as analgesic agents.[45,52]

On the other side, tetrahydronaphthalene derivatives, especially those liked to heterocyclic systems, have been of increasing interest in the field of drug discovery, since many of these compounds represent useful applications as anticancer,[53–56] antiviral,[57,58] antioxidant,[59,60] anti-inflammatory, and as analgesic agents.[61]

According to these findings, and based on the strategy of molecular hybridization,[62] we report herein on the synthesis of new heterocyclic derivatives bearing 5,6,7,8-tetrahydronaphthalene moiety aiming at producing more effective and less toxic antitumor agents.

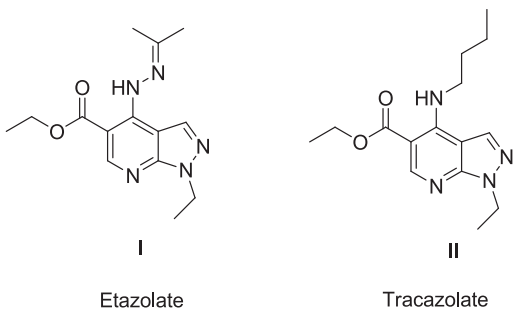


FIGURE 1 Drugs based on functionalized pyrazolo[3,4-*b*] pyridines

2 | RESULTS AND DISCUSSION

The stating compounds **3** and **5** were synthesized in good yields, starting from 2-acetyltetralin **1**,[63] as outlined in (Scheme 1). Thus, 2-oxo-4-(4-fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1,2-dihydropyridine-3-carbonitrile (**2**) was obtained in a high yield through a four-components reaction of **1** with 4-fluorobenzaldehyde, ethyl cyanoacetate, and excess ammonium acetate in *n*-butanol at reflux according to reported procedures.[64,65]

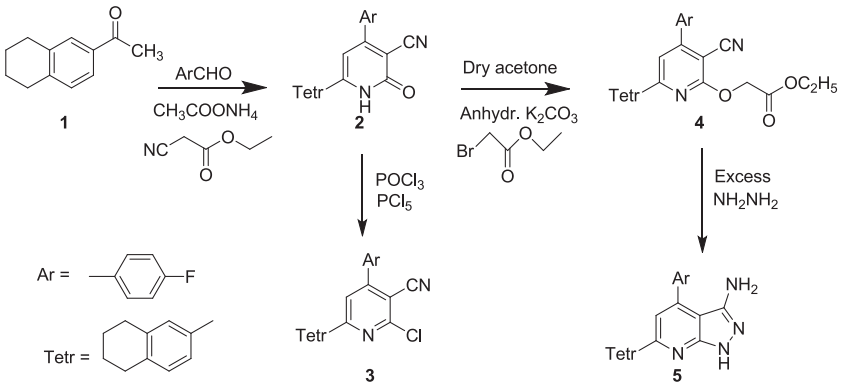
The synthetic utility of cyanopyridone **2** as a precursor for novel pyridine and pyrazolopyridine derivatives has been investigated.

Thus, chlorination of **2** by gentle heating with phosphorous oxychloride/phosphorous pentachloride mixture afforded the new 2-chloro-4-(4-fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)nicotinonitrile (**3**) in good yield. The structure of **3** was confirmed by the absence of a characteristic band of CO group in its IR spectrum. Also, its mass spectrum showed the molecular ion peaks at m/z 362 and 364 (3:1) due to the two chlorine isotopes (Scheme 1).

Alkylation of pyridin-3-carbonitrile **2** with ethyl bromoacetate in acetone in the presence of anhydrous potassium carbonate afforded the corresponding ester derivative **4.**[65]

When the ester derivative **4** reacted with excess hydrazine hydrate (98%) in ethanol at reflux for 12 h, the new desired 1*H*-pyrazolo[3,4-*b*]pyridin-3-amine **5** was obtained in good yield (Scheme 1). The structure of **5** was confirmed by elemental analyses as well as spectral data. Thus, the IR spectrum (KBr, ν cm^{-1}) revealed the absence of absorption band due to a cyano group. Moreover, it showed strong bands at 3425, 3369, and 3211 cm^{-1} due to NH_2 and NH, respectively. The ^{1}H-NMR spectrum of **5** showed the NH_2 and the NH protons as broad signals at δ 4.56 ppm and δ 12.18 ppm, respectively. Its mass spectrum showed a molecular ion peak at m/z, 358 (M^+, 58.70%), which agrees with its molecular formula $C_{22}H_{19}FN_4$.

The chlorine atom of compound **3** showed distinct activities toward different neucleophiles. Accordingly,

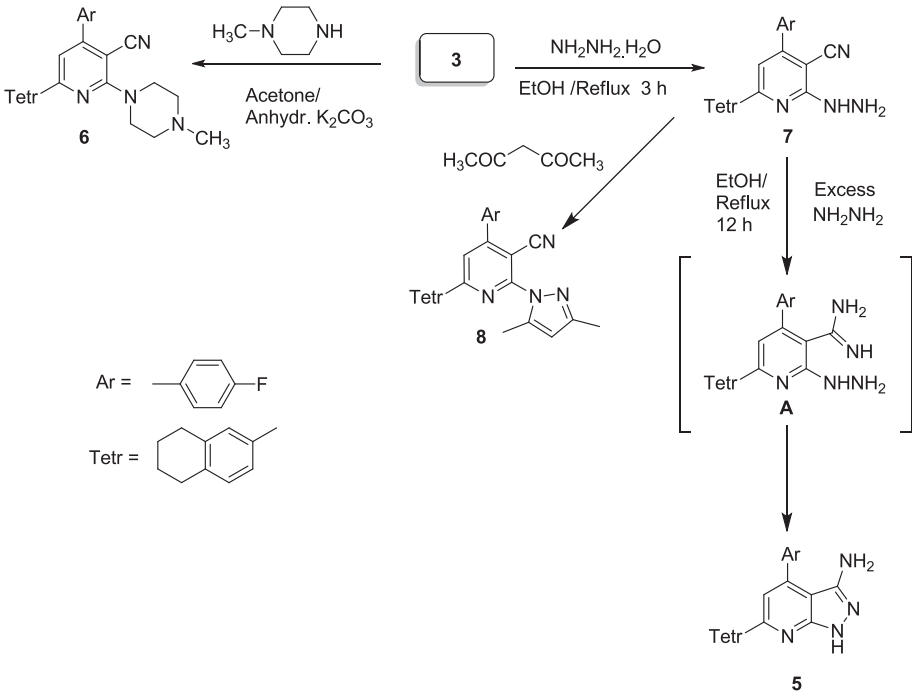


SCHEME 1 Synthesis of compounds **3** and **5**

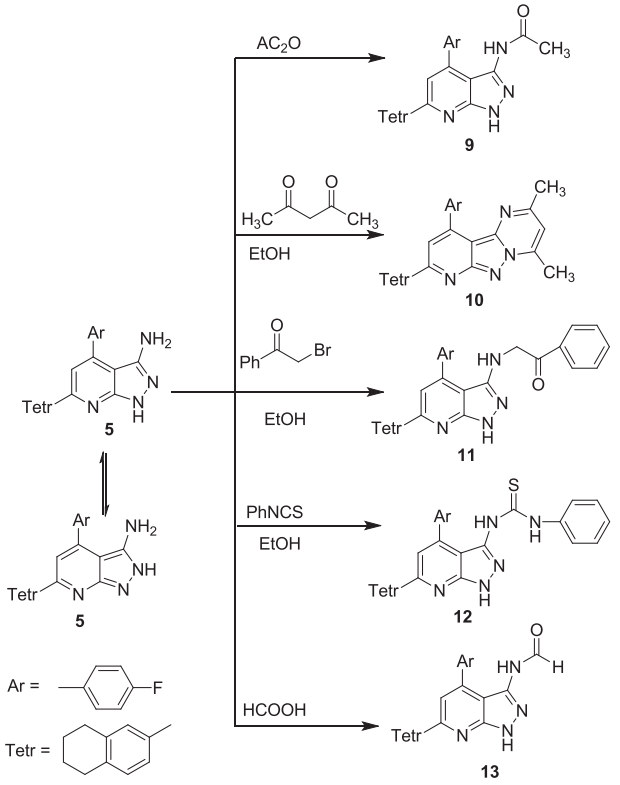
nucleophilic substitution of the chlorine atom of **3** with methyl piprazine was performed upon treatment with K_2CO_3 in acetone at reflux. The displacement of the chloride atom by *N*-methylpiperazine proceeded via nucleophilic addition and subsequent elimination reaction to give the new 4-(4-fluorophenyl)-2-(4-methylpiperazin-1-yl)-6-(5,6,7,8-tetrahydro-naphthalen-2-yl)nicotinonitrile (**6**) (Scheme 2). The structure of **6** was elucidated depending upon its spectral data. Its IR spectrum (KBr, ν cm^{-1}) showed a band at 2210 cm^{-1} characteristic for CN, while its ^{1}H-NMR spectrum showed the presence of a methyl group signal at δ 2.3 ppm in addition to the extra four methylene group of the piperazine ring at δ 2.55 and 3.70 ppm, respectively.

Nucleophilic substitution of **3** with hydrazine hydrate afforded the corresponding hydrazinyl derivative **7**. Its structure was confirmed according to its spectral data; IR (KBr, ν cm^{-1}) showed the characteristic band for CN at 2216 cm^{-1} in addition to bands at 3462, 3298, and 3200 cm^{-1} characteristic for the NH_2NH— group. Moreover, its ^{1}H-NMR showed the presence of an amino group signal at δ 4.60 ppm and a signal at δ 12.30 ppm for NH group. On the other hand, when compound **3** was heated at reflux with excess hydrazine hydrate for 12 h, the corresponding 4-(4-fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-amine (**5**) was obtained in 68% yield[66] (Scheme 2).

The reaction proceeded via initial formation of hydrazinylcyanopyridine **7** upon treatment of **3** with hydrazine hydrate. Subsequent reaction of **7** with excess hydrazine hydrate afforded **5** via the intermediate **A** (Scheme 2). The spectral characteristics of the product were completely coincident with a sample of **5** obtained by the reaction of **4** with hydrazine hydrate (Scheme 1).



SCHEME 2 Synthesis of compounds **5-8**



SCHEME 3 Synthesis of compounds **9**-**13**

Reaction of 2-hydrazinonicotinonitrile **7** with acetylacetone afforded the corresponding *N*-pyrazolo derivative **8** in 52% yield (Scheme 3). The structure of **8** was confirmed by analytical and spectral data. The IR spectrum of **8** showed a characteristic band at υ 2213 cm^{-1} for the CN group in addition to the disappearance of absorption bands for $NHNH_2$ moiety. Its ^{1}H-NMR spectrum revealed singlet signals at 2.59, 2.77, and 5.79 ppm due to both of the two methyl groups and the CH of the pyrazole moiety, respectively. In addition, the ^{13}C-NMR data of **8** displayed signals at δ 18.4, 19.3, and 117.9 ppm characteristic for the two methyl and CN groups, respectively. Its mass spectrum showed the correct molecular ion peak ($C_{27}H_{23}FN_4$) at m/z 422.

The intermediate **5** was used as a precursor to prepare novel substituted pyrazolopyridine derivatives. When compound **5** was exposed to acetylation with acetic anhydride, the corresponding pyrazolopyridine acetamide derivative **9** was obtained in a high yield. Its structure was confirmed on the basis of its spectral data. Its IR spectrum showed a characteristic band at ν 1665 cm^{-1} for the C═O of the acetyl group. The ^{1}H NMR spectrum of compound **9** displayed a singlet signal at δ 1.69 ppm, which corresponds to protons of $COCH_3$ group together with the disappearance of the singlet signal at δ 4.56 ppm which corresponds to NH_2 group (Scheme 3).

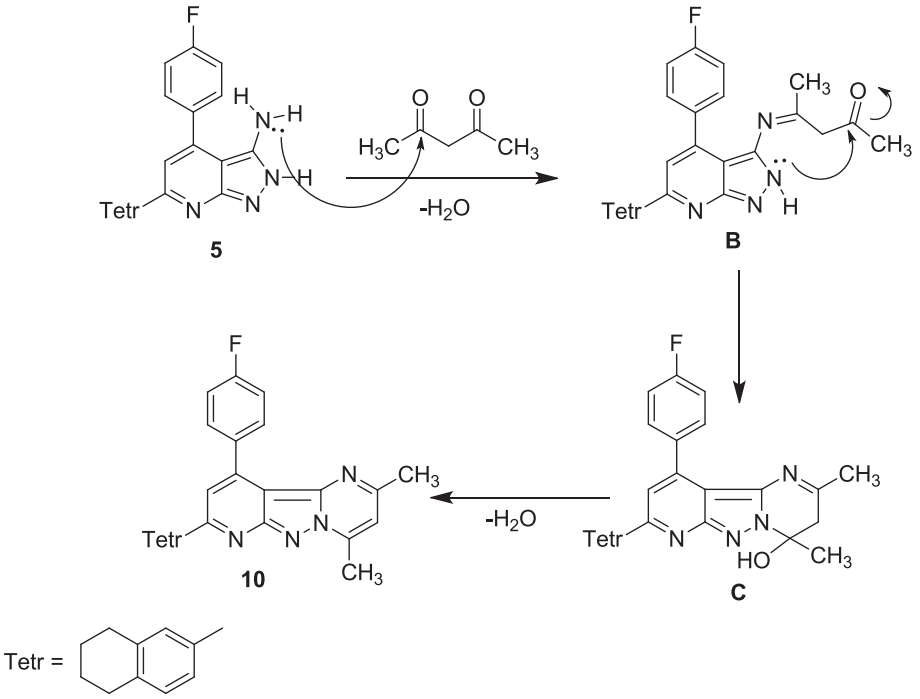
On the other hand, aminopyrazolopyridine **5** was used as a useful intermediate for cyclocondensation reaction with acetylacetone to give the corresponding new tricyclic pyridopyrazolopyrimidine derivative **10**. The structure of **10** was elucidated based on spectral data. The ^{1}H-NMR spectrum of compound **10** showed singlet signals for the two CH_3 groups at δ 2.53 and 2.73 ppm together with the disappearance of the signal corresponding to NH_2 group. The structure of the isolated product was also supported by the presence of a molecular ion peak at m/z 422 corresponding to the molecular formula ($C_{27}H_{23}FN_4$) in its mass spectrum. The mechanism for the formation of **10** is shown in Scheme 4. The reactions proceeded via initially nucleophilic attack of the NH_2 group of 5-aminopyrazolepyridine **5** onto the carbonyl group of acetylacetone to form the intermediate imine **B** by removing a water molecule. Subsequent intramolecular cyclization was performed by nucleophilic attack of the NH of pyrazole onto the other carbonyl group to form an intermediate adduct C followed by dehydration of to give **10.**[67]

Condensation of 3-aminopyrazolepyridine **5** with phenacyl bromide in ethanol gave the corresponding *N*-pyrazolopyridine derivative **11** (Scheme 3). Its ^{1}H NMR spectrum revealed a singlet signal at δ 4.78 ppm referring to the methylene protons of CH_2CO group and a singlet signal at δ 12.40 ppm due to pyrazole-NH group in addition to the aromatic protons and the other NH group of the side chain which appeared in the region δ 7.16 to 8.02 ppm.

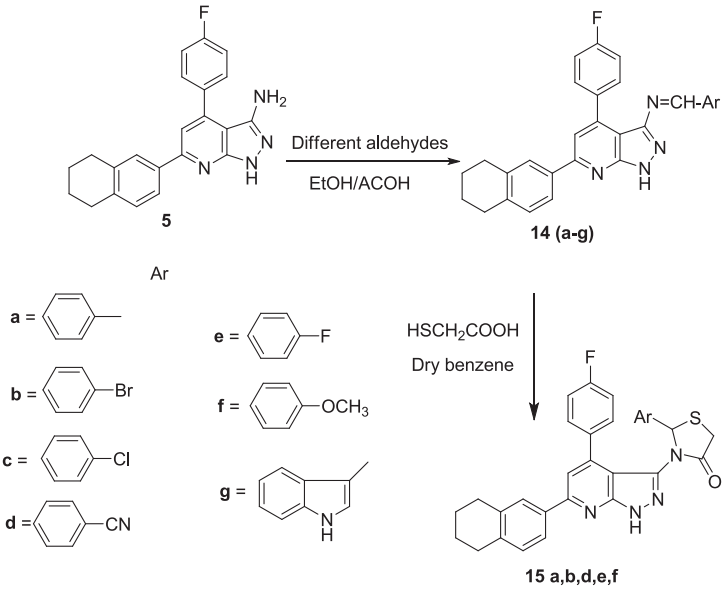
Moreover, condensation of the 3-aminopyrazolopyridine **5** with phenyl isothiocyanate in ethanol provided the corresponding phenylthiourea derivative **12**. The structure of the formed compound was confirmed by elemental analyses and its spectral features. Its ^{1}H-NMR showed characteristic signals for three NH─ groups at δ 9.49, 9.72, and 12.64 ppm, respectively, as well as the disappearance of the characteristic signal of NH_2 group. Other signals which appeared at the expected positions also supported the formation of compound **12**.

Synthesis of *N*-(4-(4-fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)formamide (**13**) was also achieved upon heating of **5** with formic acid. Its structure was confirmed by analytical and spectral data. The IR spectrum of compound **13** displayed bands at 3205 and at 1692 cm^{-1} characteristic for the NH and C═O groups, respectively. The ^{1}H-NMR spectrum of compound **13** revealed the presence of singlet signals at δ 4.59 ppm and at δ 7.95 ppm corresponding to the NH and the formyl protons, respectively (Scheme 3). The mass spectrum of **13** showed the correct molecular ion peaks at m/z = 386.

On the other hand, when 3-aminopyrazolo[3,4-*b*]pyridine **5** was heated at reflux with different aromatic aldehydes, namely benzaldehyde, *p*-bromobenzaldhyde, *p*-chlorobenzaldhyde, *p*-cyanobenzaldhyde, *p*-fluorobenzaldhyde, *p*-methoxybenzaldhyde, and 1*H*-indole-3-



SCHEME 4 A plausible mechanism for the formation of compound **10**



SCHEME 5 Synthesis of Schiff bases **14** and thiazolidinone derivatives **15**

carbaldhyde in ethanol containing few drops of glacial acetic for 6 h, the corresponding Schiff bases **14a**-**g** were obtained, respectively, in good yields (Scheme 5). Elemental analyses and spectral data confirmed the chemical structures of the new pyrazolo[3,4-*b*]pyridine derivatives **14a**-**g**. The disappearance of the absorption bands due to NH_2 in the IR spectra of **14** confirm that the NH_2 group of compound **5** completely reacted with —CHO groups of the used aldehydes to form the corresponding Schiff bases. Furthermore, the ^{1}H-NMR spectra of these compounds also revealed singlet signals at δ 8.85 to 9.13 ppm referring to the —N═CH protons of the azomethine groups, in addition to the singlet signals at δ 13.64 ppm due to NH groups of pyrazole ring. Mass spectra displayed the expected molecular ion peaks at m/z 446, 525, 480, 471, 464, 476, and 485, respectively, corresponding to the correct molecular formulae of compounds **14a**-**g**.

Furthermore, when the Schiff bases **14a**, **14b**, **14d**, **14e**, and **14f** were allowed to react with thioglycolic acid, addition to C═N took place by firstly attack of the sulfur

nucleophile on the imine carbon and subsequent intramolecular cyclization via elimination of a water molecule to give the corresponding 1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-2-phenylthiazolidin-4-ones **15a**, **15b**, **15d**, **15e**, and **15f**, respectively (Scheme 5). The IR spectra of compound **15** showed characteristic bands at υ 1674 cm^{-1}, confirming the presence of C═O group of thiazolidinone moiety and at υ 3410 cm^{-1} due to NH. Further confirmation was obtained from the ^{1}H NMR spectrum of compound **15**, which displayed a singlet signal at δ 4.59 ppm corresponding to the methylene protons of the thiazolidinone moiety in addition to the disappearance of the singlet signals at δ 8.85 to 9.13 ppm referring to the —N═CH proton of the azomethine groups. In addition, ^{13}C NMR spectra displayed two characteristic signals at δ 31.67 to 34.51 and at δ 170.08 to 173.52 ppm characteristic for CH_2 and C═O groups of thiazolidinone moiety, respectively. Their mass spectra were also in accordance with their structures.

3 | PHARMACOLOGICAL EVALUATION

3.1 | In vitro anticancer activities

Seventeen compounds were selected as representative compounds to be examined in vitro anticancer candidates against human colorectal cancer cells (HCT116) and human breast cancer cells (MCF-7) by MTT assay using Doxorubicin as a reference drug. The obtained data were expressed as IC_{50} (μM) values which were obtained by the average of at least three independent experiments (Table 1). Both Figures 2 and 3 revealed that most of the new compounds exhibited insignificant dose-dependent anticancer activities.

3.2 | Anticancer activity against the human colorectal cancer cells (HCT116)

According to Table 1, it has been noted that the conjugation of the parent tetralin nucleus with pyrazolo[3,4-*b*] pyridine ring system revealed promising cytotoxic activity against HCT116. The most potent activity was obtained by the Schiff bases compounds **14**. The phenyl, *p*-chlorophenyl, and *p*-phenylfluorophenyl analogues **14a**, **14c**, and **14e** exhibited cytotoxic activity about 1.5 to 1 folds more potent than the reference drug of IC_{50} values ranging from 6.4 to 8.1 μM, while the *p*-methoxy compound **14f** produced equipotent activity to that of doxorubicin (IC_{50}; 9.8 μM, IC_{50} doxorubicin; 9.5 μM). A significant decrease in the potency compared with the reference drug was observed by the *p*-bromophenyl and the indolyl analogues **14b** and **14g** (IC_{50}; 19.8, 16.4 μM, respectively). In addition, the cytotoxic activity slightly decreased by the parent intermediate 3-amino-pyrazolo[3,4-*b*]pyridine derivative **5** and its *N*-acetylated derivative **9** (IC_{50}; 14.4, 15.1 μM, respectively). On the other hand, about two-folds reduction in the potency was obtained by the fused pyrido-pyrazolo[1,5-*a*]pyrimidine analogue **10**. Further decrease in the potency was detected by the rest of the tested derivatives of IC_{50} values ranged from 20.1 to 26.1 μM (Figure 2).

TABLE 1 Anticancer IC_{50} values of the tested compounds using MTT assay on the human colorectal and breast cancer cells

	IC_{50} (μM) ± SD	
Compound	**HCT-116**	**MCF-7**
5	14.4 ± 3.1	41 ± 5.9
9	15.1 ± 3.3	36.4 ± 5.1
10	19.9 ± 3.5	89.6 ± 6.9
11	25.3 ± 4.1	92.4 ± 7.1
12	24.9 ± 4.1	70.3 ± 6.5
13	20.1 ± 4.1	16.1 ± 4.1
14a	6.4 ± 1.9	92.8 ± 7.1
14b	19.8 ± 4.1	69.1 ± 5.9
14c	7.6 ± 2.1	89.4 ± 6.1
14e	8.1 ± 2.3	82.1 ± 5.8
14f	9.8 ± 2.5	91 ± 6.7
14 g	16.4 ± 2.9	58.6 ± 4.9
15a	32.7 ± 4.6	70.3 ± 6.9
15b	20.0 ± 4.1	55 ± 5.1
15d	19.0 ± 3.9	42.3 ± 4.5
15e	21.0 ± 4.1	48.7 ± 4.2
15f	26.1 ± 4.3	32.6 ± 4.1
Doxorubicin	9.5 ± 2.9	65.6 ± 4.5

3.3 | Anticancer activity against human breast cancer cells (MCF-7)

The most significant anticancer activity against MCF-7 cancer cells was recorded for the pyrazolo[3,4-*b*]pyridine-formamide derivative **13**, which exhibit 4-folds more potency than the reference drug doxorubicin (IC_{50}; 16.1 μM, IC_{50} doxorubicin, 65.6 μM). In addition, the attachment of the parent tetralin-pyrazolo[3,4-*b*]pyridine scaffold with thiazolidinone ring as compounds **15a**, **15b**, **15d**, **15e**, and **15f** produced marked activity against the breast cancer cell (MCF-7) in comparison with doxorubicin. The *p*-methoxyphenyl derivative **15f**

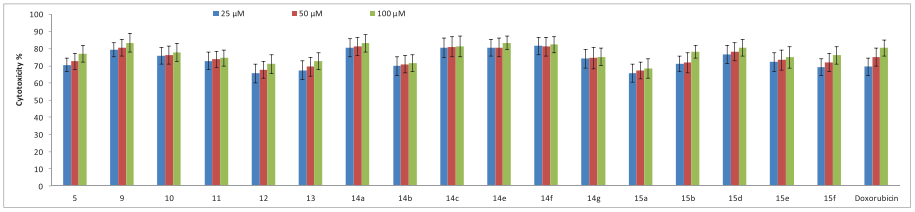


FIGURE 2 Dose-dependent anticancer percentages curve of the synthesized compounds on HCT-116 human cancer cells according to MTT assay [Color figure can be viewed at wileyonlinelibrary.com]

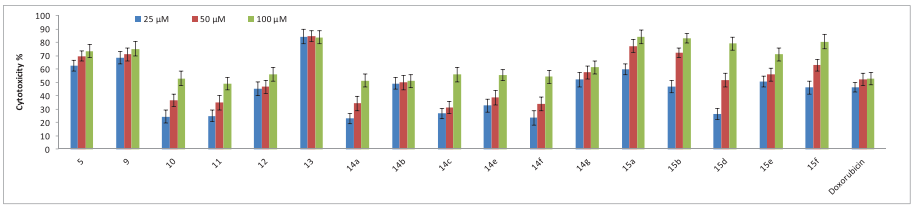


FIGURE 3 Dose dependent anticancer percentages curve of the synthesized compounds on MCF-7 human cancer cells according to MTT assay [Color figure can be viewed at wileyonlinelibrary.com]

appeared to be two folds more potent than the reference drug of IC_{50}; 32.6 μM. The activity of *p*-bromo, *p*-cyano, and *p*-fluorophenyl derivatives **15b**, **15d**, and **15e** slightly decreased but retained its superiority over doxorubicin by 1.5 to 1 folds (IC_{50}; 42.3–55 μM). Compound **15a** exhibited a slight reduction in the cytotoxic activity less than the reference drug of IC_{50}; 70.3 μM. Furthermore, it could be noted that the parent intermediate 3-amino-pyrazolo[3,4-*b*]pyridine derivative **5** and its *N*-acetylated derivative **9** disclosed more efficiency against the breast cancer cells than that against the colorectal type since they produced cytotoxic activity about 1.5 to 1.8 folds more potent than doxorubicin (IC_{50}; 41, 36.4 μM, respectively), while the phenylthiourea analogue **12** represented anticancer activity slightly less than doxorubicin of IC_{50}; 70.3 μM. The rest of the tested derivatives **10**, **11**, and **14** produced a detectable reduction in the potency of IC_{50}; 82.1 to 92.4 μM **(**Figure 3).

4 | EXPERIMENTAL

All melting points are uncorrected and were taken in open capillary tubes using an Electro-thermal IA 9100 apparatus (Shimadzu, Japan). Microanalytical data were performed by Vario El-Mentar apparatus (Shimadzu, Japan), National Research Centre (NRC), Cairo, Egypt. The found values were within ±0.4% of the theoretical values. Infrared spectra (KBr) were recorded on a Perkin-Elmer 1650 spectrophotometer, NRC.

^{1}H NMR and ^{13}C NMR spectra were determined on a Varian Mercury (run at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) spectrometer (Varian, UK; Faculty of Science, Cairo University, Egypt) or with a Bruker AVANCE (400 MHz for 1HNMR and 101 MHz for 13C NMR) spectrometer (Bruker; Aalto university school of chemical engineering, Finland) with a 5-mm BBFO probe using deuterated dimethylsulfoxide DMSO as a solvent, and the chemical shifts were expressed in δ ppm relative to TMS as an internal reference. Mass spectra were recorded at 70 eV on EI Ms-QP 1000 EX (Shimadzu, Japan), NRC. Follow-up of the reactions and checking of the purity of the compounds were made by TLC on silica gel-precoated aluminum sheets (Type 60, F 254, Merck, Darmstadt, Germany), and the spots were detected by exposure to a UV lamp at 254 nm for a few seconds. The chemical names for the prepared compounds are given according to the IUPAC system. Compounds **1**, **2**, and **4** were prepared by the reported method.[63–65]

4.1 | 2-Chloro-4-(4-fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)nicotinonitrile (3)

A suspension of pyridone compound **2** (3.44 g, 10 mmol), PCl_5 (0.5 g), and $POCl_3$ (5 mL) was heated on a water bath for 3 h. The reaction mixture was poured gradually into ice-cold water and left in the fridge till next day. The separated solid was filtered off and recrystallized from ethanol to afford the corresponding chloro derivative **3**.

Yield 64%; yellow crystals; m.p. 148 to 150°C; IR (KBr, cm^{-1}): υ 2925 (CH, alicyclic), 2223 (CN), 1582 (C═N), 1229 (C—F); ^{1}HNMR (400 MHz, DMSO-d6, δ, ppm): 1.76 (br.s, 4H, $2CH_2$ of tetrahydronaphthalene), 2.80 (m, 4H, $2CH_2$ of tetrahydronaphthalene), 7.22 (d, J = 8.0

Hz, 1H, Ar-H), 7.47 (t, J = 8.8 Hz, 2H, Ar-H), 7.84 to 7.95 (m, 4H, Ar-H), 8.18 (s, 1H, pyridine-H5); ^{13}C NMR (101 MHz, DMSO) δ: 22.4, 22.5 ($2CH_2$), 28.7 ($2CH_2$), 116.0 (CN), 105.9, 115.4, 115.8, 119.0, 122.7, 124.7, 128.1, 129.7, 131.4, 131.4, 132.5, 133.4, 137.5, 152.3, 159.2,164.6 (17 C, Ar-C); MS: m/z (%): 364.10 (M^++2, ^{37}Cl, 32.00), 362 (M^+, ^{35}Cl, 100.00); Analysis calcd. for $C_{22}H_{16}ClFN_2$ (362.83) C, 72.83; H, 4.45; Cl, 9.77; F, 5.24; N, 7.72; found: C, 72.68; H, 4.52; Cl, 9.97; F, 5.12; N, 7.85.

4.2 | 4-(4-Fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-amine (5)

- Method A: To a solution of compound 4 (4.301 g, 10 mmol) in absolute ethanol (30 ml), excess hydrazine hydrate (10 ml, 99%) was added and the reaction mixture was heated at reflux for 12 h. After cooling, the separated solid was filtered off and recrystallized from acetic acid to give compound **5**.
- Method B: A solution of compound 7 (3.584 g, 10 mmol) in absolute ethanol (30 ml) was heated at reflux for 12 h with excess hydrazine hydrate (10 ml, 99%). After cooling, the separated solid was filtered off and recrystallized from acetic acid to give compound **5**.

Yield 68%; Yellow crystals; m.p. 198 to 200°C; IR (KBr, cm^{-1}): υ 3425, 3369 (NH_2), 3211 (NH), 2925 (CH, alicyclic), 1591 (C═N), 1220 (C—F); ^{1}H NMR (400 DMSO-d_6, δ ppm): 1.77, 2.79 (m, m, 4H, 4H, $4CH_2$ of tetrahydronaphthalene), 4.56 (s, 2H, NH_2, D_2O exchangeable), 7.16 (d, J = 8.7 Hz, 1H, Ar-H), 7.37 to 7.43 (m, 3H, Ar-H), 7.71 to 7.74 (m, 2H, Ar-H), 7.86 (s, 1H, Ar-H), 7.88 (s, 1H, pyridine-H5), 12.18 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (101 MHz, DMSO) δ: 22.6, 22.7 ($2CH_2$), 28.6, 28.8 ($2CH_2$), 115.5, 115.7, 119.8, 122.1, 124.2, 127.6, 129.2, 130.0, 131.0, 133.5, 136.8, 138.0, 149.8, 153.2, 155.6, 163.6 (18C, Ar); MS: m/z (%): 360 (M^++2, 22.45), 359 (M^++1, 13.28), 358 (M^+, 58.70), 344 (100), 321 (73.92), 115 (65.54); Analysis calcd. for $C_{22}H_{19}FN_4$ (358.42): C, 73.72; H, 5.34; F, 5.30; N, 15.63; found: C, 73.51; H, 5.19; F, 5.41; N, 15.84.

4.3 | 4-(4-Fluorophenyl)-2-(4-methylpiperazin-1-yl)-6-(5,6,7,8-tetrahydro-naphthalen-2-yl)nicotinonitrile (6)

To a solution of anhydrous K_2CO_3 (0.5 gm) in acetone (12 ml), compound **3** (0.98 g, 0.003 mol) and methylpiperazine (0.003 mol) were added. The reaction mixture was heated at reflux for 5 h. The solvent was then evaporated under vacuum and the separated solid was filtered off, washed with H_2O, dried, and crystalized from ethanol to give compound **6**.

Yield 62%; yellow crystals; m.p. 158 to 160°C; IR (KBr, cm^{-1}): υ 2929 (CH, alicyclic), 2211 (CN), 1600 (C═N), 1227 (C—F); ^{1}HNMR (400 MHz, DMSO-d6, δ, ppm):1.77 (br.s, 4H, $2CH_2$ of tetrahydronaphthalene), 2.26 (s, 3H, CH_3), 2.55 (s, 4H, $4CH_2$, piprazine ring), 2.79 (m, 4H, $2CH_2$ of tetrahydronaphthalene), 3.71 (s, 4H, $4CH_2$, piprazine ring), 7.19 (d, J = 8 Hz, 1H, Ar-H), 7.39 to 7.52 (m, 3H, Ar-H), 7.78 to 8.21 (m, 4H, Ar-H + pyridine-H5); ^{13}C NMR (101 MHz, DMSO) δ: 23.0 (CH_3), 28.1 ($2CH_2$), 29.2 ($2CH_2$), 48.8 ($2CH_2$), 54.9 ($2CH_2$), 111.8 (CN), 79.2, 112.4, 116.2, 119.8, 128.3, 129.6, 131.8, 134.9, 137.5, 155.5, 157.8, 162.4, 166.0 (17C, Ar-C).; MS, m/z (%): 427 (M^++1, 86.43), 426 (M^+, 100); Analysis calcd. for $C_{27}H_{27}FN_4$ (426.54): C, 76.03; H, 6.38; F, 4.45; N, 13.14; Found: C, 75.93; H, 6.27; F, 4.38; N, 13.37.

4.4 | 4-(4-Fluorophenyl)-2-hydrazinyl-6-(5,6,7,8-tetrahydronaphthalen-2-yl) nicotinonitrile (7)

To a solution of the chloro derivative **3** (3.625 g, 0.01 mol) in absolute ethanol (10 ml), hydrazine hydrate (1.0 mL, 0.02 mol) was added. The reaction mixture was heated at reflux for 3 h. After cooling, the formed precipitate was filtered off, dried, and recrystallized from ethanol to give compound **7**.

Yield 68%; Pale yellow crystals; m.p. 130 to 132°C;.IR (KBr, cm^{-1}): υ 3462, 3299 (NH_2), 3200 (NH), 2929, (CH, alicyclic), 2216 (CN), 1600 (C═N), 1223 (C—F); ^{1}HNMR (400 MHz, DMSO-d6, δ, ppm): 1.76 (br.s, 4H, $2CH_2$ of tetrahydronaphthalene), 2.82 (m, 4H, $2CH_2$ of tetrahydronaphthalene), 4.60 (s, 2H, NH_2), 7.16 (d, J = 8.0 Hz, 1H, Ar-H), 7.42(d, J = 8.0 Hz, 3H, Ar-H), 7.73 to 7.75 (m, 3H, Ar-H), 7.89 (s, 1H, pyridine-H5), 12.35 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (101 MHz, DMSO) δ: 22.6, 22.7 ($2CH_2$), 28.6, 28.8 ($2CH_2$), 113.2 (CN), 101.7, 115.5, 115.7, 124.2, 127.6, 129.2, 130.9, 131.0, 133.5, 135.9, 138.0, 153.2, 155.6, 163.7 (17C, Ar-C); MS: m/z (%): 359 (M^++1, 24.31), 358 (M^+, 100), (M^+ −1, 45.55), Analysis calcd. for $C_{22}H_{19}FN_4$ (358.42): C, 73.72; H, 5.34; F, 5.30;N, 15.63; found: C, 73.51; H, 5.57; F, 5.21; N,15. 89.

4.5 | 2-(3,5-Dimethyl-1H-pyrazol-1-yl)-4-(4-fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)nicotinonitrile (8)

A mixture of the hydrazinyl compound **7** (1.07 g, 3 mmol) and acetylacetone (10 mL, 15 mmol) was heated at reflux

for 6 h. The formed precipitate after cooling was filtered off, dried, and recrystallized from EtOH/DMF to give the title compound **8**.

Yield 52%; yellow crystals; m.p. 250 to 252°C; IR (KBr, cm^{-1}): υ 2923 (CH, alicyclic), 2213 (CN), 1625 (C═N), 1221 (C—F); ^{1}HNMR (400 MHz, DMSO-d6, δ, ppm): 1.79 (m, 4H, $2CH_2$ of tetrahydronaphthalene), 2.59 (s, 3H, CH_3), 2.77 (m, 3H, CH_3), 2.89 (m, 4H, $2CH_2$ of tetrahydronaphthalene), 5.79 (s, 1H, pyrazole proton), 7.17 (d, J = 8 Hz, 1H, Ar-H), 7.23 to 7.51 (m, 3H, Ar-H), 7.80 (s, 1H, Ar-H), 8.06 to 8.16 (m, 3H, Ar-H + pyridine-H5); ^{13}C NMR (101 MHz, DMSO) δ: 12.7 (CH_3), 13.0 (CH_3), 22.1 ($2CH_2$), 27.7 ($2CH_2$), 117.9 (CN), 92.0, 104.8, 114.2, 120.2, 127.0, 128.6, 129.5, 130.7, 133.8, 135.40, 137.5, 142.4, 151.9, 156.4, 160.3, 162.6, 166.6 (20C, Ar).; MS: m/z (%): 422 (M^+, 39.63), 421 (M^+-1, 27.94), 357 (34.14), 356 (100), 69 (38.30); Analysis calcd. for $C_{27}H_{23}FN_4$ (422.51): C, 76.76; H, 5.49; F 4.50; N, 13.26; found: C, 76.63; H, 5.58; F 4.42; N,13.66

4.6 | N-(4-(4-Fluorophenyl)-6-(5, 6, 7, 8-tetrahydronaphthalen-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)acetamide (9)

Pyrazolo pyridine derivative **5** (3.58 g, 10 mmol) was heated at reflux in acetic anhydride (20 mL) for 5 h, then the mixture was allowed to attain room temperature. The deposited solid was filtered, washed with petroleum ether (60-80°C) and recrystallized from ethanol to give compound **9**.

Yield 89%; yellow crystals; m.p. 256 to 258°C; IR (KBr, cm^{-1}): υ 3414, 3256 (2NH), 2925 (CH, alicyclic), 1665 (C═O, amide), 1601 (C═N), 1226 (C—F); ^{1}H NMR (400 DMSO-d_6, δ, ppm): 1.69 (s, 3H, $COCH_3$), 1.78, 2.80 (m, m, 4H, 4H, $4CH_2$ of tetrahydronaphthalene), 7.19 (d, J = 8.7 Hz, 1H, Ar-H), 7.33 (t, J = 9 Hz, 2H, Ar-H), 7.65-7.68 (m, 3H, Ar-H), 7.91 (s, 1H, Ar-H), 7.94(s, 1H, pyridine-H5), 9.84 (s, 1H, NHCO, exchangeable with D_2O), 13.42 (s, 1H, NH pyrazole, exchangeable with D_2O); ^{13}C NMR (101 MHz, DMSO) δ: 23.1 ($2CH_2$), 23.1 ($CO\underline{C}H_3$), 29.3 ($2CH_2$), 167.8 (C═O), 82.2, 115.5, 124.9, 125.1, 128.2, 129.8, 130.0, 131.2, 137.5, 138.9, 149.6, 153.5, 155.2, 165.2 (18C, Ar-C).; MS: m/z (%): 401.27 (M^++1, 2.70), 400 (M^+, 6.27), 84 (74.92), 54 (96.34), 42 (100); Analysis calcd. for $C_{24}H_{21}FN_4O$ (400.46): C, 71.98; H, 5.59; F, 4.74; N, 13.99; found: C, 71.76; H, 5.36; F, 4.69; N, 14.19.

4.7 | 10-(4-Fluorophenyl)-2,4-dimethyl-8-(5,6,7,8-tetrahydronaphthalen-2-yl) pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine (10)

To a solution of compound **5** (3.58 g, 10 mmol) in ethanol (20 mL), acetyl acetone (1 mL, 10 mmol) was added and the reaction mixture was heated at reflux for10 h. The solvent was then removed under reduced pressure and the obtained residue was recrystallized from ethanol/DMF to give compound **10**.

Yield 78%; bright yellow crystals; m.p. 250-252°C; IR (KBr, cm^{-1}): υ 2919 (CH, alicyclic), 1622, 1600 (C═N), 1219 (C—F); ^{1}H NMR (300 DMSO-d_6, δ, ppm): 1.79 (br.s, 4H, 2 CH_2 of tetrahydronaphthalene), 2.53, 2.73 (s, s, 3H, 3H, $2CH_3$), 2.88 (m, 4H, $2CH_2$ of tetrahydronaphthalene), 7.19 (d, J = 7.8 Hz, 1H, Ar-H), 7.35 to 7.41 (m, 3H, Ar-H), 7.73 (s, 1H, Ar-H), 7.99 to 8.12 (m, 4H, Ar-H + pyridine-H5); ^{13}C NMR (101 MHz, DMSO) δ: 13.9 (CH_3), 22.5 ($2CH_2$), 25.5 (CH_3), 28.5 ($2CH_2$), 103.9, 107.9, 115.7, 118.2, 120.8, 127.0, 129.4, 131.0, 134, 136.5, 137.3, 142,5, 147.8, 151.4, 153.2, 158.6, 162.6, 166.4 (21C, Ar-C).; MS: m/z (%):422 (M^+, 21.53), 421 (M^+−1, 27.35), 420 (M^+−2, 11.15), 334 (83.64), 305 (39), 201 (63), 183 (74), 85 (100), 54 (76.91); Analysis calcd. for $C_{27}H_{23}FN_4$ (422.51): C, 76.76; H, 5.49; F 4.50; N, 13.26; found: C, 76.81; H, 5.36; F 4.48; N; 13.41.

4.8 | 2-((4-(4-Fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)amino)-1-phenylethan-1-one (11)

To a solution of compound **5** (3.58 g, 10 mmol) in absolute ethanol (20 mL), phenacyl bromide (1.9 g, 10 mmol) was added. The reaction mixture was heated at reflux for 7 h. The solution was concentrated and left to cool. The precipitate was filtered off and recrystallized from ethanol to give compound **11**.

Yield 79 %; dark yellow crystals; m.p. 258-260°C; IR (KBr, cm^{-1}): υ 3433 (br.s, 2NH), 2924 (CH, alicyclic), 1631 (C═O), 1233 (C—F); ^{1}H NMR (300 DMSO-d_6, δ, ppm): 1.77, 2.79 (m, m, 4H, 4H, $4CH_2$ of tetrahydronaphthalene), 4.78 (s, 2H, CH2), 7.17 (d, J = 8.4 Hz, 1H, Ar-H), 7.43 to 7.58 (m, 5H, Ar-H), 7.65 to 8.02 (m, 8H, Ar-H + NH exchangeable with D_2O), 12.41(s, 1H, NH exchangeable with D_2O); ^{13}C NMR (101 MHz, DMSO) δ: 22.7 ($2CH_2$), 29.0, 31.3 ($2CH_2$), 92.2, 116.5, 120.1, 122.4, 127.7, 129.3, 131.9, 133.9, 137.2, 138.8, 158.2, 162.5, 165.5 (25C, Ar-C). 207.1 (C═O); MS, m/z (%): 476 (M+, 10), 82 (90.97), 80 (100), 78 (66.20), 77 (50.42); Analysis calcd. for $C_{30}H_{25}FN_4O$ (476.56): C, 75.61; H, 5.29; F, 3.99; N, 11.76; found: C, 75.53; H, 5.09; F, 3.80; N, 11.98.

4.9 | 1-(4-(4-Fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-3-phenylthiourea (12)

To a solution of compound **5** (0.358 g, 0.001 mol) in absolute ethanol (30 mL), phenyl isothiocynate (0.135 g, 0.001 mol) was added and the reaction mixture was heated at reflux temperature for 8 h. The formed precipitate was filtered off, washed with petroleum ether, dried, and recrystallized from AcOH to give **12**.

Yield 77%; pale yellow crystals; m.p. 230 to 232°C. IR (KBr, cm^{-1}): υ 3408, 3150 (NH), 2925 (CH, alicyclic), 1600 (C═N), 1369 (C═S), 1228 (C—F); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.79, 2.84 (2 br.s, 4H, 4H, 4CH_2 of tetrahydronaphthalene), 7.12 to 7.20 (m, 2H, Ar-H), 7.22 to 7.33 (m, 6H, Ar-H), 7.69 (s, 1H, Ar-H), 7.80 to 7.83 (m, 3H, Ar-H), 7.95 (s, 1H, pyridine H5), 9.49, 9.7212.64 (2 s, 2H, 2NH, exchangeable with D_2O), 12.64 (s, H, NH, pyrazole, exchangeable with D_2O); ^{13}C NMR (101 MHz, DMSO) δ: 22.3 (2CH_2), 26.8 (2CH_2), 181.8 (C═S), 97.8, 116.1, 119.9, 121.6, 126.12, 128.4, 129.4, 131.1, 133.7, 135.3, 136.6, 138.6, 138.7, 150.7, 154.3, 155.0, 162.7 (24C, Ar-C). MS: m/z (%): 494 (M^+ +1, 3.41), 493 (M^+, 10.30), 491 (M^+−1, 2.77), 459 (100), 400 (94.67); Analysis calcd. for $C_{29}H_{24}FN_5S$ (493.60): C, 70.57; H, 4.90; F, 3.85; N, 14.19; S, 6.50; found: C, 70.32; H, 4.85; F, 3.95; N, 14.38; S, 6.35.

4.10 | N-(4-(4-Fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)formamide (13)

A solution of **5** (3.58 g, 10 mmol) and formic acid (10 mL) was heated at reflux for 6 h. The mixture was then allowed to cool and poured into cold water. The solid precipitate so formed was filtered off and recrystallized from ethanol to give formamide derivative **13**.

Yield 80%; off-white crystals; m.p. 238 to 240°C; IR (KBr, cm^{-1}): υ 3205 (br.s, 2NH), 2929 (CH, alicyclic), 1692 (C═O, formamide), 1600 (C═N), 1228 (C—F); ^{1}H NMR (400 DMSO-d_6, δ, ppm): 1.78 (br.s., 4H, 2CH_2 of tetrahydronaphthalene), 2.82 (m, 4H, 2CH_2 of tetrahydronaphthalene), 4.59 (s,1H,NH exchangeable with D_2O), 7.15 to 7.21 (m, 1H, Ar-H), 7.30 to 7.44 (m, 3H, Ar-H), 7.66 to 7.77 (m, 3H, Ar-H), 7.89 (s, 1H, pyridine-H5), 7.95 (s, 1H, CHO), 12.33, (s, 1H, NH-Pyrazol); ^{13}C NMR (101 MHz, DMSO) δ: 23.15, 23.21(2CH_2), 29.15, 29.37 (2CH_2), 159.93 (C═O), 96.75, 116.01, 116.22, 119.13, 124.73, 128.12, 129.74, 131.48, 134.04, 136.50, 137.38, 138.54, 147.65, 152.69, 153.52, 156.14,162.82 (18C, Ar-C).; MS: m/z(%): 387.14 (M^++1, 54.28), 386.13 (M^+, 80.66), 358.13 (100), 357.09 (71.43) ; Analysis cald. For $C_{23}H_{19}FN_4O$ (386.43): C, 71.49; H, 4.96; F, 4.92; N, 14.50%; found: C, 71.26; H, 4.87; F 4.82; N, 14.84%.

4.11 | General procedures for the synthesis of compounds (14a-g)

To a solution of 3-amino pyrazolopyridine **5** (0.538 g, 1.5 mmol) in absolute ethanol (30 ml) containing few drops glacial acetic, the appropriate aromatic aldehyde (1.5 mmol) was added and the reaction mixture was heated at reflux for 6 h. The formed solid was filtered off and recrystallized from acetic acid to afford Schiff bases **14a**-**g**, respectively.

4.12 | N-(4-(4-Fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-1-phenylmethanimine (14a)

Yield 85%; off-white crystals; m.p. 230 to 232°C; IR (KBr, cm^{-1}): υ 3429 (NH), 2931 (CH, alicyclic), 1597 (C═N), 1226 (C—F); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.79 (br.s, 4H, 2CH_2 of tetrahydronaphthalene), 2.82 (m, 4H, 2CH_2 of tetrahydronaphthalene), 7.22 (d, J = 8 Hz, 1H, Ar-H), 7.36 (t, J = 8.6 Hz, 2H, Ar-H), 7.53 (t, J = 8.6 Hz, 3H, Ar-H), 7.76 to 7.84 (m, 3H, Ar-H), 7.93 to 7.98 (m, 4H, Ar-H + pyridine-H5), 8.94 (s, 1H, N═CH), 13.60 (s, 1H, NH, pyrazole, exchangeable with D_2O); ^{13}C NMR (101 MHz, DMSO) δ: 22.5, 22.6 (2CH_2), 28.6, 28.8 (2CH_2), 102.5, 116.0, 119.6, 124.5, 127.9, 129.4, 131.1, 131.2, 133.7, 135.0, 137.0, 138.9, 145.5, 150.2, 152.9, 155.9, 164.2 (24C, Ar-C). 157.16 (CH═N); MS: m/z (%): 447 (M^++1, 7.06), 446 (M^+, 26.39), 445 (M^+−1, 15, 45), 210 (100), 212 (48.24); Analysis calcd. for $C_{29}H_{23}FN_4$ (446.53): C, 78.01; H, 5.19; F, 4.25; N, 12.55; found: C, 77.91; H, 4.91; F, 4.35; N, 12.85.

4.13 | 1-(4-Bromophenyl)-N-(4-(4-fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)methanimine (14b)

Yield 72%; yellow crystals; m.p. 310 to 312°C; IR (KBr, cm^{-1}): υ 3410 (NH), 2922 (CH, alicyclic), 1600 (C═N), 1227 (C—F); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.79 (br.s, 4H, 2CH_2 of tetrahydronaphthalene), 2.82 (m, 4H,

$2CH_2$ of tetrahydronaphthalene), 7.21 to 7.74 (m, 4H, Ar-H), 7.76 to 7.98 (m, 8H, Ar-H+ pyridine-H5), 8.93 (s,1H, N=CH), 13.63 (s,1H, NH, pyrazole, exchangeable with D_2O); ^{13}C NMR (101 MHz, DMSO) δ: 22.1 ($2CH_2$), 28.5 ($2CH_2$), 105.9, 116.2, 119.1, 122.5, 125.4, 128.8, 129.4, 130.8, 131.8, 132.0, 135.1, 144.9, 147.2, 157.8, 158.1, 158.5, 164.1 (24C, Ar-C),158.96 (CH=N); MS: m/z (%): 526 (M^++1, 3.9), 525 (M+, 5.19), 96 (23.48) , 719 (95.57), 57 (100) ; Analysis calcd. for $C_{29}H_{22}BrFN_4$ (525.43): C, 66.29; H, 4.22; Br, 15.21; F, 3.62; N, 10.66; found: C, 65.99; H, 4.12; Br, 15.32; F, 3.51; N, 10.96.

4.14 | 1-(4-Chlorophenyl)-N-(4-(4-fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)methanimine (14c)

Yield 82%; yellow crystals; m.p. 260 to 262°C; IR (KBr, cm^{-1}): υ 3439 (NH), 2925 (CH, alicyclic), 1600 (C=N), 1227 (C—F); ^1H NMR (300 MHz DMSO-d_6, δ ppm): 1.79 (m, 4H, alicyclic $2CH_2$ of tetrahydronaphthalene), 2.82 (m, 4H, $2CH_2$ of tetrahydronaphthalene), 7.21 (d, J = 8.7 Hz, 1H, Ar-H), 7.35 (t, J = 8.8 Hz, 2H, Ar-H), 7.58 (d, J = 8.4 Hz, 2H, Ar-H), 7.75 (s, 1H, Ar-H), 7.83 (d, J = 8.4 Hz, 2H, Ar-H), 7.91-7.97 (m, 4H, Ar-H + pyridine-H5), 8.94 (s, 1H, N=CH), 13.64 (s, 1H, NH, pyrazole, exchangeable with D_2O); ^{13}C NMR (101 MHz, DMSO) δ: 23.1, 23.2 ($2CH_2$), 29.3 ($2CH_2$), 06.3, 115.0, 115.2, 118.1, 124.8, 128.3, 129.4, 130.8, 132.8, 134.9, 135.2, 136.1, 136.8, 138.9, 144.7, 152.9, 153.8, 155.7, 162.2 (24C, Ar-C), 159.5 (CH=N); MS: m/z (%):483 (M^++3, 10.4), 482 (M^++2, 33.4), 481 (M^++1, 39.12), 480 (M^+, 100) ; Analysis calcd. for $C_{29}H_{22}ClFN_4$ (480.97): C, 72.42; H, 4.61;Cl, 7.37; F, 3.95; N, 11.65; found: C, 72.21; H, 4.89; Cl, 7.22; F, 4.05;N, 11.74.

4.15 | 4-(((4-(4-Fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)imino)methyl) benzonitrile (14d)

Yield (88%); pale yellow crystals; m.p. 303 to 305°C; IR (KBr, cm^{-1}): υ 3429 (NH), 2925 (CH, alicyclic), 2213 (CN), 1227 (C—F); ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 1.78 (br. s, 4H, $2CH_2$ of tetrahydronaphthalene), 2.78 (m, 4H, $2CH_2$ of tetrahydronaphthalene), 7.14 to 7.9 (m, 12H, Ar-H + pyridine-H5), 9.01 (s, 1H, N=CH), 13.64 (s, 1H, NH, pyrazole, exchangeable with D_2O); ^{13}C NMR (101 MHz, DMSO) δ: 22.4 ($2CH_2$), 28.8, 29.8 ($2CH_2$), 118.5 (CN), 105.3, 113.4, 116.2, 119.1, 122.4, 125.4, 128.2, 129.7, 130.6, 133.1, 137.3, 138.9, 142.8, 145.5, 157.8, 162.3 (24C, Ar-C), 158.2 (CH=N); MS: m/z (%): 473 (M^++2, 5.06), 471 (M^+, 12.62), 75 (100), 342 (24.02), 499 (17.22); Analysis calcd. for $C_{30}H_{22}FN_5$ (471.54):C, 76.42; H, 4.70; F, 4.03; N, 14.85; found: C, 76.25; H, 4.72; F, 3.93; N, 15.02.

4.16 | 1-(4-Fluorophenyl)-N-(4-(4-fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)methanimine (14e)

Yield (73%); yellow crystals; m.p. 252 to 254°C; IR (KBr, cm^{-1}): υ 3432 (NH), 2926 (CH, alicyclic), 1605 (C=N), 1230 (C—F); ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 1.78 (br.s, 4H, $2CH_2$ of tetrahydronaphthalene), 2.82 (br. s, 4H, $2CH_2$ of tetrahydronaphthalene), 7.21 (d, J = 8.0 Hz, 1H, Ar-H), 7.35 (t, J = 8.4 Hz, 4H, Ar-H), 7.76 (d, J = 8.0 Hz, 1H, Ar-H), 7.83 –8.04 (m, 6H, Ar-H + pyridine-H5), 8.94 (s, 1H, N=CH) , 13.62 (s, 1H, NH, pyrazole, exchangeable with D_2O); ^{13}C NMR (101 MHz, DMSO) δ: 22.4 ($2CH_2$), 28.4 ($2CH_2$), 106.0, 115.0, 116.9, 119.5, 122.2, 128.6, 129.3, 130.5, 133.5, 135.1, 136.4, 139.6, 150.2, 150.8, 151.7, 155.4, 163.8, 168.5 (23C, Ar-C), 157.1 (CH=N); MS: m/z (%): 464 (M^+, 84.35), 463 (M^+−1, 30.80), 191 (100), 351 (76.10), 398 (73.39) ; Analysis calcd. for $C_{29}H_{22}F_2N_4$ (464.52): C, 74.98; H, 4.77; F, 8.18; N, 12.06; found: C, 74.78; H, 4.56; F, 8.27; N, 12.36.

4.17 | N-(4-(4-Fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-1-(4-methoxyphenyl)methanimine (14f)

Yield (73%); yellow crystals; m.p. 252 to 254°C; IR (KBr, cmYield 89%; yellow crystals; m.p. 260 to 262°C; IR (KBr, cm^{-1}): υ 3432 (NH), 2925 (CH, alicyclic), 1631 (C=N), 1236 (C—F); ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 1.79 (br.s, 4H, $2CH_2$ of tetrahydronaphthalene), 2.80 (m, 4H, $2CH_2$ of tetrahydronaphthalene), 3.85 (s, 3H, OCH_3), 7.06 (d, J = 8.7 Hz, 2H, Ar-H), 7.22 (d, J = 8.5 Hz, 1H, Ar-H), 7.36 (t, J = 8.8 Hz, 2H, Ar-H), 7.68 to 7.82 (m, 3H, Ar-H), 7.88 to 8.01 (m, 4H, Ar—H+ pyridine-H5), 8.85 (s, 1H, N=CH), 13.60 (s, 1H, NH, pyrazole, exchangeable with D_2O); ^{13}C NMR (101 MHz, DMSO) δ: 22.0, 23.1 ($2CH_2$), 29.2 ($2CH_2$), 55.2 (CH_3), 106.0, 113.0, 116.1, 119.3, 123.3, 127.7, 129.9, 130.6, 132.7, 135.8, 136.3, 139.2, 146.7, 152.4, 151.3, 156.2, 163.4 164.5, (24C, Ar-C) 157.3 (CH=N); MS: m/z (%): 478 (M^++2, 27.84), 476 (M^+, 22.03), 358 (100), 356 (88.15), 257 (83.03); Analysis calcd. for: $C_{30}H_{25}FN_4O$ (476.56):C, 75.61; H, 5.29; F, 3.99; N, 11.76; found: C, 75.41; H, 5.18; F, 3.87; N, 11.98.

4.18 | N-(4-(4-Fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-1-(1H-indol-3-yl)methanimine (14g)

Yield 68%; m.p. 334 to 336°C; IR (KBr, cm^{-1}): υ 3411 (NH), 2923 (CH, alicyclic), 1599 (C═N), 1224 (C—F); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.78 (br.s, 4H, $2CH_2$ of tetrahydronaphthalene), 2.78 (m, 4H, $2CH_2$ of tetrahydronaphthalene), 7.06 (d, J = 8 Hz, 1H, Ar-H), 7.09 to 7.66 (m, 5H, A-H), 7.91(s, 1H, Ar-H), 7.92 to 8.04 (m, 6H, Ar—H+ pyridine-H5), 9.13 (s, 1H, N═CH), 11.82 (s, 1H, NH, indol), 13.60 (s, 1H, NH, pyrazole, exchangeable with D_2O); ^{13}C NMR (101 MHz, DMSO) δ: 22.5 ($2CH_2$), 29.3 ($2CH_2$), 101.4, 106.5, 108.9, 115.5, 121.0, 123.2, 124.9, 128.6, 129.8, 132.6, 136.3, 137.0, 137.6, 143.2, 145.1, 153.3, 155.8, 157.1, 168.50, (26C, Ar-C), 159.6 (CH═N); MS: m/z (%): 486.71 (M^++1, 6), 485.53 (M^+, 38), 484.66 (M^+−1, 6), 60.55 (36.71), 59.92 (100); Analysis calcd. for $C_{31}H_{24}FN_5$ (485.57): C, 76.68; H, 4.98; F, 3.91; N, 14.42; found: C, 76.53; H, 4.92; F, 3.80; N, 14.65.

4.19 | General procedure for the synthesis of thiazolidinone (15a, 15b, 15d, 15e, 15f)

To a solution of the appropriate imine **14a**, **14b**, **14d**, **14e**, and **14f** (0.446 g; 0.001 mol) in dry benzene (80 mL), thioglycolic acid (0.165 g; 0.0015 mol) was added. The reaction mixture was heated at reflux for 6 h. Progress of the reaction was checked by TLC using benzene-ether as an eluent. After evaporation of the solvent under reduced pressure, the resulting viscous liquid was treated with saturated sodium bicarbonate solution to remove unreacted thioglycolic acid. The product separated out was washed with water, dried, and recrystallized from alcohol to give compound **15a**, **15b**, **15d**, **15e**, and **15f**, respectively.

4.20 | 3-(4-(4-Fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-2-phenylthiazolidin-4-one (15a)

Yield (52%); light brown powder; m.p. 190 to 192°C; IR spectrum (KBr, cm^{-1}): υ 3427 (NH), 2923 (CH, alicyclic), 1674 (CO), 1601 (C═N), 1226 (C—F); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.78 (br.s, 4H, $2CH_2$ of tetrahydronaphthalene), 2.79 (m, 4H, $2CH_2$ of tetrahydronaphthalene), 4.60 (s, 2H, SCH_2CO - 2 thiazolidine-H5), 7.20 (s, 1H, CH-S thiazolidine-H2), 7.44 to 7.90 (m, 13H, Ar-H), 12.36 (s, 1H, NH, pyrazole, exchangeable with D_2O); ^{13}C NMR (101 MHz, DMSO) δ: 22.6 ($2CH_2$), 29.1 ($2CH_2$), 32.8 (SCH_2CO), 75.6 (NCHS), 171.1 (C═O), 95.3, 115.6, 118.9, 124.2, 126.6, 127.2, 128.0, 129.4, 130.8, 135.8, 136.2, 139.9, 149.9, 154.6, 157.0, 164.2 (24C, Ar-C); MS: m/z (%): 520 (M^+, 7), 358 (44), 245 (16), 121 (27), 105 (35), 91 (100).; Analysis calcd. for: $C_{31}H_{25}FN_4OS$ (520.63): C, 71.52; H, 4.84; F, 3.65; N, 10.76; S, 6.16; found: C, 71.38; H, 4.76; F, 3.59; N, 10.89; S, 6.05.

4.21 | 2-(4-Bromophenyl)-3-(4-(4-fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)thiazolidin-4-one (15b)

Yield (58%); pale yellow powder; m.p. 210 to 212°C; IR spectrum (KBr, cm^{-1}): υ 3436 (NH), 2923 (CH, alicyclic), 1671 (CO), 1602 (C═N), 1228 (C—F); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.78 (br.s, 4H, $2CH_2$ of tetrahydronaphthalene), 2.78 (m, 4H, $2CH_2$ of tetrahydronaphthalene), 4.59 (s, 2H, $COCH_2S$ −2 thiazolidine-H5), 7.17 (s, 1H, CH-S thiazolidine-H2), 7.34 to 7.95 (m, 12H, Ar-H), 12.33 (s, 1H, NH, pyrazole, exchangeable with D_2O); ^{13}C NMR (101 MHz, DMSO) δ: 22.2 ($2CH_2$), 25.3 ($2CH_2$), 33.6 (SCH_2CO), 69.5 (NCHS), 91.7, 116.1, 119.1, 120.4, 122.3, 127.7, 128.4, 129.9, 130.5, 131.6, 132.0, 135.3, 136.6, 138.7, 139.8, 151.2, 152.8, 154.5, 155.4, 165.1 (24C, Ar-C), 171.3 (C═O); MS: m/z (%): 601 (M^+ +2, 4), 599 (M^+, 6), 598 (M^+−1, 3), 170 (39), 168 (41), 91 (42), 85 (65), 57.07 (100). Analysis calcd. for: $C_{31}H_{24}BrFN_4OS$ (599.52): C, 62.11; H, 4.04; Br, 13.33; F, 3.17; N, 9.35; S, 5.35; found: C, 61.91; H, 3.94; Br, 13.28; F, 2.98; N, 9.68; S, 5.28

4.22 | 4-(3-(4-(4-Fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-oxothiazolidin-2-yl)benzonitrile (15d)

Yield (61%); pale yellow powder; m.p. 214 to 216°C; IR spectrum (KBr, cm^{-1}): υ 3433 (NH), 2922 (CH, alicyclic), 2227 (CN), 1670 (CO), 1599 (C═N), 1229 (C—F); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.78 (s, 4H, $2CH_2$ of tetrahydronaphthalene), 2.83 (m, 4H, $2CH_2$ of tetrahydronaphthalene), 4.57 (s, 2H, $COCH_2S$ - 2 thiazolidine-H5), 7.21(s, 1H, CH-S thiazolidine-H2), 7.42 to 7.94 (m, 12H, Ar-H), 12.18(s, 1H, NH, pyrazole, exchangeable with D_2O); ^{13}C NMR (101 MHz, DMSO) δ: 22.5 ($2CH_2$), 25.5 ($2CH_2$), 33.6 (SCH_2CO), 74.9 (NCHS), 118.7 (CN), 91.7, 111.1, 115.7, 120.1, 123,0, 128.8, 129.5, 130.8, 132.0, 136.4, 137.2, 140.5, 150.8, 151.9, 155.0, 163.6, (24C, Ar-C), 170.0 (C═O). MS: m/z (%): 545 (M+,

8), 544 (M^+−1, 3), 127 (14), 113 (15), 99 (20), 85 (62), 57 (100). Analysis calcd. for: $C_{32}H_{24}FN_5OS$ (545.64): C, 70.44; H, 4.43; F, 3.48; N, 12.84; S, 5.88; found: C, 70.53; H, 4.59; F, 3.46; N, 12.97; S, 5.86.

4.23 | 2-(4-Fluorophenyl)-3-(4-(4-fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)thiazolidin-4-one (15e)

pale yellow powder; m.p. 170 to 172°C; IR spectrum (KBr, cm^{-1}): υ 3429 (NH), 2922 (CH, alicyclic), 1672 (CO), 1602(C═N), 1227 (C—F); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.79 (br.s, 4H, $2CH_2$ of tetrahydronaphthalene), 2.81 (m, 4H, $2CH_2$ of tetrahydronaphthalene), 4.58 (s, 2H, $COCH_2S$), 7.16 (s, 1H, thiazolidine-H2), 7.17 to 8.14 (m, 12H, Ar-H), 13.60 (s, 1H, NH exchangeable with D_2O); ^{13}C NMR (101 MHz, DMSO) δ: 22.2 ($2CH_2$), 26.8 ($2CH_2$), 31.6 ($S\underline{C}H_2CO$), 69.2 (NCHS), 91.3, 115.4, 116.5, 119.1, 121.7, 128.4, 129.1, 130.1, 133.3, 134.9, 136.8, 140.3, 150.4, 150.8, 154.3, 155.8, 162.7, 163.3, (24C, Ar-C), 169.0 (C═O). MS: m/z (%): 538 (M^+, 13), 537 (M^+-1, 5), 99 (32), 85 (76), 57 (100); Analysis calcd. for: $C_{31}H_{24}F_2N_4OS$ (538.62): C, 69.13; H, 4.49; F, 7.05; N, 10.40; S, 5.95; found: C, 69.08; H, 4.38; F, 6.96; N, 10.53; S, 5.83.

4.24 | 3-(4-(4-Fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-2-(4-methoxyphenyl)thiazolidin-4-one (15f)

Yield (45%); pale yellow powder; m.p. 180 to 182°C; IR spectrum (KBr, cm^{-1}): υ 3429 (NH), 2922 (CH, alicyclic), 1672 (CO), 1602(C═N), 1227 (C-F); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.78 (br.s, 4H, $2CH_2$ of tetrahydronaphthalene), 2.79 (m, 4H, $2CH_2$ of tetrahydronaphthalene), 3.76 (s, 3H, OCH_3), 4.59 (s, 2H, $COCH_2S$-2 thiazolidine-H5), 7.17 (s, 1H, CH-S thiazolidine-H2), 7.20 to 7.95 (m, 12H, Ar-H), 12.34 (s, 1H, NH, pyrazole, exchangeable with D_2O); ^{13}C NMR (101 MHz, DMSO) δ: 22.6 ($2CH_2$), 28.9 ($2CH_2$), 34.5 ($S\underline{C}H_2CO$), 54.1 (OCH_3), 74.0 (NCHS), 92.1, 114.5, 115.0, 119.0, 123.9, 128.4, 129.3, 130.3, 131.2, 135.1, 136.6, 139.8, 149.5, 154.5, 155.4, 158.6, 161.6 (24C, Ar-C), 173.5 (C═O); MS: m/z (%): 551.1 (M^+ +1, 2), 550 (M^+, 5), 549 (M^+-1, 3), 400 (27), 386 (45), 358 (100), 357 (58); Analysis calcd. for: $C_{32}H_{27}FN_4O_2S$ (550.65): C, 69.80; H, 4.94; F, 3.45; N, 10.17; S, 5.82; found: C, 69.69; H, 4.67; F, 3.34; N, 10.34; S, 5.69.

4.25 | In vitro anticancer activities

The anticancer activities on HCT116 (colorectal carcinoma) and MCF-7 (human breast adenocarcinoma) human cell lines were assessed using the 3-[4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) assay.[68–70] These cancer cell lines were purchased from ATCC (Rockville, MD, USA). The cells were cultured in a 96-well sterile microplate (5×10^4 cells per well) at 37°C in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% heat-inactivated fetal bovine serum (FBS) and 100 U/mL of both penicillin and streptomycin in a 5% CO_2 humidified atmosphere. After 24 h, the media were removed and fresh serum-free media (90 uL/well) were added together with 10 uL of series of each compound or doxorubicin (positive control) concentrations in DMSO for 48 h. Then, media were removed and MTT (40 μL of 2.5 mg/mL) was added to each well and incubated for 4 hours. DMSO (200 μL) were added to solubilize the formazan dye crystals (purple color). Using a SpectraMax Paradigm Multi-Mode microplate reader, the absorbance was measured at 570 nm. Each experiment was repeated on three different days and conducted in triplicate. The relative cell cytotoxicity was measured according to the following equation:

$$\%\ cytotoxicity = (1 - A_s/A_b)*100,$$

where A_s = Absorbance of each sample and A_b = Absorbance of the blank. The probit analysis using the SPSS software program (version 20, SPSS Inc., Chicago, IL, USA) was used to determine each IC_{50}.

5 | CONCLUSION

Different synthetic approaches were used to construct new derivatives of tetralin nucleus coupled with various substituted pyrazolo[3,4-*b*]pyridine ring system. The sensitivity of two human cancer cell lines, namely HCT116 (human colorectal carcinoma) and breast adenocarcinoma (MCF-7) cell lines, were examined against most of newly synthesized compounds. The parent intermediate 3-amino-pyrazolo[3,4-*b*]pyridine derivative **5** and its *N*-acetylated derivative **9** appeared to be of dual potency against both types of cancer cells. The sensitivity of HCT116 cells was highest against the Schiff bases compounds **14**, while MCF-7 cell line represented the most sensitivity against the formamide derivative **13** and the thiazolidinone derivatives **15**. Accordingly, the new synthesized compounds provided significant anticancer activities and could be considered as promising anticancer agents.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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