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Antioxidant and Anticancer Potentials of Some Pyrazole and Pyrimidine Derivatives of 1,3-Diphenylprop-2-en-1-one

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Abstract

The diverse biological activities of chalcones and their heterocyclic derivatives have garnered significant attention in the field of medicinal chemistry due to their broad range of pharmacological effects. In this study, the chalcone derivative 1,3-diphenylprop-2-en-1-one (**1**) was synthesized by the reaction of benzaldehyde and acetophenone in the presence of 40% aqueous sodium hydroxide at room temperature. This intermediate chalcone (**1**) was then converted into the pyrazoline derivative, 1,3,5-triphenyl-2-pyrazoline (**2**), through a reaction with phenylhydrazine. In parallel, another reaction of chalcone **1** with guanidine hydrochloride resulted in the formation of a pyrimidine derivative, 4,6-diphenylpyrimidine-2-amine (**3**). Moreover, phenyl(3-phenyloxiran-2-yl)methanone (**4**) was synthesized by reacting chalcone **1** with hydrogen peroxide, which was then further subjected to phenylhydrazine to yield 1,3,5-triphenyl-1*H*-pyrazol-4-ol (**5**). All the synthesized compounds were thoroughly characterized using ^{1}H NMR and IR spectroscopy to confirm their chemical structures. To evaluate the potential biological activity of these compounds, their cytotoxicity and antioxidant properties were assessed. The cytotoxicity assay, using HeLa cells, revealed that compounds **1**, **3**, and **5** exhibited potent antiproliferative effects, with cell survival rates dropping to less than 5%. In parallel, the antioxidant activity was evaluated using the DPPH (1,1-diphenyl-2-picrylhydrazyl) free radical scavenging assay, which showed that the compounds exhibited varying levels of antioxidant activity, with IC_{50} values ranging from 37.30 to 281.76 µg/ml. Additionally, the drug-likeness, physicochemical properties, and pharmacokinetic profiles of these compounds were comprehensively analyzed using the SwissADME web tool, providing valuable insights into their potential for further development as therapeutic agents.

Key words: Chalcone, pyrazole, pyrimidine, DPPH, HeLa cell, drug-likeness.

Introduction

Chalcones are a category of chemicals characterized by a molecular structure including two aromatic rings connected by a conjugated α,β-unsaturated carbonyl system. This structural framework functions as a versatile platform for the synthesis of a wide range of derivatives with enhanced or novel pharmacological properties. One promising approach to modifying chalcone derivatives involves the incorporation of pyrazole and pyrimidine rings, which have been shown to improve the therapeutic potential of these compounds. Pyrimidine is a heterocyclic molecule that consists of six members, and it contains two nitrogen atoms at positions 1 and 3. In addition, pyrimidine derivatives are well-known for their biological actions, which include anticancer, antitumor, anti-HIV, antibacterial, antileishmanial and so on (Bano *et al*., 2012; Tylińska *et al*., 2021). Pyrazole derivatives were reported to act as

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antimicrobial, anticancer, anti-inflammatory, etc. (Shaik *et al*., 2020). The resulting chalcone-based derivatives have exhibited a broad spectrum of biological activities, showcasing their versatility in medicinal chemistry. With ongoing research into the diverse pharmacological activities of chalcone derivatives, this class of compounds continues to show significant promise in the design of multifaceted drugs that can address a wide range of medical conditions.

Oxidative stress is a biological state characterized by a disproportion between the generation of free radicals, and the organism's capacity to neutralize or rectify the ensuing damage. The oxidative cascade initiated by reactive oxygen species (O_2^-, H_2O_2, and •OH) compromises cellular integrity through deleterious modifications to essential macromolecules including nucleic acids, proteins, and lipid membranes. Over time, this oxidative damage accumulates and is thought to facilitate the formation and progression of numerous chronic diseases, including cancer, diabetes and neurodegenerative disorders, etc. To combat the damaging effects of oxidative stress, the body relies on antioxidant molecules that can scavenge free radicals, reduce reactive oxygen species formation, and activate internal repair systems to restore cellular function. Antioxidants play a crucial role in maintaining cellular homeostasis, and protecting the body against diseases. However, an overwhelming or prolonged exposure to oxidative stress can overwhelm these protective mechanisms, leading to pathological conditions (Abrescia and Golino, 2005; Feletou *et al*.; Hua *et al*., 2009; Lahera *et al*., 2007; Victor *et al*., 2009). Pyrazole and pyrimidine derivatives might serve as antioxidant elements (Rani *et al*., 2017; Shaik *et al*., 2020).

Cancer is a significant global health crisis, responsible for millions of deaths annually. It has emerged as one of the leading causes of both morbidity and mortality across the world, a trend driven by its rising prevalence, particularly in aging populations. The disease's complex and multifactorial nature further complicates efforts to control it. Characterized by the uncontrolled division and growth of abnormal cells, cancer has the ability to invade surrounding tissues and spread throughout the body, leading to metastatic disease. This makes its treatment particularly challenging, as each type of cancer behaves uniquely and requires tailored therapeutic approaches. In recent years, advancements in early detection and diagnostic techniques have improved, yet the search for effective and targeted anticancer drugs continues to be a formidable task. Researchers and clinicians are constantly exploring new avenues for therapy, focusing on not only traditional treatments like chemotherapy and radiation but also on immunotherapies, targeted therapies and personalized medicine. Despite significant progress, cancer remains one of the most formidable adversaries in the field of medicine, and the need for innovative, more effective treatments remains critical in the ongoing battle against this devastating disease. In order to obtain new anticancer drugs of cytotoxic class, new drug molecules are required and in this case, the pyrazole and pyrimidine derivatives might play a vital role (Albratty and Alhazmi, 2022; Mahapatra *et al*., 2021; Shaik *et al*., 2020).

Dual-function compounds, which are molecules that serve as both antioxidants and anticancer medicines, are a potential and rising area of interest in the arena of drug discovery. The idea that oxidative stress is a substantial factor to both the beginning stages of cancer and its progression is the foundation upon which this novel method is built. Dual-function medications try to correct this imbalance inside cancer cells by addressing the pathways that are involved in oxidative stress through their treatment (Di Domenico *et al*., 2012; Mileo and Miccadei, 2016).

Based on the facts, in this study, a chalcone, 1,3-diphenylprop-2-en-1-one chalcone (**1**), was produced by condensing acetophenone and benzaldehyde. It was transformed into many heterocyclic derivatives, such as 1,3,5-triphenyl-2-pyrazoline (**2**), 4,6-diphenylpyrimidine-2- amine (**3**), phenyl(3-phenyloxiran-2-yl)methanone (**4**) and 1,3,5-triphenyl-

1*H*-pyrazol-4-ol (**5**). All of these synthetic compounds (**1**–**5**) were tested for their antioxidant and anticancer properties by an *in vitro* free radical scavenging experiment using DPPH and an antiproliferative assay utilizing a HeLa cell line, respectively. In addition, *in silico* drug- likeliness properties were also computed.

Methods and Materials

General Experimental: Melting points were determined in open capillary tubes. A Shimadzu visible spectrometer was used to record UV spectra in dry EtOH, while an FTIR spectrophotometer was used to capture IR spectra. Using TMS as an internal reference, ^{1}H spectra were captured using a Bruker DPX-400 spectrometer (400-MHz). UV light was used to visualize the spots after analytical thin-layer chromatography (TLC) was carried out on precoated silica gel 60 F_{254} (Merck). Silica gel (60-120 mesh) was used for column chromatography. Merck (Germany) and Loba Chemie (India) provided the reagents.

*Synthesis of 1,3-diphenylprop-2-en-1-one (**1**):* 0.01 mole (1.20 g) of acetophenone and 0.01 mole (1.06 g) benzaldehyde were mixed in 20 ml of ethanol. Then, 40% aqueous NaOH solution was slowly added to the mixture with continuous stirring for 6 hours at room temperature. TLC was performed at every hour and at the end, kept it in refrigerator for overnight. A light yellow colored solid was obtained.

Light yellow colored solid, mp 50-52 °C; IR (cm^{-1}): 3061, 1660, 1602-1496, 1447-1339, 1216; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (3H, m, H-3', H-4', H-5'), 7.50 (2H, t, J = 7.8 Hz, H-3", H-5"), 7.55 (1H, d, J = 16.2 Hz, H-2), 7.59 (1H, m, H-4''), 7.63 (2H, m, H-2', H-6'), 7.81 (1H, d, J = 16.2 Hz, H-3), 8.03 (2H, d, J = 7.8 Hz, H-2", H-6").

*Synthesis of 1,3,5-triphenyl-2-pyrazoline (**2**):* 0.001 mole (0.20 g) of 1,3-diphenylprop-2-en-1-one chalcone (**1**) and 0.001 mole (0.108g) of phenyl hydrazine were added in 25 ml of ethanol along with few drops of acetic acid. Then the mixture was refluxed at 70-75 °C for 6 hours. TLC was performed to monitor the progress. Once the reaction was finished, the mixture was allowed to cool using ice-cold water. The solid precipitate was gathered, rinsed with water, and subjected to recrystallization using ethanol, resulting in the formation of yellow colored solid.

Yellow colored solid, mp 138-140 °C; IR (cm^{-1}): 3027, 1595, 1068; ^{1}H NMR (400 MHz $CDCl_3$): δ 3.14 (1H, dd ,J = 17.2, 7.2 Hz, H-4a), 3.84 (1H, dd , J = 17.2, 12.4 Hz, H-4b), 5.25 (1H, dd, J = 12.4, 7.2 Hz, H-5), 6.80 – 7.95 (15 x Ar-H).

*Synthesis of 4,6-diphenylpyrimidine-2-amine (**3**):* 0.001 mole (0.20 g) of chalcone (**1**) and 0.001 mole (0.095g) of guanidine hydrochloride were taken in 20 ml ethanol. Then, 5 ml freshly prepared 40% aqueous NaOH solution was added. Then it was refluxed at 70-75 °C for 8 hours. At the end of reflux, solution was added to ice-cold water. A brown solid was precipitated and it was recrystallized by ethanol.

Brown colored solid, mp 195-198 °C; IR (cm^{-1}): 3314, 1563, 1540; ^{1}H NMR (400 MHz $CDCl_3$): δ 5.30 (2H, br, s, NH_2-2), 7.48 (1H, s, H-5), 7.11-8.05 (10 x Ar-H).

*Synthesis of phenyl(3-phenyloxiran-2-yl)methanone (**4**):* 0.001 mole (0.20 g) of chalcone (**1**) was measured, transferred to a round bottom flask and 15 ml of ethanol was added to it. Then 20 ml acetone and 8% of sodium hydroxide (12 ml) were included in the solution followed by addition of 30% of 5 ml hydrogen peroxide. Subsequently, the mixture was subjected to reflux for 6 hours. Then the solution was kept in room temperature for an hour. It was subjected to extraction with 50 ml of hexane using a separating funnel. Then the solution was air dried by normal air and a colorless solid was observed.

Colorless solid, mp 72-75 °C; IR (cm^{-1}): 1686, 1231; ^{1}H NMR (400 MHz $CDCl_3$): δ 4.07 (1H, d, J = 1.6 Hz, H-3), 4.30 (1H, d, J = 1.6 Hz, H-2), 7.36-8.10 (10 x Ar-H).

*Synthesis of 1,3,5-triphenyl-1H-pyrazol-4-ol (**5**):* 0.001 mole (0.224g) of epoxide (**4**) was dissolved in 25 ml ethanol and 0.001 mole (0.108 g) of phenyl hydrazine was added. The solution was refluxed with stirring for a duration of 5 hours. Then the solution

was cooled by ice cold water and brown colored solid was collected.

Brown colored solid, mp 156-158 °C; IR (cm^{-1}): 3300, 3030, 1590, 1070; ^1H NMR (400 MHz $CDCl_3$): δ 5.13 (4-OH, s), 6.82 -7.90 (15 x Ar-H).

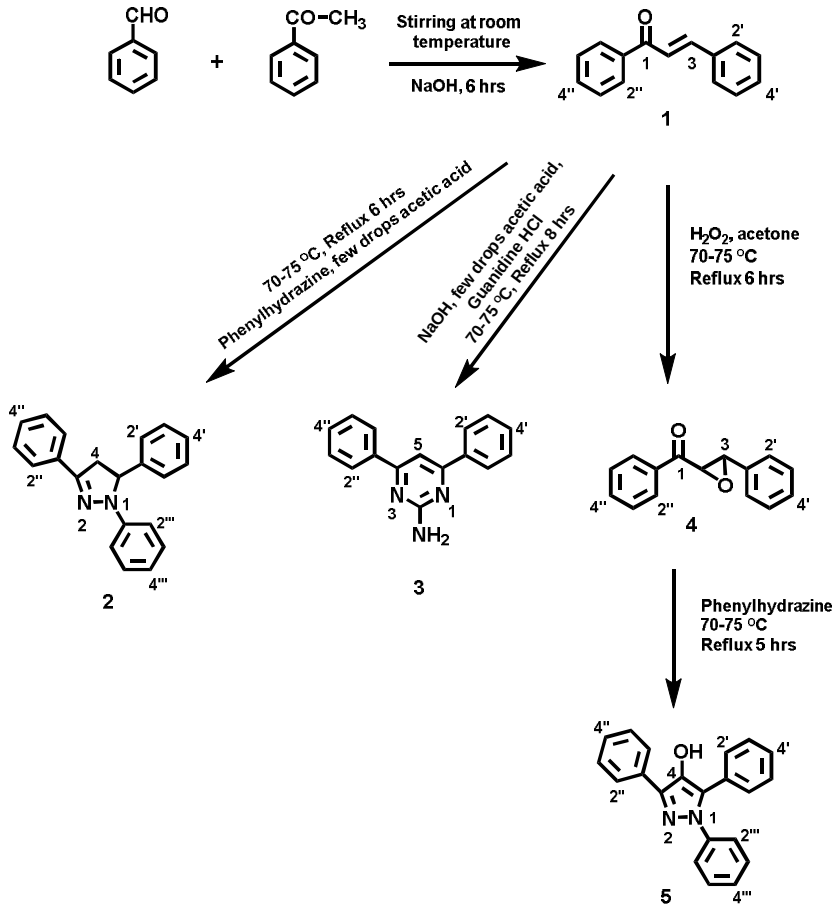

Figure 1. Synthetic pathway of compounds **1-5**.

Cytotoxicity assay: In order to culture a human cervical cancer cell line known as HeLa, DMEM was supplemented with 10% foetal bovine serum (FBS) as a source of nutrients for cell growth, 0.2% gentamycin to maintain the medium's sterility, and 1% penicillin-streptomycin (1:1). A final concentration of 3.33 mg/ml was obtained by dissolving a 10 mg sample of the target chemical in 3 ml of diluted DMSO. 2.0×10^4/100 µl of cells were seeded in a 96-well plate and kept in an incubator at 37°C with 5% CO_2. Each well received 25 µl of the filtered material after 24 hours. After being treated with the chosen drug, the cell culture plate was put in an incubator at 37°C with 5% CO_2 for 24 hours. An inverted light microscope was used to evaluate the cytotoxicity following a 24-hour incubation period. Every sample was examined in three separate wells (Ganji *et al.*, 2023; Hassanshahi *et al.*, 2020).

Assessment of DPPH (1,1-diphenyl-2-picrylhydrazyl) free radical scavenging capacity: The DPPH free radical scavenging experiment is frequently employed to evaluate the antioxidant efficacy of diverse substances. In this assay, antioxidants mitigate the DPPH radical by donating an electron or hydrogen atom, resulting in a color transition from purple to yellow as the radical is decreased. The extent of this color shift is directly correlated with the compound's capacity to scavenge

free radicals. This assay is esteemed for its simplicity, affordability and dependability, rendering it an ideal instrument for assessing both natural and synthetic antioxidant compounds. It is essential for selecting prospective patients for the treatment of illnesses related to oxidative stress. This prevalent method evaluates the antioxidant activity of a product by measuring its efficacy in scavenging free radicals. This assay assesses the antioxidant capacity of various biological and chemical constituents in a straightforward, rapid and precise manner (Ahmed and Rahman, 2016; Brand-Williams *et al*., 1995). The free radical scavenging activity of the substances was assessed using the stable 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical, a standard in antioxidant evaluations. To conduct the assay, 1.5 ml of a DPPH solution was combined with 1 ml of the compound solution dissolved in methanol. The mixture was thereafter incubated in darkness for 30 to 60 minutes to avert any light-induced alterations that would affect the results. Subsequent to incubation, the absorbance of the resultant solution was quantified at 517 nm, taking methanol as a blank to adjust for the solvent's influence. To measure the free radical scavenging capability of the test compound, the absorbance of the DPPH solution devoid of the compound was also measured. The percentage inhibition was computed from the absorbance difference between the test solution and the DPPH solution alone, and this data was utilized to generate a % inhibition curve. The IC_{50} value, representing the concentration of test compounds necessary to inhibit fifty percent of DPPH radicals was obtained from this curve. This approach offers significant insights into the antioxidant capacity of the evaluated substances (Sökmen and Akram Khan, 2016).

$$\% \text{ Inhibition of free radical} = \frac{\text{Absorbance of DPPH} - \text{Absorbance of Sample}}{\text{Absorbance of DPPH}} \times 100$$

Results and Discussion

Compound **1** appeared as a light-yellow colored solid and exhibited a yellow spot upon thin-layer chromatography (TLC) on silica gel PF_{254}, thereafter treated with vanillin-sulfuric acid and heated at 90 °C for 5 minutes. The chemical exhibited solubility in multiple solvents, including methanol, chloroform, and ethyl acetate. The IR data of the compound **1** showed characteristic peaks at frequency (cm^{-1}) at 3061 for Csp^2-H stretching, 1660 for C=O stretching, 1602 to 1496 for C=C stretching of aromatic ring and vinyl group, 1447-1339 for C-C stretching and 1216 for C-O stretching (Chovatia *et al*., 2006). The ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **1** exhibited multiplets at δ 7.41 and 7.63, corresponding to three aromatic protons (H-3', H-4', and H-5') and two aromatic protons (H-2' and H-6'), respectively. A triplet was observed at δ 7.50 (J = 7.8 Hz), corresponding to two aromatic protons (H-3" and H-5"). The deshielding of a wide doublet at δ 8.03 (J = 7.8 Hz) for two aromatic protons (H-2" and H-6") may be ascribed to an adjacent electronegative keto group (C-1) in a side chain. A separate multiplet at δ 7.59 may be ascribed to an aromatic hydrogen (H-4"). Furthermore, two doublets detected at δ 7.55 and δ 7.81, with a substantial J value of 16.2 Hz, correspond to H-2 and H-3 in an *E*- alkene. Upon examining the aforementioned IR and NMR data in conjunction with previously reported findings (Hu *et al*., 2004; Ibieta Jiménez *et al.*, 2016; Mameda *et al.*, 2016), the structure of compound **1** was confirmed as a chalcone *(E)*-1,3-diphenylprop-2-en-1-one.

Compound **2** appeared as a yellow colored solid and displayed a greenish spot when analyzed by TLC on silica gel PF_{254}, subsequently treated with vanillin-sulfuric acid and heated at 80-85 °C for 5-10 minutes. The chemical exhibited solubility in multiple solvents, including methanol, chloroform and ethyl acetate. Infrared observations indicated that the N-N stretching band was detected at 3027 cm^{-1}, while the C=N stretching band was found at 1595 cm^{-1}. The C-N band was also observed at 1068 cm^{-1} in the infrared spectrum (Safaei-Ghomi *et al.*, 2006). The ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **2**

exhibited a double doublet at δ 3.14 (J = 17.2, 7.2 Hz) indicating the presence of a single hydrogen atom of pyrazoline ring, denoted as H-4a. Another double doublet was observed at δ 3.84 (J = 17.2, 12.4 Hz) representing a different proton H-4b. Notably, this peak appeared at a slightly higher chemical shift than H-4a. Furthermore, a more deshielded double doublet peak was identified at δ 5.25 (J = 12.4, 7.2 Hz) indicating the presence of H-5. Multiplets at δ 6.80-7.95 demonstrated the presence of fifteen aromatic protons. Based on the overall spectral features and comparison with previously published information of related compounds (Palaska *et al*., 1996; Safaei-Ghomi *et al*., 2006), the structure of the compound **2** was confirmed as 1,3,5-triphenyl-2-pyrazoline.

Compound **3** was brown colored solid in appearance and exhibited a yellow spot when subjected to TLC on silica gel PF_{254} followed by spraying with vanillin-sulfuric acid and heating at a temperature range of 80-85 °C for 5-10 minutes. The compound showed solubility in various solvents such as methanol, chloroform and ethyl acetate. IR data of compound **3** displayed a stretching band of free NH_2 functional group at 3314 cm^{-1}. Other stretching bands for C=C and C=N were appeared at 1563 and 1540 cm^{-1}, respectively (Albratty and Alhazmi, 2022; Kumar *et al*., 2017). The ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **3** showed a broad singlet at δ 5.30 for two protons of amino group at C-2 of a pyrimidine ring. A singlet observed at δ 7.48 for one proton intensity could be assigned to H-5. Multiplets were observed at δ 7.11 - 8.05 for ten proton intensity of two aromatic rings attached to C-4 and C-6. The singlet for H-5 and multiplets for aromatic protons might be found as overlap. Based on the above analyses and comparison with the previously published ^{1}H NMR data of related compounds (De *et al*., 2022; Kumar *et al*., 2017; Safaei-Ghomi *et al*., 2006), the structure of the compound **3** was confirmed as 4,6-diphenylpyrimidine-2-amine.

Compound **4** was colorless powder and exhibited a greenish spot when subjected to TLC on silica gel PF_{254} followed by spraying with vanillin-sulfuric acid and heating at a temperature range of 80-85 °C for a duration of 5-10 minutes. The compound demonstrated solubility in various solvents such as methanol, chloroform and ethyl acetate. IR data represented that a stretching band for C=O functional group exhibited at 1686 cm^{-1} and another stretching band for C-O-C showed at 1231 cm^{-1} in the IR spectrum. The ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of this compound showed a doublet peak at δ 4.07 (J = 1.6 Hz) for a proton of epoxide skeleton indicated as H-3. Additionally, a doublet peak at δ 4.30 (J = 1.6 Hz) corresponded to a single hydrogen of epoxide chain which is attached to aromatic ring designated as H-2. Multiplets spanning at δ 7.36 - 8.10 were integrated for ten aromatic protons. After analyzing and comparing the IR and ^{1}H NMR data with the published article (Ke *et al*., 2015; Thirunarayanan and Vanangamudi, 2016), it was confirmed that the structure of compound **4** was phenyl(3-phenyloxiran-2-yl)methanone.

Compound **5** was brown colored solid in appearance and exhibited a greenish spot when subjected to TLC on silica gel PF_{254} followed by spraying with vanillin-sulfuric acid and heating at a temperature range of 80-85 °C for 5-10 minutes. The compound showed solubility in various solvents such as methanol, chloroform and ethyl acetate. Infrared observations indicated that the stretching band for OH functional group was exhibited at 3300 cm^{-}1, N-N stretching band was detected at 3030 cm^{-1}, while the C=N stretching band was discovered at 1590 cm^{-1}. The C-N band was also observed at 1070 cm^{-1} in the infrared spectrum (Safaei-Ghomi *et al*., 2006). The ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of this compound showed a singlet peak at δ 5.13 for OH-4 of a pyrazole ring. Multiplets spanning at δ 6.82 - 7.90 were integrated for 15 aromatic protons. Based on the analyses of the aforementioned NMR data with previously published data (Fahmy, 2017), it was confirmed that compound under investigation was 1,3,5-triphenyl-1*H*-pyrazol-4-ol.

Cancer research relies heavily on reliable cell models to evaluate the effectiveness of new compounds. One of the most widely used models is

the HeLa cell line, derived from cervical cancer. HeLa cells are known for their rapid growth and resilience, making them ideal for testing the cytotoxic (cell-killing) potential of experimental drugs. Because these cells mimic certain behaviors of cancer in the human body, they provide valuable early insights whether a compound could be useful in cancer treatment (Hassanshahi *et al*., 2020). In this study, HeLa cells were used to assess the cytotoxicity of the synthesized compounds. The results showed that compounds **1**, **3**, and **5** had strong antiproliferative effects, reducing cell survival to less than 5% (Table 1), suggesting potent anticancer activity. Compound **4** was not included in the test due to limited sample availability. These findings highlight the potential of some of the synthesized molecules as promising candidates for further anticancer research.

Table 1. HeLa cell mediated cell viability assay of synthesized compounds 1-5.

Sample ID	Survival of cells HeLa	Remarks
Media without vehicle	100 %	Negative
Media with vehicle	>95%	Negative
1	<5%	Cytotoxic
2	>95%	Not cytotoxic
3	<5%	Cytotoxic
4	--	Not tested
5	<5%	Cytotoxic

The 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay is widely used in drug development to evaluate the antioxidant capacity of a broad range of substances. This method assesses a compound's ability to neutralize free radicals through electron or hydrogen donation in a simple and cost-effective manner. The DPPH assay is particularly valuable in the early stages of drug discovery, as it helps identify compounds with potential to treat diseases associated with oxidative stress. Antioxidants are crucial in therapeutic research because oxidative stress plays a key role in the progression of numerous chronic conditions, including cancer, neurological disorders, and cardiovascular diseases. In this study, the DPPH assay demonstrates a clear, dose-dependent decrease in radical absorbance, directly reflecting the compounds' free radical scavenging ability. As compound concentration increases and absorbance decreases, it indicates effective neutralization of free radicals. This dose-dependent response highlights the compounds' strong antioxidant potential (Brand-Williams *et al*., 1995). In the current study, the highest scavenging activity was exhibited by compound **2** (IC_{50} value 37.3 µg/ml) shown in table 2. The observed antioxidant activity might be ranked as BHT > **2** > **5** > **3** > **1** > **4**.

Table 2. Estimation of IC_{50} using DPPH free radical sequestering method

Sample	IC_{50} ± standard deviation (μg/ml)
Butylated hydroxytoluene (BHT)	10.7 ± 0.33
1	78.6 ± 1.76
2	37.3 ± 1.24
3	48.9 ± 1.53
4	281.76 ± 9.92
5	43.75 ± 3.08

Expression of results were as mean ± standard deviation, where n=3.

The drug-likeness, physicochemical properties, and pharmacokinetic profiles of compounds **1** to **5** were assessed using the SwissADME web tool (http://www.swissadme.ch/) (Daina *et al.*, 2017). These substances had good intestinal absorption, which suggests that they have a high bioavailability. Furthermore, all of these substances showed encouraging blood-brain barrier (BBB) permeability data indicating that they could be able to pass across the BBB. With topological polar surface area (TPSA) values ranging from 15.6 Å² to 51.8 Å², these compounds were found to have moderate polarity. Subsequent investigation showed that compounds **2**, **3**, and **5** could effectively inhibit cytochrome P-450 enzymes, including 1A2, 2C19, and 2D6. Additionally, **2** and **3** might be able to inhibit 2C9 and 3A4. Except for compound **2**, which showed a

violation, the properties of other compounds were in accordance with Lipinski's rule of five (Chen *et al.*, 2020). Additional drug-likeness filters were also used, such as those suggested by Veber, Ghose, and Egan (Daina *et al.*, 2017). In the Muegee filter, **1** and **2** displayed one violation. All compounds showed positive drug-likeness potential in spite of this small variation. The results are mentioned in table **3**.

Table 3. *In silico* physicochemical, pharmacokinetics and drug likeliness properties of compounds 1-5.

Molecule	1	2	3	4	5
A) Physicochemical features					
Formula	$C_{15}H_{12}O$	$C_{21}H_{18}N_2$	$C_{16}H_{13}N_3$	$C_{15}H_{12}O_2$	$C_{21}H_{16}N_2O$
Molecular weight	208.26	298.38	247.29	224.25	312.36
Heavy atoms number	16	23	19	17	24
Aromatic heavy atoms number	12	18	18	12	23
Rotatable bonds number	3	3	2	3	3
H-bond acceptors number	1	1	2	2	2
H-bond donors number	0	0	1	0	1
Molar refractivity (MR)	66.25	102.26	77.31	64.9	96.46
TPSA	17.07	15.6	51.8	29.6	38.05
XLOGP3	3.08	5.02	3.18	2.83	4.86
WLOGP	3.47	3.96	3.4	2.69	4.91
MLOGP	3.44	4.46	2.49	2.2	3.74
B) Pharmacokinetics					
GI absorption	++	++	++	++	++
BBB permeant	+	+	+	+	+
P-glycoprotein substrate	-	-	+	-	+
CYP1A2 suppressor	-	+	+	-	+
CYP2C19 suppressor	+	+	+	+	+
CYP2C9 suppressor	-	+	-	-	-
CYP2D6 suppressor	-	+	+	-	+
CYP3A4 suppressor	-	-	+	-	+
C) Drug likeness					
Lipinski deviation	0	1	0	0	0
Ghose deviation	0	0	0	0	0
Veber deviation	0	0	0	0	0
Egan d deviation	0	0	0	0	0
Muegge deviation	1	1	0	0	0
Bioavailability score	0.55	0.55	0.55	0.55	0.55
Synthetic accessibility	2.41	3.36	2.04	2.64	2.74

Here, CYP, cytochrome P450; TPSA, Topological polar surface area; MLOGP: Moriguchi octanol-water partition coefficient; XLOGP: atom-additive method-based octanol/water partition coefficient; WLOGP: atomistic method to calculate partition coefficient; +, positive; -, negative; The SwissADME filter criteria were as: Lipinski: MLOGP ≤ 4.15; HBD ≤ 5; HBA ≤ 10; MW ≤ 500, Egan: WLOGP ≤ 5.88; TPSA ≤ 131.6, Ghose: 40 ≤ MR ≤ 130; 20 ≤ atoms ≤ 70; − 0.4 ≤ WLOGP ≤ 5.6; 160 ≤ MW ≤ 480, Veber: TPSA ≤ 140 $Å^2$; Rotatable bonds ≤ 10. Muegge: Number of carbons > 4; − 2 ≤ XLOGP ≤ 5; RB ≤ 15; TPSA ≤ 157; Number of heteroatoms > 1; HBA ≤ 10; 200 ≤ MW ≤ 600; HBD ≤ 5; Number of rings ≤ 7.

Conclusion

1,3-Diphenylprop-2-en-1-one (**1**), 1,3,5-triphenyl-2-pyrazoline (**2**), 4,6-diphenylpyrimidine-2-amine (**3**), phenyl(3-phenyloxiran-2-yl)methanone (**4**), and 1,3,5-triphenyl-1*H*-pyrazol-4-ol (**5**) were successfully synthesized. In the cytotoxicity assay, compounds **1**, **3**, and **5** exhibited potent activity, resulting survival less than 5%. The DPPH free

radical scavenging assay yielded IC_{50} values ranging from 37.30 to 281.76 µg/mL for the synthesized compounds. The physicochemical properties, pharmacokinetic profiles and drug-likeness of compounds **1-5** were comprehensively evaluated using a web-based tool. Taken together, these compounds may be considered potential lead molecules for future research.

Conflict of interest

There is no conflict of interest with respect to publication of this manuscript.

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