Asian Journal of Chemistry; Vol. 36, No. 3 (2024), 669-676

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2024.30317

A New Series of Indole and Azaindole Derivatives with Oxo-dihydropyridines: Synthesis, Characterization and Cytotoxicity Studies against Breast Malignant Cell Lines

ARAVINDA KUMAR MADUGULA[1,†], K. JAGADEESH[2,*,†], D.B.N. SURESH VARMA[2], K. GANESH KADIYALA[2], SRINIVASA RAO PEDADA[1], RAMA SWAMY GUTTULA[3], U. NAGABABU[4] and GURURAJA RANGAIAH[1,*]

[1]Centre for Research and Development, PRIST University, Thanjavur-613403, India
[2]Department of Chemistry, Shri Vishnu Engineering College for Women, Bhimavaram-534202, India
[3]Department of Chemistry, Vishnu Institute of Technology, Bhimavaram-534202, India
[4]Department of Engineering Chemistry, S.R.K.R. Engineering College, Chinna Amiram-534204, India
†Both the authors have equal contribution

*Corresponding author: E-mail: kadali.jc@gmail.com

Received: 19 September 2023; *Accepted*: 2 February 2024; *Published online*: 28 February 2024; AJC-21560

In this investigation, a novel series of indole and azaindole comprising oxo-dihydropyridine derivatives was synthesized. From their spectral (^{1}H NMR and FTIR) as well as elemental (MS) investigations, the structures of all the synthesized 12 oxo-dihydropyridine derivatives were determined. Cytotoxicity of synthesized twelve compound was evaluated against MDA-MB-231 malignant breast cells had been assessed. Compound 1,6-diamino-4-(1*H*-indol-3-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile showed more percent of inhibition of growth and four more derivatives showed moderate percent of inhibition of growth counter to MDA-MB-231 malignant breast cells. The derivative 1,6-diamino-4-(1*H*-indol-3-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile showed the highest effectiveness when assessing the IC_{50} value against the malignant breast cell line MDA-MB-231. Each of the compounds synthesized has a druggable character and meets Lipinski's criteria of five.

Keywords: Dihydropyridine derivatives, MDA-MB-231 cell line, Breast cancer, Lipinski's criteria, Inhibition of growth.

INTRODUCTION

Despite advancements in the field of cancer prevention and treatment, cancer continues to be the second leading cause of mortality on a global scale. However, the effectiveness of cancer treatment in the 21st century continues to be a matter of worry, which underscores the need for further research on novel and safer anticancer drugs that exhibit a broader range of cytotoxicity towards tumour cells [1,2]. The emergence of many cancers can be attributed to the intrinsic resistance of cells to undergo apoptosis and their capacity for unrestricted proliferation. Tumour cells possess the capacity to promote their own proliferation, leading to the development of cancer, mostly through biological processes such as meiotic cell division [3,4]. According to projections, it is anticipated that by the conclusion of year 2020, there will be an estimated population of around 7.8 million women who have been diagnosed with breast cancer within the preceding five-year period and are still living. Moreover, it is anticipated that breast cancer will have achieved the designation of being the most prevalent type of cancer on a global scale [5]. After the period of adolescence, females has the capacity to develop breast cancer in any given geographic region. Nevertheless, it is important to highlight that the incidence rates of this particular ailment have a tendency to increase as individuals become older.

The present study demonstrates that N-containing heterocyclic compounds have received considerable attention in recent years due to their notable biological and pharmacological features, as evidenced by a thorough examination of the available literature [6,7]. The compound known as dihydropyridine is characterized by the presence of a nitrogen atom and a six-membered aromatic heterocyclic ring. The structures that are most commonly observed and widely recognized are 1,2- and 1,4-dihydropyridine. The scientific community has shown considerable interest in the 1,2-dihydropyridines owing to their capacity to engage with various biological processes

on a structural level. Recent studies have provided evidence that compounds generated from 1,2-dihydropyridine exhibit significant anticancer properties [8,9].

A significant number of bioactive compounds utilized in the pharmaceutical industry consist of 1,4-dihydropyridine derivatives [10-12]. In contemporary times, there has been an increasing scholarly focus on the amalgamation of hybrid bioactive substances, encompassing various heterocyclic frameworks including two or more constituents [13,14]. Several studies have been carried out to examine various synthetic approaches that have been devised for the synthesis of oxo-dihydropyridines. These compounds demonstrate remarkable physiological activity, which suggests they may have therapeutic values [15-20].

Additional study toward developing a new variety of indole and azaindole compounds, particularly dihydropyridine derivatives, was considered essential based on the reported literature. A new class of hybrid compounds containing indole and azaindole has been synthesized, known as oxo-dihydropyridines, due to its broad pharmacological features and easy availability from the common starting components. In this report, we present the synthesis of newly developed derivatives of oxo-dihydropyridines, incorporating indole and azaindole moieties. The synthesized compounds were thoroughly characterized and their cytotoxic effects on breast cancer cells (MDA-MB-231) were evaluated using the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) assay.

EXPERIMENTAL

The reagent standard chemicals required for the synthetic process were purchased from Sigma-Aldrich, Bangalore, India as well as from SDFCL, Mumbai, India.

Synthesis procedures

Substituted indole/azaindole containing malononitrile derivatives (2a-l): A mixture containing 1.34 g (20 mmol) of malononitrile, 2.9 g (20 mmol) of substituted indole aldehyde/azaindole aldehyde (**1a-l**) and 20 mL of dichloromethane with 1.0 mL of triethylamine was subjected to agitation for 30-60 min at room temperature. In order to obtain the desired intermediates (**3a-l**) in a pure form, a yellow solid was obtained with a yield ranging from 85% to 89%. The resulting precipitate was subjected to filtration, followed by washing using dichloromethane and subsequently air dried at 50-60 ºC.

Indole/azaindole comprising 2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile derivatives (3a-l): A solution was prepared by combining 1.34 g (20 mmol) of malononitrile, 2.9 g (20 mmol) of substituted indole aldehyde/azaindole aldehyde (**1a-l**) and 20 mL of dichloromethane with 1.0 mL of triethylamine. The resulting mixture was then agitated for 30-60 min at ambient temperature. To achieve the required intermediates (**2a-l**) in a purified state, a yellow solid was obtained with a yield ranging from 85% to 89%. The precipitate obtained was filtered, then washed with dichloromethane and afterwards dried using ambient air at a temperature range of around 50-60 ºC.

One pot reaction method: indole/azaindole containing 2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile derivatives (3a-l): A mixture was prepared by combining malononitrile (1.34 g, 20 mmol), piperidine (2.0 mL) and substituted indole aldehyde/azaindole aldehyde (**1a-l**) (2.9 g, 20 mmol) with 100% ethanol (20 mL). The resulting mixture was then stirred for 30 to 60 min at room temperature and refluxed for another duration of 30 to 60 min containing 2.0 g (20 mmol) of cyanoacetic acid hydrazide. The solid substance that resulted from the cooling process was collected using filtration. The crude product obtained from ethanol was subjected to crystallization and subsequently air dried at 50-60 ºC. This procedure yielded pale brown to offwhite solid powder, which were identified as pure products (**3a-l**) with a yield ranging from 58% to 72%.

Characterization: Tetramethylsilane (TMS) was utilized as an internal reference compound to obtain the ^{1}H NMR spectra of indole and azaindole derivatives containing oxo-dihydropyridines (**3a-l**) using a Varian-AS NMR spectrometer operating at a frequency of 400 MHz. The Perkin-Elmer spectrum 100 Model FT-IR spectrometer to record infrared spectra of the synthesized oxo-dihydropyridine derivatives (**3a-l**). The mass spectra of synthesized indole and azaindole compounds, namely oxo-dihydropyridine derivatives (**3a-l**), were obtained utilizing an electro spray ionization (ESI)-equipped instrument (Waters make Micro mass Q-Tof Micro). The Buchi melting point B-545 instrument was utilized to determine the melting points of the synthesized oxo-dihydropyridine derivatives (**3a-l**). Thin layer chromatography was employed to monitor the progress reactions by utilizing coated silica 60 F_{254} and 0.25 mm aluminium sheets manufactured by Merck, USA.

Cytotoxicity activity: The MDA-MB-231 tumour cell lines of breast were propagated in T25 flasks, trypsinized soon after 70-80% confluent growth and their viability was inspected using the trypan blue stain exclusion approach 50,000 seeded cells per well in a 96-well plate were left incubated over 24 h at 37 ºC with CO_2 humidity 5%. In different quantities that ranged from 0-100 µM (2-fold variability), compounds (**3a-l**) were examined in RPMI, medium devoid of fetal bovine serum and incubated over 24 h. The medium was withdrawn from the wells following compound incubation and DDTB (5 mg/10 mL; 100 µL/well) was applied. After incubating with the MTT reagent, the medium was eliminated from the wells, formazan was diluted with 100 mL of aqueous DMSO, and the absorbance was measured at approximately 590 nm. The percentage of inhibition was calculated by using the following equation:

$$\text{Inhibition (\%)} = 100 - \frac{\text{Sample}}{\text{Control}} \times 100$$

The relative cell vitality (%) was calculated in triplicate for each experiment and provided in % in comparison to untreated control cells.

Evaluation of drug likeness for compounds (3a-l): The Lipinski rule pertains to the molecular criteria governing the pharmacokinetics of a drug within an individual's body. This encompasses several aspects such as absorption, circulation, metabolism and elimination [21,22]. The aforementioned rule holds significant importance in the development of pharma-

ceuticals, as it entails the iterative enhancement of the activity, selectivity and drug-like properties of a pharmacologically powerful lead structure. The Molinspiration approach tool was utilized to assess the drug-like properties of specific molecules [23,24].

RESULTS AND DISCUSSION

As depicted in **Scheme-I**, a simple methodology was employed to facilitate the synthesis of novel oxo-dihydropyridine derivatives (**3a-l**) containing indole and azaindole moieties. The indole and aza-indole aldehydes were synthesized following the established protocols described in the relevant scientific literature. To synthesize the methylene malononitrile indole derivatives (**2a-l**), a reaction was conducted between substituted indoles-3-aldehydes or substituted aza-indoles-3-aldehydes (**1a-l**) and malononitrile. The reaction was conducted in the presence of triethylamine (TEA) as base, employing dichloromethane as solvent. Compounds **2a-l** resulting from the reaction were subjected to a further reaction with cyanoacetic acid hydrazide, utilizing piperidine as a base in ethanol at reflux temperature. The reaction exhibited a favourable yield, resulting in the formation of oxo-dihydropyridine derivatives of substituted indoles or substituted aza-indoles (**3a-l**). Various types of substituted indoles-3-aldehydes and substituted aza-indoles-3-aldehydes (**1a-l**) were also employed in the synthesis of the titled compounds (**3a-l**) (**Scheme-I**).

Compound 3a: Pale brown solid, yield: 92%, m.p.: 342-346 ºC. IR (KBr, ν_{max}, cm^{-1}): 3420, 3319 (NH_2), 2209 (C≡N), 1670 (C=O), 1583 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.64 (s, 2H, N-H), 7.11-7.22 (m, 2H, Ar-H), 7.49 (t, *J* = 8.8 Hz, 2H, Ar-H), 7.83 (s, 1H, Ar-H), 8.42 (br s, 2H, N-H), 11.86 (s, 1H, N-H). (ESI) *m/z*: 291.1 $[M+H]^+$.

Compound 3b: Off white solid, yield: 87%, m.p.: 342-346 ºC. IR (KBr, ν_{max}, cm^{-1}): 3419, 3282 (NH_2), 3113, 3046 (Ar-CH), 2212 (C≡N), 1668 (C=O), 1558 (C=C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.39 (s, 3H, CH_3), δ 5.63 (s, 2H, N-H), 7.02-7.04 (m, 1H, Ar-H), 7.26 (s, 1H, Ar-H), 7.38 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.75 (s, 1H, Ar-H), 8.26 (br s, 2H, N-H), 11.91 (s, 1H, N-H). (ESI) *m/z*: 305.1 $[M+H]^+$.

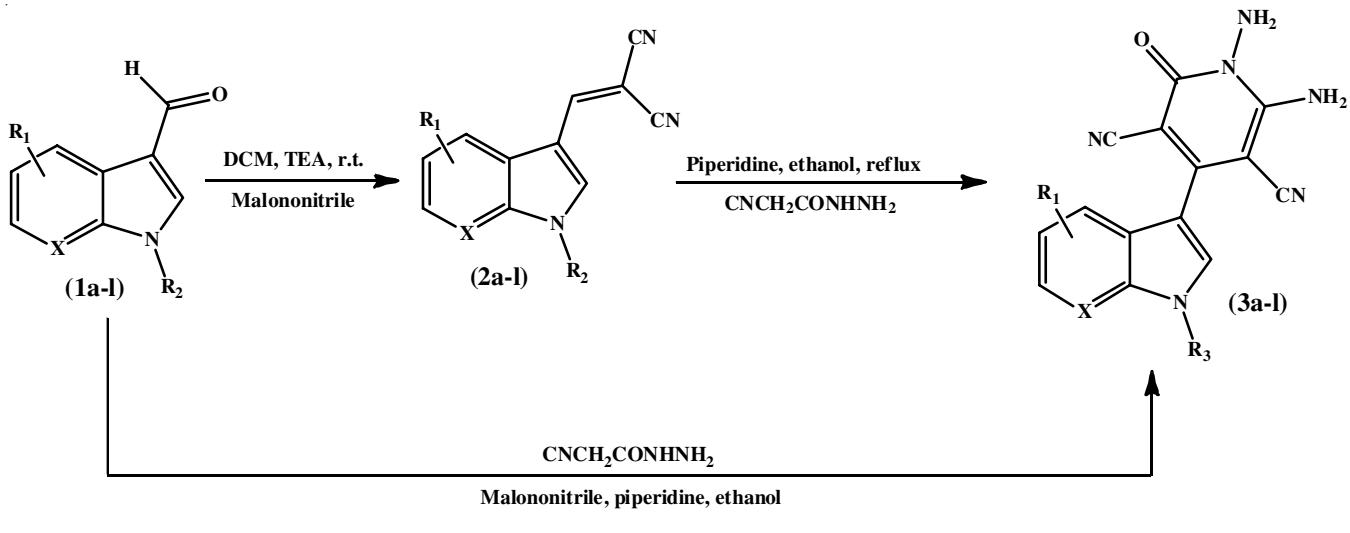
Compound 3c: Off white solid, yield: 83%, m.p.: 383-385 ºC. IR (KBr, ν_{max}, cm^{-1}): 3420, 3297 (NH_2), 3110, 3041 (Ar-CH), 2219 (C≡N), 1671 (C=O), 1546 (C=C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 5.64 (s, 2H, N-H), 7.07 (td, *J* = 9.2, 2.4, 1H, Ar-H), 7.20 (dd, *J* = 10, 2.4 Hz, 1H, Ar-H), 7.51 (dd, *J* = 9.2, 4.4 Hz, 1H, Ar-H), 7.91 (s, 1H), 8.30 (br s, 2H, N-H), 11.97 (s, 1H, N-H). (ESI) *m/z*: 309.1 $[M+H]^+$.

Compound 3d: Pale brown solid, yield: 86%, m.p.: 365-367 ºC. IR (KBr, ν_{max}, cm^{-1}): 3418, 3283 (NH_2), 3108 (Ar-CH), 2213 (C≡N), 1669 (C=O), 1559 (C=C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 5.62 (s, 2H, N-H), 7.32 (dd, *J* = 8.6, 2.0 Hz, 1H, Ar-H), 7.48 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.63 (d, *J* = 2.0 Hz, 1H), 7.87 (s, 1H, Ar-H), 7.49 (d, *J* = 7.6 Hz, 1H, Ar-H). (ESI) *m/z*: 370.1 $[M+H]^+$.

Compound 3e: Off white solid, yield: 91%, m.p.: 356-358 ºC. IR (KBr, ν_{max}, cm^{-1}): 3480, 3343 (NH_2), 3101, 3062 (Ar-CH), 2204 (C≡N), 1683 (C=O), 1537 (C=C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.90 (s, 3H, N-CH_3), δ 5.63 (s, 2H, N-H), 7.18 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.27 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.49 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.56 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.85 (s, 1H, Ar-H), 8.30 (br s, 2H, N-H). (ESI) *m/z*: 305.1 $[M+H]^+$.

Compound 3f: Off white solid, yield: 87%, m.p.: 311-313 ºC. IR (KBr, ν_{max}, cm^{-1}): 3392, 3289 (NH_2), 2215 (C≡N), 1663 (C=O), 1592 (C=C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.41 (s, 3H, CH_3), 3.87 (s, 3H, N-CH_3), δ 5.63 (s, 2H, N-H), 7.09-7.11 (m, 1H, Ar-H), 7.27 (s, 1H, Ar-H), 7.44 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.79 (s, 1H, Ar-H), 8.32 (br s, 2H, N-H). (ESI) *m/z*: 319.1 $[M+H]^+$.

Compound 3g: Off white solid, yield: 79%, m.p.: 342-344 ºC. IR (KBr, ν_{max}, cm^{-1}): 3419, 3284 (NH_2), 3129, 3054



a: X = C, R_1 = H, R_2 = H
b: X = C, R_1 = CH_3, R_2 = H
c: X = C, R_1 = F, R_2 = H
d: X = C, R_1 = Br, R_2 = H
e: X = C, R_1 = H, R_2 = CH_3
f: X = C, R_1 = CH_3, R_2 = CH_3
g: X = C, R_1 = F, R_2 = CH_3
h: X= C, R_1 = Br, R_2 = CH_3
i: X= N, R_1 = H, R_2 = H
j: X= N, R_1 = Cl, R_2 = H
k: X= N, R_1 = H, R_2 = CH_3
l: X= N, R_1 = Cl, R_2 = CH_3

Scheme-I: Synthesis of new series of indole or aza-indole containing oxo-dihydropyridine derivatives

(Ar-CH), 2216 (C≡N), 1653 (C=O), 1592 (C=C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.91 (s, 3H, N-CH$_3$), δ 5.64 (s, 2H, N-H), 7.14 (td, *J* = 9.4, 2.4 Hz, 1H, Ar-H), 7.23 (dd, *J* = 10, 2.4 Hz, 1H, Ar-H), 7.59 (dd, *J* = 9.0, 4.4 Hz, 1H, Ar-H), 7.94 (s, 1H, Ar-H), 8.36 (br s, 2H, N-H). (ESI) *m/z*: 323.1 [M+H]$^+$.

Compound 3h: Pale yellow solid, yield: 88%, m.p.: 291-293 ºC. IR (KBr, ν_{max}, cm^{-1}): 3424, 3214 (NH$_2$), 3051 (Ar-CH), 2214 (C≡N), 1667 (C=O), 1607 (C=N), 1555 (C=C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.90 (s, 3H, N-CH$_3$), δ 5.63 (s, 2H, N-H), 7.40 (dd, *J* = 8.8, 1.6 Hz, 1H, Ar-H), 7.56 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.65 (d, *J* = 1.6 Hz, 1H, Ar-H), 7.91 (s, 1H, Ar-H), 8.34 (br s, 2H, NH). (ESI) *m/z*: 380.9 [M-H]$^+$.

Compound 3i: Off white solid, yield: 85%, m.p.: 325-327 ºC. IR (KBr, ν_{max}, cm^{-1}): 3434, 3287 (NH$_2$), 2215 (C≡N), 1668 (C=O), 1620 (C=N), 1547 (C=C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 5.66 (s, 2H, N-H), 7.22 (dd, *J* = 8.2, 4.8 Hz, 1H, Ar-H), 7.92 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.0 (s, 1H, Ar-H), 8.34 (d, *J* = 4.8 Hz, 3H, Ar-H), 12.49 (br s, 1H, N-H). (ESI) *m/z*: 290.0 [M-H]$^+$.

Compound 3j: Pale brown solid, yield: 91%, m.p.: 263-265 ºC. IR (KBr, ν_{max}, cm^{-1}): 3341, 3163 (NH$_2$), 2216 (C≡N), 1656 (C=O), 1608 (C=N), 1541 (C=C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 5.67 (s, 2H, N-H), 7.30 (d, *J* = 5.2 Hz, 1H, Ar-H), 7.96 (s, 1H, Ar-H), 8.29 (d, *J* = 4.4 Hz, 1H, Ar-H). (ESI) *m/z*: 326.0 [M+H]$^+$.

Compound 3k: Off white solid, yield: 84%, m.p.: 351-353 ºC. IR (KBr, ν_{max}, cm^{-1}): 3410, 3297 (NH$_2$), 3089 (Ar-CH), 2214 (C≡N), 1610 (C=N), 1533 (C=C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.93 (s, 3H, N-CH$_3$), δ 5.64 (s, 2H, N-H), 7.26 (dd, *J* = 8.0, 4.8 Hz, 1H, Ar-H), 7.94 (dd, *J* = 7.6, 1.6 Hz, 1H, Ar-H), 8.08 (s, 1H, Ar-H), 8.32 (br s, 2H, N-H), 8.39 (dd, *J* = 4.8, 1.6 Hz, 1H, Ar-H). (ESI) *m/z*: 306.1 [M+H]$^+$.

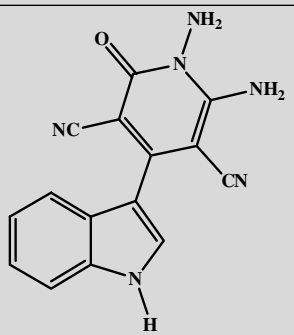
Compound 3l: Off white solid, yield: 89%, m.p.: 376-378 ºC. IR (KBr, ν_{max}, cm^{-1}): 3395, 3268 (NH$_2$), 3107 (Ar-CH), 2216 (C≡N), 1672 (C=O), 1620 (C=N), 1546 (C=C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.93 (s, 3H, N-CH$_3$), δ 5.66 (s, 2H, N-H), 7.35 (d, *J* = 5.2 Hz, 1H, Ar-H), 8.04 (s, 1H, Ar-H), 8.34 (s, 1H, Ar-H), 8.35 (br s, 2H, N-H). (ESI) *m/z*: 340.0 [M+H]$^+$.

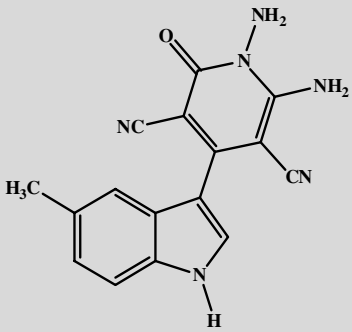
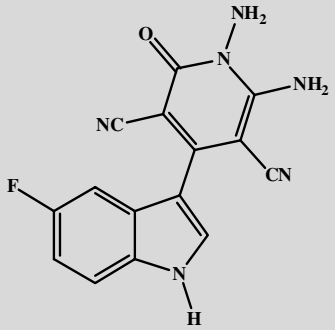
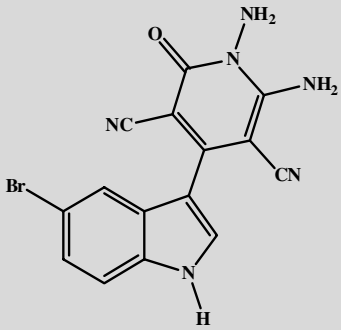
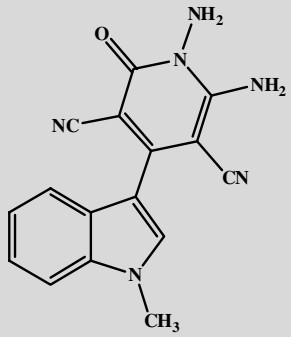
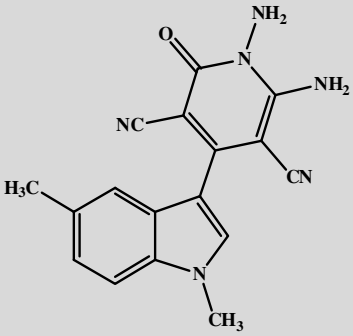
The mass spectra of a synthesized series of indole and azaindole derivatives with oxo-dihydropyridines (**3a-l**) were examined and matched with molecular weights. The IR spectra of compounds **3a-l** showed absorbance at around 3420, 3319 cm^{-1} for NH$_2$ group, 2210 cm^{-1} for C≡N and pyridone C=O at 1670 cm^{-1}. Also, the NMR spectra of compounds **3a-l** showed indole NH at δ 11.86 ppm and aza-indole NH at δ 12.49 ppm. The presence of N-NH$_2$ at around δ 5.64 ppm, C-NH$_2$ at around δ 8.42 ppm and disappearance of the CH$_2$ protons further confirmed structures of the synthesized compounds **3a-l**. The aromatic protons matched their respective multiplicities.

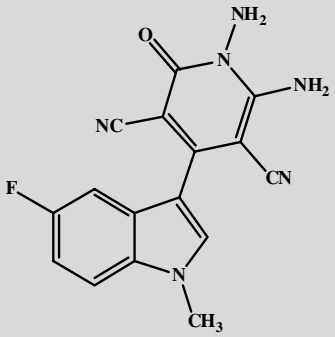
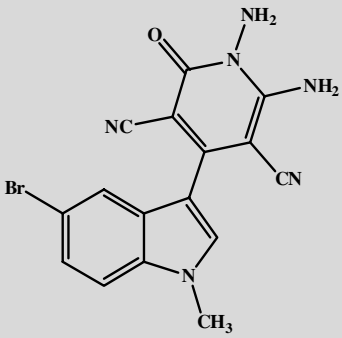
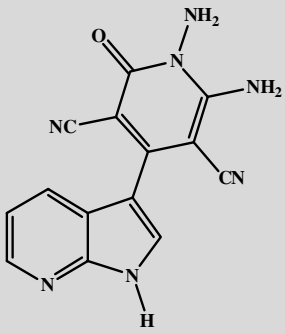
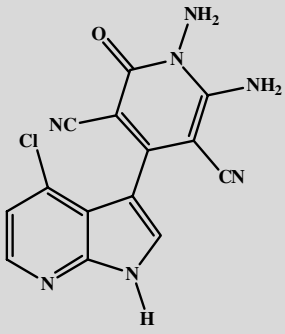
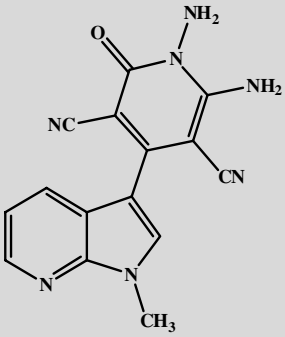
Cytotoxicity activity: The potential cytotoxic efficacy of all newly synthesized target compounds **3a-l** was assessed on MDA-MB-231 breast cancer cell lines using the MTT assay technique. The MTT technique employs the utilization of mitochondrial dehydrogenases as a means to assess the functionality of the viable cells. When prepared in medium or salt solutions without phenol red, the key component MTT produces a solution with a yellow colour. In order to generate a purple formazan compound that is insoluble, the enzymes found in the mitochondria of live cells are responsible for cleaving the tetrazolium ring structure of the suspended MTT. DMSO was utilized as solvent to dissolve the water-insoluble purple formazan. A spectrophotometric examination was conducted on the resulting purple solution at a wavelength of 590 nm. The amount of formazan generated exhibits variations in accordance with alterations in cell population, indicating the extent of cytotoxicity induced by the experimental compound. The relative cell vitality (%) is represented as a percentage in relation to the untreated control cells. The inhibition % statistics are presented in Table-1.

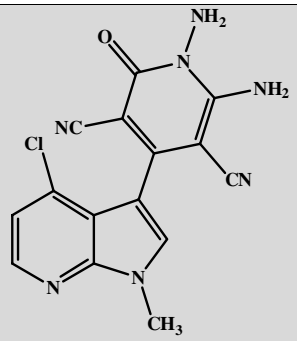
Among them, compound **3a** showed more percent of inhibition of growth and compounds **3b**, **3c**, **3k** and **3l** showed moderate percent of inhibition of growth against MDA-MB-231 breast malignancy cell lines (Fig. 1). The 50% inhibitory concentration (IC$_{50}$) value of compound **3a** was 62.69 (Fig. 2). It is confirmed that compound **3a**, which consists of simple indole oxo-dihydropyridines without substitution, exhibited a higher percentage of inhibition in the growth of cancer cells. The further compounds, namely **3b** (with a methyl substitution on indole ring), **3c** (with fluoro substitution on indole ring), **3k** (with an N-methyl azaindole ring) and **3l** (with a chloro substitution on N-methyl azaindole ring), exhibited moderate activity against the MDA-MB-231 breast cancer cells.

TABLE-1
CYTOTOXICITY OF EXAMINED SUBSTANCES (**3a-l**) TOWARDS MDA-MB-231 BREAST MALIGNANCY CELLS

Compound No.	Structure	Quantity (μM)	Absorbance obtained	Inhibition (%) (n = 3)
Control			0.5965	0.00
3a		6.25	0.5597	6.17
		12.5	0.5038	15.54
		25	0.4281	28.23
		50	0.3869	35.14
		100	0.2646	55.64

3b		6.25 12.5 25 50 100	0.5709 0.5335 0.4988 0.4221 0.3811	4.29 10.56 16.38 29.24 36.11
3c		6.25 12.5 25 50 100	0.5638 0.5334 0.4844 0.4329 0.4044	5.48 10.58 18.79 27.43 32.20
3d		6.25 12.5 25 50 100	0.5767 0.5447 0.4918 0.4562 0.4377	3.32 8.68 17.55 23.52 26.62
3e		6.25 12.5 25 50 100	0.5845 0.5565 0.5036 0.4661 0.4238	2.01 6.71 15.57 21.86 28.95
3f		6.25 12.5 25 50 100	0.5889 0.5678 0.5416 0.5036 0.4851	1.27 4.81 9.20 15.57 18.68

3g		6.25 12.5 25 50 100	0.5835 0.5545 0.5177 0.4884 0.4673	2.18 7.04 13.21 18.12 21.66
3h		6.25 12.5 25 50 100	0.5818 0.5662 0.5424 0.4811 0.4293	2.46 5.08 9.07 19.35 28.03
3i		6.25 12.5 25 50 100	0.5691 0.5388 0.5275 0.5062 0.4711	4.59 9.67 11.57 15.14 21.02
3j		6.25 12.5 25 50 100	0.5865 0.5651 0.5189 0.4971 0.4923	1.68 5.26 13.01 16.66 17.47
3k		6.25 12.5 25 50 100	0.5763 0.5443 0.4988 0.4267 0.3828	3.39 8.75 16.38 28.47 35.83

3l		6.25 12.5 25 50 100	0.5691 0.5437 0.5024 0.4691 0.4016	4.59 8.85 15.78 21.36 32.67

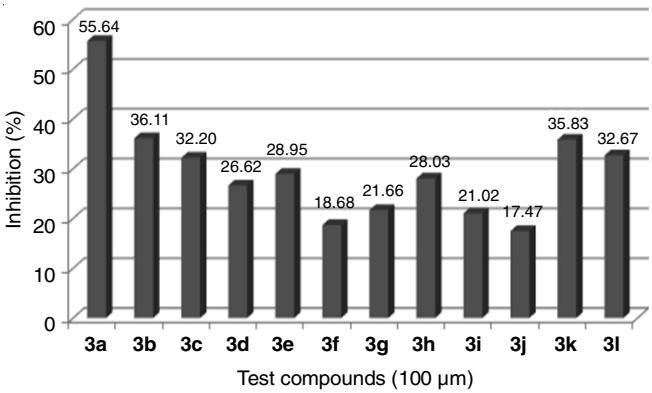


Fig. 1. Inhibition profile of test compounds at 100 µM against MDA-MB-231 breast malignant cell

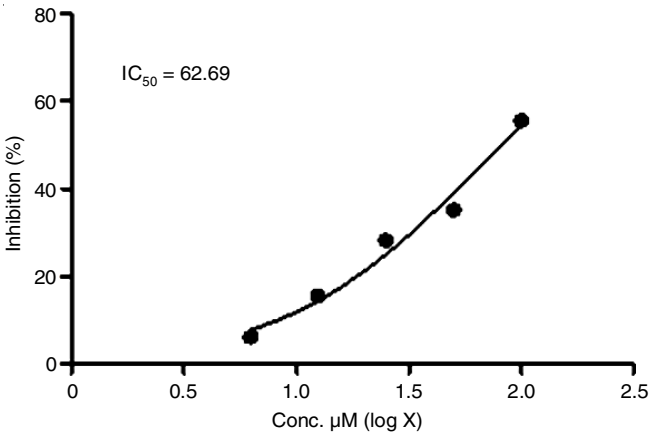


Fig. 2. Half maximal inhibitory concentration (IC_{50}) of **3a**

Drug likeness of compounds: In order to further the study of cytotoxicity, the evaluation of the synthesized compounds **3a-l** drug similarity activity is conducted in accordance with Lipinski's criterion, which consists of five assessments. According to this rule, it is required that a drug possesses a molecular weight that does not exceed 500 µg/mol. Additionally, the drug should have a partition coefficient, log P, that is not greater than 5. Furthermore, the drug should contain a maximum of five hydrogen bond donors, specifically -OH and -NH groups and a maximum of 10 hydrogen bond acceptors, particularly N and O. The recently synthesized compounds **3a-l** exhibit compliance with Lipinski's rule and possess a pharmacologically viable nature. The results have been aggregated and presented in Table-2.

TABLE-2
DRUG LIKE ASSETS OF INDOLE AND INDOLE-INDOLE CONTAINING OXO-DIHYDROPYRIDINE DERIVATIVES

Compd.	m.w.	log P	nON	nOHNH
3a	245.08	0.90	7	5
3b	261.64	1.33	7	5
3c	250.01	0.07	7	5
3d	262.96	1.69	7	5
3e	262.02	0.97	7	4
3f	278.58	1.40	7	4
3g	266.95	0.14	7	4
3h	279.90	1.76	7	4
3i	240.90	0.00	8	5
3j	254.46	0.61	8	5
3k	257.86	0.07	8	4
3l	271.40	0.68	8	4

Conclusion

A novel set of derivatives of oxo-dihydropyridines (**3a-1**) were successfully synthesized by incorporating indole and azaindole moieties. Subsequently,their cytotoxic properties were also evaluated. All of the synthesized compounds **3a-l** possess druggable properties and conform to Lipinski's rule of 5.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. S. Chen, Y. Zhao, S. Liu, J. Zhang, Y.G. Assaraf, W. Cui and L. Wang, *Drug Resist. Updat.*, **61**, 100821 (2022); https://doi.org/10.1016/j.drup.2022.100821
2. N. Gupta, T.T. Huang, S. Horibata and J.M. Lee, *Pharmacol. Res.*, **178**, 106162 (2022); https://doi.org/10.1016/j.phrs.2022.106162
3. S.M. Tu, C.C. Guo, D.S. Chow and N.M. Zacharias, *Cancers*, **14**, 1548 (2022); https://doi.org/10.3390/cancers14061548
4. X. Li, M. Li, M. Huang, Q. Lin, Q. Fang, J. Liu, X. Chen, L. Liu, X. Zhan, H. Shan, D. Lu, Q. Li, Z. Li and X. Zhu, *Biomed. Pharmacother.*, **150**, 113064 (2022); https://doi.org/10.1016/j.biopha.2022.113064
5. S. Lukasiewicz, M. Czeczelewski, A. Forma, J. Baj, R. Sitarz and A. Stanislawek, *Cancers*, **13**, 4287 (2021); https://doi.org/10.3390/cancers13174287
6. N. Kerru, L. Gummidi, S. Maddila, K.K. Gangu and S.B. Jonnalagadda, *Molecules*, **25**, 1909 (2020); https://doi.org/10.3390/molecules25081909

7. A. Majumder, R. Gupta and A. Jain, *Green Chem. Lett. Rev*., **6**, 151 (2013); https://doi.org/10.1080/17518253.2012.733032
8. R.N. Goto, L.M. Sobral, L.O. Sousa, C.B. Garcia, N.P. Lopes, J. Marín-Prida, E. Ochoa-Rodríguez, Y. Verdecia-Reyes, G.L. Pardo-Andreu and C. Curti, *Eur. J. Pharmacol.,* **819**, 198 (2018); https://doi.org/10.1016/j.ejphar.2017.12.009
9. Y. Ling, Z.Y. Hao, D. Liang, C.L. Zhang, Y.F. Liu and Y. Wang, *Drug Des. Devel. Ther*., **15**, 4289 (2021); https://doi.org/10.2147/DDDT.S329547
10. A.M. Vijesh, A.M. Isloor, S.K. Peethambar, K.N. Shivananda, T. Arulmoli and N.A. Isloor, *Eur. J. Med. Chem*., **46**, 5591 (2011); https://doi.org/10.1016/j.ejmech.2011.09.026
11. D. Viradiya, S. Mirza, F. Shaikh, R. Kakadiya, A. Rathod, N. Jain, R. Rawal and A. Shah, *Anticancer Agents Med. Chem.,* **17**, 1003 (2017); https://doi.org/10.2174/1871520616666161206143251
12. A.P. Makam, *RSC Adv*., **12**, 29253 (2022); https://doi.org/10.1039/d2ra04589c
13. K. Bozorov, J. Zhao and H.A. Aisa, *Bioorg. Med. Chem*., **27**, 3511 (2019); https://doi.org/10.1016/j.bmc.2019.07.005
14. V. Khwaza, S. Mlala, O.O. Oyedeji and B.A. Aderibigbe, *Molecules*, **26**, 2401 (2021); https://doi.org/10.3390/molecules26092401
15. O.V. Ershov, S.V. Fedoseev, M.Yu. Belikov and M.Y. Ievlev, *RSC Adv.*, **5**, 34191 (2015); https://doi.org/10.1039/C5RA01642H
16. S.V. Fedoseev, K.V. Lipin and O.V. Ershov, *Pharm. Chem. J*., **56**, 325 (2022); https://doi.org/10.1007/s11094-022-02638-7
17. V.V. Dotsenko, A.A. Russkih, N.A. Aksenov and I.V. Aksenova, *Proceedings*, **41**, 24 (2019); https://doi.org/10.3390/ecsoc-23-06523
18. D.S. Malhi, H.S. Sohal, K. Singh, Z.M. Almarhoon, A.B. Bacha and M.I. Al-Zaben, *ACS Omega*, **7**, 16055 (2022); https://doi.org/10.1021/acsomega.2c01316
19. R. Mathur, K.S. Negi, R. Shrivastava and R. Nair, *RSC Adv*., **11**, 1376 (2021); https://doi.org/10.1039/d0ra07807g
20. C. Safak and R. Simsek, *Mini Rev. Med. Chem*., **6**, 747 (2006); https://doi.org/10.2174/138955706777698606
21. L.Z. Benet, C.M. Hosey, O. Ursu and T.I. Oprea, *Adv. Drug Deliv. Rev*., **101**, 89 (2016); https://doi.org/10.1016/j.addr.2016.05.007
22. A. Mullard, *Nat. Rev. Drug Discov*., **17**, 777 (2018); https://doi.org/10.1038/nrd.2018.197
23. R. Srivastava, *ACS Omega*, **6**, 24891 (2021); https://doi.org/10.1021/acsomega.1c03736
24. T. Khan, S. Dixit, R. Ahmad, S. Raza, I. Azad, S. Joshi and A.R. Khan, *J. Chem. Biol*., **10**, 91 (2017); https://doi.org/10.1007/s12154-017-0167-y