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New multi-functionalized pyridines: Facile synthesis, anti-cancer evaluation and *in silico* molecular docking

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Abstract

Developing new compounds with bioactivity, especially against tumors, targeting G-quadruplexes is of great importance. In this direction, some new phthalimide-incorporating pyridine derivatives were synthesized using the phthalimido-acetophenone derivative **1** as a key precursor. Three-component cyclocondensation of compound **1** with various aryl aldehydes and ethyl cyanoacetate or malononitrile utilizing ammonium acetate as the nitrogen source afforded the 4-substituted-6-(4-phthalimidophenyl)pyridin-2-one-3-carbonitriles **2a-e** or the 2-amino-4-substituted-6-(4-phthalimidophenyl)pyridine-3-carbonitriles **3a,b**, respectively. Moreover, the characterization of these derivatives was identified on the basis of elemental analysis and spectroscopic tools. Additionally, the potency of the targeted molecules as anticancer agents was assessed against two carcinogenic human cell lines, namely, colon cancer (HCT-116) and human prostate cancer (PC3) cells. They exhibited promising cytotoxicity in which compounds **2a** and **2b** have the strongest potency comparable with doxorubicin (**Dox**). The conducted molecular docking studies revealed a good correlation between the anti-cancer activities of compounds and their binding effectiveness with both *c-MYC* and *KRAS* G-quadruplexes.

Keywords: Pyridine; Phthalimide; Anticancer agents; Molecular docking.

1. Introduction

Huge death cases due to different cancer types in both genders made cancer as one of the biggest health issues [1]. It accounted for about 9.6 million deaths in 2018 and there will likely be twelve million cancer-related deaths globally by 2030, according to projections [2]. The technological advancement of our culture is one of the main factors contributing to the rise in cancer incidences [3, 4]. Because of issues like severe toxicity and drug resistance, creation of novel, potent anticancer drugs are seen as being extremely important. Heterocyclic nitrogen systems are very important [5] due to their essential function in biological systems, Various heterocyclic nitrogen rings have demonstrated incredibly complex biological properties, elevating them to the position of one of the most significant groups in medicinal chemistry molecules [6].

Both pyridine and its analogues are found in nature and are essential to the study of synthetic heterocyclic chemistry [7]. Furthermore, it was highly present in natural products, such as alkaloids like trigonelline and coenzymes like nicotinamide adenine dinucleotide (NAD), as well as vitamins like niacin and vitamin B_6 [8-10] as well as bioactive substances. Moreover, pyridine derivatives of many heterocyclic compounds have demonstrated significant pharmacological characteristics, including insecticidal, antifungal, and antitubercular effects [11-13].

The biological activities of heterocyclic pyridine derivatives have been found to include antibacterial [14-17,11], antiviral [18-20], antioxidant [21-23], cytotoxic with anticancer, and antitumor properties [24-31,18]. These activities have been observed to be widespread and important [25-31]. In the past half-century, the identification of several bioactive pyridines through various firms has led to an even greater need for pyridine and its derivatives. For more than a century, scientists have been creating procedures for pyridine synthesis because pyridines have large applicability in several chemical fields and a broad range of biological activities [32- 34,11].

Phthalimide is a crucial piece of pharmacophore [35, 36]. It has frequently been used in the development of possible therapeutic candidates for immunomodulatory [37, 38], antiangiogenic [39, 40], anticancer [41, 42], and anti-inflammatory [36]. With such a bright future, the pharmacophoric fragment strategy of phthalimide has been a popular topic in recent studies.

The promoter regions of the c-*MYC* and *KRAS* genes contain G-quadruplex structure, and it is anticipated that small compounds that stabilize G-quadruplexes will simultaneously block these genes [43,44]. The expression of the target genes of oncogene promoters is downregulated when tiny molecules stabilize G-quadruplexes within them. The fact that G-quadruplexes are discrete folded globular DNA structures means that compounds may be developed to specifically recognize and stabilize them, offering a significant advantage over other approaches. This is comparable to therapeutic targeting of folded protein molecules [45].

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In this work, some novel multi-functionalized pyridines were synthesized using the phthalimido-acetophenone derivative **1**, some functionalized aldehydes and active methylene compounds in a one-pot facile procedure. The new compounds' structures were identified using spectroscopy and elemental analysis. In addition, their cytotoxicity was evaluated to inhibit the proliferation of prostate (PC3) and colon (HCT-116) cancer cells, and all results were discussed. Moreover, molecular docking was achieved to check the ability of the compounds to bind with two G-quadruplexes including *c-MYC* and *KRAS*.

2. Experimental protocols

2.1. Materials

Sigma-Aldrich was the source of all utilized compounds, and El Nasr Chemicals provided the solvents. Reported yields are for products that have been purified. Regular examination of reactions was done by silica gel thin-layer chromatography (TLC) (Kieselgel 60 F_{254}), and UV light was used to visualize the results. Melting points in degree Celsius were measured with Gallen-Kamp and the measurements are incorrected. The smart OMNIC-transmission, Nicolet iS10 FT-IR spectrophotometer at Benha University, was used for recording IR spectra (KBr disc). Tetramethylsilane (TMS) as an internal reference and DMSO-d_6 as the solvent were used in the NMR spectra, which were obtained at Zagazig University using a Bruker NMR 400 MHz spectrophotometer. The anti-cancer experiments were conducted at Pharmacognosy Department, Faculty of Pharmacy, Mansoura University.

2.2. Synthesis

2.2.1. Synthesis of 2-(4-acetylphenyl) isoindoline-1,3-dione (1)

1.48 g (10 mmol) of phthalic anhydride and 1.35 g of *p*-aminoacetophenone (10 mmol) in glacial acetic acid (30 mL) were heated at 120 ℃ for 4 h in a reflux system. While hot, the formed solid was filtered and purified by recrystallization from ethanol to give compound **1** in a needle-like shape. The melting point is 233-235 °C, with 90% yield [46]. ^{1}H NMR (DMSO-d_6, δ ppm): 8.15–8.17 (d, 2H, *J* = 7.5 Hz, Ar–H), 7.99–8.02 (d, 2H, *J* = 7.6 Hz, Ar–H), 7.94–7.97 (d, 2H, *J* = 7.8 Hz, Ar–H), 6.74–6.77 (d, 2H, *J* = 7.4 Hz, Ar–H), 2.49 (s, 3H, CH_3).

2.2.2. Synthesis of the functionalized pyridines 2a-e & 3a,b

To an equimolar amount of compound **1** (1.325 g, 5 mmol) and various aryl aldehydes was added ethyl cyanoacetate or malononitrile (5 mmol) and ammonium acetate (3.08 g, 40 mmol, 8 equiv.). Glacial acetic acid (15 mL) was introduced, and the mixture was heated for 12-16 h under reflux. After completion and cooling, crushed ice was used to solidify the products that were filtered out. Pure products were obtained *via* recrystallization from ethanol/DCM mixture.

4-(4-(Dimethylamino)phenyl)-6-(4-(1,3-dioxoisoindolin-2-yl)phenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (2a)

Brown crystals, Yield: 77%, m.p.=130-132 °C. IR (KBr, ν cm^{-1}): 3393 (NH), 3111, 3048 ($CH_{arom.}$), 2993, 2919 ($CH_{aliph.}$), 2208 (CN), 1706, 1679 (CO). ^{1}H NMR (DMSO-d_6, δ ppm): 10.11 (s, 1H, NH), 6.86 (s, 1H, Py.), 7.99-6.80 (m, 12H, Ar-H), 3.15 (s, 6H, $2CH_3$). Anal. calcd. for $C_{28}H_{20}N_4O_3$: C, 73.03; H, 4.38; N, 12.17, Found: C, 73.09; H, 4.36; N, 12.22.

4-(4-(Diethylamino)-2-hydroxyphenyl)-6-(4-(1,3-dioxoisoindolin-2-yl)phenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (2b)

Orange crystals, Yield: 70%, m.p.=210-212 °C. IR (KBr, ν cm^{-1}): 3387, 3317 (OH, NH), 3190, 3097 ($CH_{arom.}$), 2922, 2851 ($CH_{aliph.}$), 2219 (CN), 1735, 1677 (CO). ^{1}H NMR (DMSO-d_6, δ ppm): 11.3 (s, 1H, NH), 10.28 (s, 1H, OH), 6.58 (s, 1H, Py.), 7.99-6.51 (m, 11H, Ar-H), 3.44 (q, 4H, $2CH_2$), 1.12 (t, *J* = 6.76 Hz, 6H, $2CH_3$). Anal. calcd. for $C_{30}H_{24}N_4O_4$: C, 71.42; H, 4.79; N, 11.10, Found: C, 71.36; H, 4.81; N, 11.14.

6-(4-(1,3-Dioxoisoindolin-2-yl)phenyl)-4-(4-hydroxy-3-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (2c)

Off-white crystals, Yield: 78%, m.p.=200-202 °C. IR (KBr, ν cm^{-1}): 3373 (OH, NH), 3138, 3057 ($CH_{arom.}$), 2985, 2939 ($CH_{aliph.}$), 2219 (CN), 1789, 1716, 1680 (CO). ^{1}H NMR (DMSO-d_6, δ ppm): 10.50 (s, 1H, NH), 9.21 (s, 1H, OH), 8.09-6.95 (m, 11H, Ar-H), 6.90 (s, 1H, Py.), 2.70 (s, 3H, OCH_3). Anal. calcd. for $C_{27}H_{17}N_3O_5$: C, 69.97; H, 3.70; N, 9.07, Found: C, 69.93; H, 3.74; N, 9.12.

4-(3,4-Dimethoxyphenyl)-6-(4-(1,3-dioxoisoindolin-2-yl)phenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (2d)

Yellow crystals, Yield: 67%, m.p.=140-142 °C. IR (KBr, ν cm^{-1}): 3344 (NH), 3184, 3058 ($CH_{arom.}$), 2933, 2838 ($CH_{aliph.}$), 2215 (CN), 1774, 1717, 1676 (CO). ^{1}H NMR (DMSO-d_6, δ ppm): 10.25 (s, 1H, NH), 7.97-7.00 (m, 11H, Ar-H), 6.88 (s, 1H, Py.), 3.86 (s, 6H, $2OCH_3$). Anal. calcd. for $C_{28}H_{19}N_3O_5$: C, 70.43; H, 4.01; N, 8.80, Found: C, 70.47; H, 3.94; N, 8.83.

6-(4-(1,3-Dioxoisoindolin-2-yl)phenyl)-2-oxo-4-(thiophen-2-yl)-1,2-dihydropyridine-3-carbonitrile (2e)

Off-white crystals, Yield: 89%, m.p.=142-144 °C. IR (KBr, ν cm^{-1}): 3422, 3349 (NH), 3086, 3027 ($CH_{arom.}$), 2975, 2827 ($CH_{aliph.}$), 2218 (CN), 1716, 1679, (CO). ^{1}H NMR (DMSO-d_6, δ ppm): 10.57 (s, 1H, NH), 8.22 (d, *J* = 6.8 Hz, 2H), 8.11 (d, *J* = 7.6 Hz, 4H), 7.60-7.99 (m, 8H, Ar-H), 6.96 (s, 1H, Py.). Anal. calcd. for $C_{24}H_{13}N_3O_3S$: C, 68.08; H, 3.09; N, 9.92; S, 7.57, Found: C, 68.15; H, 3.03; N, 9.99; S, 7.52.

2-Amino-4-(4-(dimethylamino)phenyl)-6-(4-(1,3-dioxoisoindolin-2-yl)phenyl)nicotinonitrile (3a)

Brown crystals, Yield, 85%, m.p.=161-163 °C. IR (KBr, ν cm^{-1}): 3393 (NH_2), 3075, 3004 ($CH_{arom.}$), 2923, 2865 ($CH_{aliph.}$), 2209 (CN), 1717, 1673 (CO). ^{1}H NMR (DMSO-d_6, δ ppm): 6.84 (s, 2H, NH_2), 8.11 (s, 1H, Py.), 6.80-7.99 (m, 11H, Ar-H), 3.10 (s, 6H, $2CH_3$). Anal. calcd. for $C_{28}H_{21}N_5O_2$: C, 73.19; H, 4.61; N, 15.24, Found: C, 73.17; H, 4.55; N, 15.29.

2-Amino-4-(4-(diethylamino)-3-hydroxyphenyl)-6-(4-(1,3-dioxoisoindolin-2-yl)phenyl)nicotinonitrile (3b)

Orange crystals, Yield: 80%, m.p.= 190-192 °C. IR (KBr, ν cm^{-1}): 3481 (OH), 3360 (NH_2), 3100, 3075 ($CH_{arom.}$), 2975, 2932 ($CH_{aliph.}$), 2222 (CN), 1788, 1719 (CO). ^{1}H NMR (DMSO-d_6, δ ppm): 9.60 (s, 1H, OH), 8.11 (s, 1H, Py.), 6.80-8.09 (m, 11H, Ar-H), 6.60 (s, 2H, NH_2), 3.48 (q, 4H, $2CH_2$), 1.13 (t, 6H, $2CH_3$). Anal. calcd. for $C_{30}H_{25}N_5O_3$: C, 71.56; H, 5.00; N, 13.91, Found: C, 71.61; H, 4.97; N, 13.85.

2.3. Anti-tumor evaluation

The potential cytotoxicity of the produced derivatives against prostate cancer (PC3) and colon cancer (HCT-116) in human cells has been assessed. Their effect to inhibit the growth of the aforementioned cell lines was evaluated by tetrazolium bromide (MTT) assay [47, 48]. The basis of this colorimetric method depends on transforming the yellow MTT by succinate dehydrogenase in mitochondria into purple (formazan derivative). RPMI-1640 media modified by 10% fetal bovine serum was used to cultivate cell lines. At 37 °C in an incubator with 5% CO_2, 100 units/mL of penicillin and 100 µg/mL of streptomycin were introduced as antibiotics. The cell lines were seeded at 1.0 x 10^4 cells/well in a 96-well plate at 37 °C for 48 h with 5% CO_2. Following incubation, the cells were subjected to several concentrations of chemicals and left for a full day of incubation. 20 µL of 5 mg/mL MTT solution was added and incubated for 4 h after the medication treatment had been going on for 24 h. The developed formazan was dissolved by adding 100 µL of dimethyl sulfoxide to each well. Through a plate reader, the percent of viable cells was calculated by measuring the absorbance at 570 nm.

Cell viability% = (A570 of treated samples/A570 of untreated sample) x 100.

2.4. Molecular docking

The tested compounds, **2a**, **2b**, **2d**, **3a** and **Dox,** were subjected to a separate docking with various G-quadruplexes. The 3D-crystal coordinates for these G-quadruplexes; c-*MYC* (PDB ID: 6AU4), and *KRAS* (PDB ID: 6N65) were downloaded from the protein data bank website. The docking and visualizations were performed through the software package of molecular operating environment (MOE) version 2022.02.

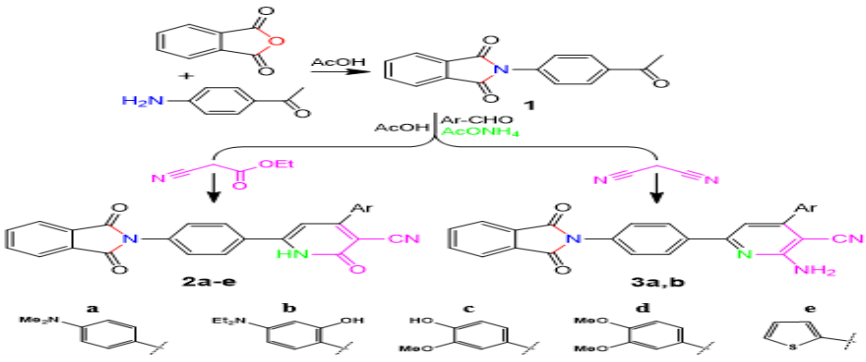
G-quadruplex DNA structures were fixed for any missing atoms by the preparation module in MOE. Using default parameters, 3D-protonation, energy-minimization to a selected gradient and partial charges calculations were applied. The triangle matcher placement method with rigorous receptor refinement was set up to be used by the docking algorithm. For each molecule, fifty poses were created through the programmed triangular match algorithm, however five poses were obtained using the induced fit refining method. Moreover, conformations with the lowest binding energies (the greatest absolute values) were selected using the GBVI/WSA approach as the docking function. Redocking ligands into the receptors enabled the validation of the docking methodology.

3. Results and discussion

3.1. Chemistry

Pyridines and pyridones possess excellent bioactivity against many targets, especially cancer cells. In this work, a facile synthesis for some new multi-functionalized pyridines bearing phthalimide moiety was completed. Primarily, 2-(4-acetylphenyl)isoindoline-1,3-dione (**1**), was obtained according to the literature [46], by condensation of 4-aminoacetophenone with phthalic anhydride. Cyclocondensation of **1**, aryl aldehydes, ethyl cyanoacetate or malononitrile and NH_4OAc [49] afforded 3-cyanopyridin-2-one derivatives **2a-e** or 3-cyanopyridine-2-amine derivatives **3a,b**, respectively, (Scheme 1).

Chemical structures of the derivatives **2a-e, 3a,b** were deduced *via* elemental analysis and spectroscopic data. For instance, the IR of **2d** showed bands for NH and CN at 3344, 2215 cm^{-1}, respectively, and at 1774, 1717 and 1676 cm^{-1} for the three C=O groups. In addition, two singlet signals at 3.86 ppm for two methoxy groups and at 10.25 ppm for NH group appeared in the ^{1}H NMR spectrum.



Scheme 1. Synthetic route for the target cyanopyridine derivatives **2a-e** and **3a,b.**

3.2. In vitro anti-tumor activity

In comparison to the standard doxorubicin (**Dox**) as an anticancer drug, the synthesized compounds showed different levels of inhibitory activity against the assessed human tumor cell lines. Among the series that were examined, compounds **2a** and **2b** showed the greatest cytotoxic effect toward PC3 and HCT-116 with IC_{50} ranges between 8 and 16 mg/mL (**Table 1 and Figures 1,2**). The highest anti-tumor activity against HCT-116 was shown by compounds **2a**, **2b**, and **3a** with IC_{50} values between very strong and moderate. However, the highest antitumor activity against PC3 was shown by the same compounds. On the other hand, others displayed antitumor activity that ranged from moderate to weak toward carcinogenic human cell lines (**Table 1**).

Table 1. IC_{50} (µM) values of the synthesized pyridines against colon (HCT-116) and prostate (PC3) cancer cell lines.

No.	IC_{50} (µM)	
	HCT-116	PC3
2a	**7.99±0.6**	**9.45±0.8**
2b	16.15±1.3	22.51±1.5
2c	53.04±3.2	67.51±3.5
2d	75.38±3.9	84.33±4.2
2e	42.73±2.4	35.08±2.1
3a	64.27±3.6	72.80±3.7
3b	31.77±1.9	50.14±2.9
Dox*	**5.23±0.3**	**8.87±0.6**

Dox* = Doxorubicin

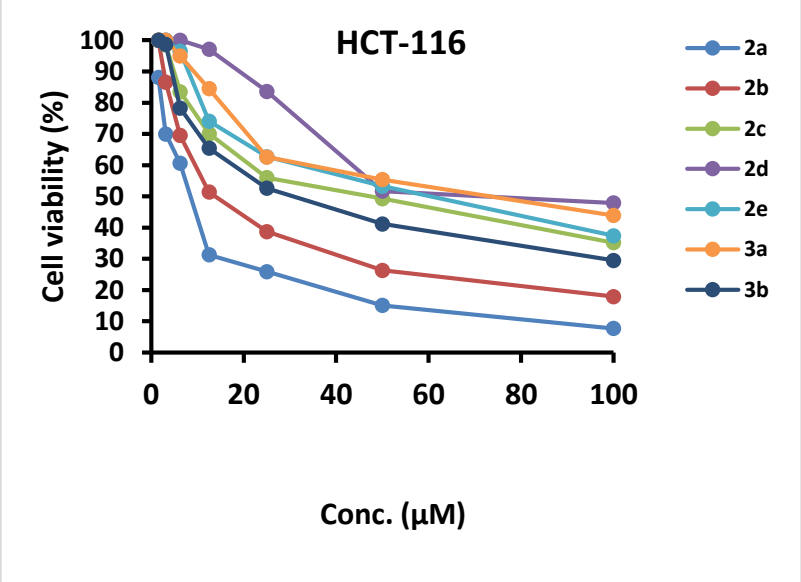


Figure 1. Diagram of average of relative viability of cells (%) of samples against colorectal carcinoma colon cancer (HCT-116).

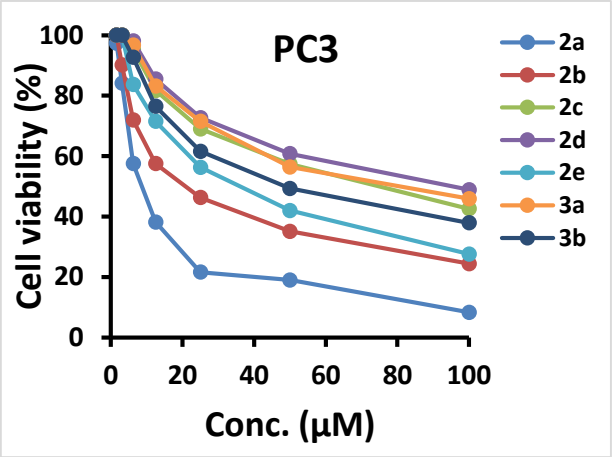


Figure 2. Diagram of average of relative viability of cells (%) of samples against human prostate cancer (PC3).

3.3. Molecular docking studies

The c-*MYC* and *KRAS* genes are key oncogenes that impact cell metabolism, growth, proliferation, and apoptosis. They are linked to several pathways in the development of cancer. Tumorigenesis is induced by enhanced expression of c-*MYC* and *KRAS*, which are seen in around 80% of human cancer cells. Thus, it would be a useful method of preventing cancer by stabilizing G-quadruplexes. Therefore, compounds **2a, 2b, 2d, 3a,** and **Dox** were subjected to docking into the crystal structure

of *c-MYC* and *KRAS* G-quadruplexes that may be useful in anticipating how these compounds will function as anti-cancer drugs.

Binding with c-MYC G-quadruplex

Figures 3 & 4 and **Table 2** show the docking and binding data results for the tested compounds with *c-MYC* G4. Compounds **2a, 2d** and **3a** have similar binding styles to *c-MYC* G4 with maximum strength to **2a** (BE = -7.650 Kcal/mol). Pyridone derivatives **2a** and **2d** could form one hydrogen bond with A21 nucleotide (**Table 2** and **Figure 3**) while the aminopyridine **3a** stabilized *c-MYC via* forming two H-bonds with A21 and A22 (**Figure 4A,C**).

Doxorubicin (**Dox**) with its functionalized structure exhibited a comparable binding efficiency with different binding behavior. It formed 3 hydrogen bonds with A12, G13, G14 and intermolecular arene-arene interactions with G15 (**Figure 4B,D** and **Table 2**). This helped in a good stabilization of the G-quadruplex structure.

Table 2. Binding data of the synthesized compounds and Dox with *c-MYC* G4.

Ligand	BE[a] (Kcal/mol)	RMSD[b]	*c-MYC* G4 interactions	
			H-Bond	Arene-Arene
2a	- 7.650	1.878	A21	--
2b	- 7.400	1.861	A21	--
2d	- 6.670	1.348	A21	--
3a	- 7.625	1.003	A21, A22	--
Dox	- 7.514	1.731	A12, G13, G14	G15

BE[a]: Binding energy; **RMSD[b]:** Root-mean square deviation.

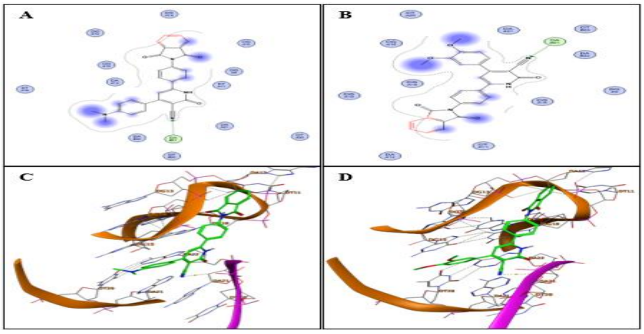


Figure 3. (A,B) 2D-binding modes of *c-MYC* G-quadruplex with **2a** and **2d**, respectively showing H-bond interactions. (C,D) 3D-binding profiles of *c-MYC* G-quadruplex with **2a** and **2d**, respectively.

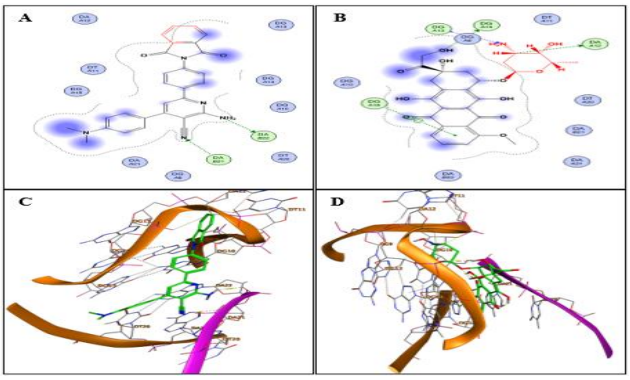


Figure 4. (A,B) 2D-binding modes of *c-MYC* G-quadruplex with **3a** and **Dox**, respectively showing H-bond interactions. (C,D) 3D-binding profiles of *c-MYC* G-quadruplex with **3a** and **Dox**, respectively.

Binding with KRAS G-quadruplex

The results for docking the synthesized pyridine derivatives with *KRAS* G4 are depicted in **Figures 5 & 6** and **Table 3**. Regarding the binding strength, **Dox** showed the strongest binding followed by compound **2a** while **2d** exhibited the weakest binding (**Table 3**). Except **2b**, all compounds formed at least two hydrogen bonds with nucleotides (**Figures 5A,C & 6**). They share binding with the same guanine nucleotide (G13), however **2b** might acquire its binding by strong fitting to the pocket of *KRAS* G-quadruplex (**Figures 5B,D** and **Table 3**).

Table 3. Binding data of the synthesized compounds as well as Dox with *KRAS* G4.

Ligand	BE (Kcal/mol)	RMSD	*KRAS* G4 interactions
			H-Bond
2a	- 7.634	1.904	G13, G20
2b	- 7.486	1.319	--
2d	- 7.062	1.619	G13, A22
3a	- 7.532	1.798	G13, A17
Dox	- 7.713	1.343	G13, G18, A22
Ligand	**BE (Kcal/mol)**	**RMSD**	***KRAS* G4 interactions**
			H-Bond
2a	- 7.634	1.904	G13, G20
2b	- 7.486	1.319	--
2d	- 7.062	1.619	G13, A22
3a	- 7.532	1.798	G13, A17
Dox	- 7.713	1.343	G13, G18, A22

Collectively, the investigated compounds possess a good correlation between their anti-cancer activities and binding effectiveness with both *c-MYC* and *KRAS* G-quadruplexes. This may suggest that such derivatives acquired their activity against cancer by inhibiting the replication of the cell-DNA through the stabilization of G-quadruplexes.

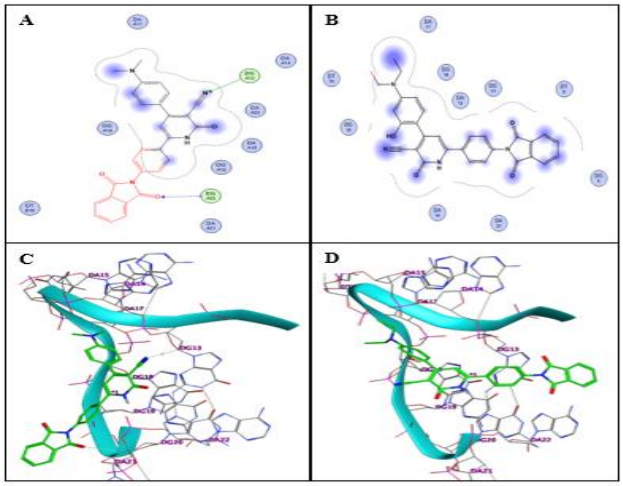


Figure 5. (A,B) 2D-binding modes of *KRAS* G-quadruplex with **2a** and **2b**, respectively showing H-bond interactions. (C,D) 3D-binding profiles of *KRAS* G-quadruplex with **2a** and **2b**, respectively.

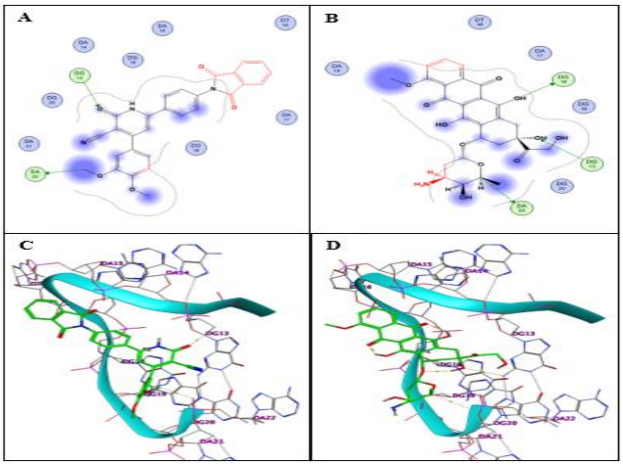


Figure 6. (A,B) 2D-binding modes of *KRAS* G-quadruplex with **2d** and **Dox**, respectively showing H-bond interactions. (C,D) 3D-binding profiles of *KRAS* G-quadruplex with **2d** and **Dox**, respectively.

4. Conclusion

In this work, the reported phthalimide-bearing acetophenone was used as a novel methyl ketone for the synthesis of some new functionalized pyridine derivatives in a one-pot facile procedure. This includes refluxing it separately with a variety of aldehydes, ethyl cyanoacetate or malononitrile in the presence of ammonium acetate. The structures of the formed pyridines were inferred from IR, NMR and elemental analysis. In addition, they were tested to inhibit the proliferation of two cancer cell lines (colon and prostate) and some results were promising. It was expected that these derivatives could stop the cell growth by stabilizing the formation of G-quadruplexes DNA. This was supported by carrying out a molecular docking study to check their binding with such G-quadruplex structures.

5. Conflicts of Interest

No conflicts of interest to be declared by the authors.

6. Institutional Review Board Statement

The study was conducted and approved according to the guidelines of the declaration of the ethical committee of the Faculty of Science, Benha University (BUFS-REC-2024-223 Chm).

7. References

[1] Ali I., Rahis-Uddin, Saleem K., Rather M. A., Wani W. A., Haque A., *Current Cancer Drug Targets*, 11, 135-146 (2011).
[2] World Health Organization, (2024). https://www.who.int/health-topics/cancer (accessed July 2024)
[3] Ali I., Wani W. A., Saleem K., *Cancer Therapy*, 8, 56-70 (2011).
[4] Ali I., Rahis-Uddin, Saleem K., Aboul-Enein H. Y., Rather A., *Cancer Therapy*, 8, 6-14 (2011).
[5] Mahinpour R., Moradi L., Zahraei Z., Pahlevanzadeh N. *Journal of Saudi Chemical Society*, *22*(7), 876-885 (2018).
[6] Mermer A., Keles T., Sirin Y. *Bioorganic Chemistry*, *114*, 105076 (2021).
[7] Li X., Yang H., Xiao J., Zhang J., Zhang J., Liu M., Ma L. *Bioorganic Chemistry*, 96, 103553 (2020).
[8] Bull J. A., Mousseau J. J., Pelletier G., Charette A. B. *Chemical Reviews*, 112(5), 2642-2713 (2012).
[9] Farhanullah A. N., Goel A., Ram V. J. *The Journal of Organic Chemistry*, 68(7), 2983-2985 (2003).
[10] Henry G. D. *Tetrahedron*, 29(60), 6043-6061 (2004).
[11] Pandit A. B., Savant M. M., Ladva K. D. *Journal of Heterocyclic Chemistry*, *55*(4), 983-987 (2018).
[12] Holla B. S., Prasanna C. S., Poojary B., Rao K. S., Shridhara K., Bhat U. G. *Indian Journal of Chemistry*, 43, 864-868 (2004).
[13] Chavan V. P., Sonawane S. A., Shingare M. S., Karale B. K. *Chemistry of Heterocyclic Compounds*, 42, 625-630 (2006).
[14] Raghu M. S., Kumar K., Shamala T., Alharti F. A., Prashanth M. K., Jeon B. H. *Journal of Biomolecular Structure and Dynamics*, *42*(7), 3307-3317 (2024).
[15] Darwish E. S., Abdel Fattah A. M., Attaby F. A., Al-Shayea O. N. *International Journal of Molecular Sciences*, 15(1), 1237-1254 (2014).
[16] Patel N. B., Agravat S. N., Shaikh F. M. *Medicinal Chemistry Research*, 20, 1033-1041 (2011).
[17] El-Sayed H. A., Moustafa A. H., El-Torky A. E., Abd El-Salam E. A. *Russian Journal of General Chemistry*, 87, 2401-2408 (2017).
[18] Abele E., Abele R., Lukevics E. *Chemistry of Heterocyclic Compounds*, 39, 825-865 (2003).
[19] El-Hawash S. A., Abdel Wahab A. E., El-Demellawy M. A. *Archiv der Pharmazie: An International Journal Pharmaceutical and Medicinal Chemistry*, 339(1), 14-23 (2006).
[20] Bernardino A. M., Pinheiro L. C., Ferreira V. F., Azevedo A. R. *Heterocyclic Communications*, *10*(6), 407-410 (2004).
[21] Worachartcheewan A., Prachayasittikul S., Pingaew R., Nantasenamat C., Tantimongcolwat T., Ruchirawat S., Prachayasittikul V. *Medicinal Chemistry Research*, 21, 3514-3522 (2012).
[22] Lavanya M., Asharani I. V., Thirumalai D. *Chemical Biology & Drug Design*, 93(4), 464-472 (2019).
[23] Al-Omar M. A., Youssef K. M., El-Sherbeny M. A., Awadalla S. A. A., El-Subbagh H. I. *Archiv der Pharmazie: An International Journal Pharmaceutical and Medicinal Chemistry*, 338(4), 175-180 (2005).
[24] Kanat O., O'Neil B. H. *Medical Oncology*, *30*, 1-10 (2013).
[25] Kumpan K., Nathubhai A., Zhang C., Wood P. J., Lloyd M. D., Thompson A. S., Threadgill M. D. *Bioorganic & Medicinal Chemistry*, 23(13), 3013-3032 (2015).
[26] Ghosh P. S., Manna K., Banik U., Das M., Sarkar P. *International Journal of Pharmacy and Pharmaceutical Science*, 6, 39-42 (2014).
[27] Bass A. K., Abdelhafez E., El-Zoghbi M., Mohamed M. F., Badr M., Abuo-Rahma G. E. D. A. *Journal of Advanced Biomedical and Pharmaceutical Sciences*, 4(2), 81-86 (2021).
[28] Cheney I. W., Yan S., Appleby T., Walker H., Vo T., Yao N., Wu J. Z. *Bioorganic & Medicinal Chemistry Letters*, 17(6), 1679-1683 (2007).
[29] Bayazeed A. A., Alnoman R. B. *Russian Journal of General Chemistry*, 90, 2004-2011 (2020).
[30] Rani C. S., Reddy A. G., Susithra E., Mak K. K., Pichika M. R., Reddymasu S., Rao M. V. B. *Medicinal Chemistry Research*, 30, 74-83 (2021).
[31] Ibrahim B. A., Mohareb, R. M. *Journal of Heterocyclic Chemistry*, 57(11), 4023-4035 (2020).
[32] Abbas H. A. S., Abo Zeina E. A., Radwan H. A., Shati A. A., Alfaifi M. Y., Elbehairi S. E. I. *Journal of Heterocyclic Chemistry*, 59(11), 1971-1989 (2022).
[33] Bashford K. E., Burton M. B., Cameron S., Cooper A. L., Hogg R. D., Kane P. D., Warne M. R. *Tetrahedron Letters*, 44(8), 1627-1629 (2003).
[34] Döpp D., Hassan A. A., Mourad A. F. E., El-Din A. M. N., Angermund K., Krüger C., Rust J. *Tetrahedron*, 59(27), 5073-5081 (2003).
[35] Hashimoto Y. *Archiv der Pharmazie: An International Journal Pharmaceutical and Medicinal Chemistry*, 341, 536–547 (2008).
[36] Meng X., Han D., Zhang S., Guo W., Cui R., Li, Z. *Carbohydrate Research*, 342, 1169–1174 (2007).
[37] Stewart S. G., Spagnolo D., Polomska M. E., Sin M., Karimi M., Abraham L. J. *Bioorganic and Medicinal Chemistry Letters*, 17, 5819-5824 (2007).
[38] Man H. W., Schafer P., Wong L. M., Patterson R. T., Corral L. G., Raymon H., Blease K., Leisten J., Shirley M. A., Tang Y., Babusis D. M., Chen R., Stirling D., Muller G. W. *Journal of Medicinal Chemistry*, 52, 1522–1524 (2009).

[39] Noguchi T., Fujimoto H., Sano H., Miyajima H., Hashimoto Y. *Bioorganic and Medicinal Chemistry Letters*, 15, 5509–5513 (2005).
[40] Sano H., Noguchi T., Miyajima A., Hashimoto Y. Miyachi H., *Bioorganic and Medicinal Chemistry Letters*, 16, 3068–3072 (2006).
[41] Kok S. H. L., Gambari R., Chui C. H., Yuen M. C. W., Lin E., Wong R. S. M., Lau F. Y., Cheng G. Y. M., Lam W. S., Chan S. H., Lam K. H., Cheng C. H., Lai P. B. S., Yu M. W. Y., Cheung F., Tang J. C. O., Chan A. S. C. *Bioorganic and Medicinal Chemistry*, 16, 3626–3631 (2008).
[42] Chan S. H., Lam K. H., Chui C. H., Gambari R., Yuen M. C. W., Wong R. S. M., Cheng G. Y. M., Lau F. Y. L., Au Y. K., Cheng C. H., Lai P. B. S., Kan C. W., Kok S. H. L., Tang J. C. O., Chan A. S. C. *European Journal of Medicinal Chemistry*, 44, 2736–2740 (2009).
[43] Zhai Q., Gao C., Ding J., Zhang Y., Islam B., Lan W., Hou H., Deng H., Li J., Hu Z., Mohamed H. I., Xu S., Cao C., Haider S. M., Wei D., Selective recognition of c-MYC Pu22 G-quadruplex by a fluorescent probe, *Nucleic Acids Research*, 47, 2190–2204 (2019).
[44] Mohamed H. I., Gao C., Gui Z., Song Z., Wei D., A novel fluorescent probe with a pyrazolo[4,3-c]quinoline core selectively recognizes c-MYC promoter G-quadruplexes, New Journal of Chemistry, 46, 8619-8625 (2022).
[45] Gao C., Liu Z., Hou H., Ding J., Chen X., Xie C., Song Z., Hu Z., Feng M., Mohamed H. I., Xu S., Parkinson G. N., Haider S., Wei D., BMPQ-1 binds selectively to (3+1) hybrid topologies in human telomeric G-quadruplex multimers, *Nucleic Acids Research*, 48, 11259–11269 (2020).
[46] Hosny M. A., Zaki Y. H., Mokbel W. A., Abdelhamid A. O. Synthesis of novel thiazole, pyranothiazole, thiazolo[4,5-*b*]pyridines and thiazolo[5′,4′:5,6]pyrano[2,3-*d*]pyrimidine derivatives and incorporating isoindoline-1,3-dione group. *BMC Chemistry* 13, 37 (2019).
[47] Mosmann T. *Journal of Immunological Methods*, 65(1-2), 55-63 (1983).
[48] Denizot F., Lang R. *Journal of Immunological Methods*, 22, 271-277 (1986).
[49] Abbas I., Gomha S., Elaasser M., Bauomi M. *Turkish Journal of Chemistry*, 39(2), 334-346 (2015).