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Synthesis And Pharmacological Evaluation of Some Novel Benzhydryl Piperazine Derivatives for Anti-Cancer Activity

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ABSTRACT

The creation of novel anticancer drugs is required to address the issues of toxicity and adverse effects. Derivatives of benzohydryl piperazine have recently been discovered to have cytotoxic and nanomolar epidermal growth factor receptor (EGFR) inhibitory action. The impact of benzhydryl piperazine derivatives on anticancer activity has been investigated in this work. Using gefitinib as the reference, a panel of three cancer cell lines—human pancreatic carcinoma (MIAPaCa-2), human colon carcinoma (HCT-116), and adenocarcinomic human alveolar basal epithelial cells (A-549)—were used to assess a series of six benzhydryl piperazine derivatives. According to the data, the majority of the compounds had encouraging efficacy; however, compound 3c was the most active, exhibiting cytotoxicity significantly superior to that of gefitinib. 4.63 µM against the HCT-116 colon cancer line, 30.11 µM against the MIAPaCa-2 cell line, and 5.71 µM against the A-549 cell line were its IC50 values. These substances will be discovered to be well suited to the active site and might be demonstrating anticancer potential through EGFR inhibition.

Keywords: *Cancer, Piperazine, Cell line, characterization.*

1. INTRODUCTION

Unchecked cell development causes cancer, which is still one of the most deadly diseases in the world [1]. According to data from the International Agency for Research on Cancer, there were 8.2 million cancer-related deaths and 14.1 million new cases of cancer globally in 2012. By 2030, there will likely be 13 million cancer-related deaths and 21.7 million new cancer cases worldwide. Even if there are many anticancer medications available, medicinal chemists have focused more on developing anticancer drugs because of the prevalence of side effects [2-4]. Up to 85% of individuals with non-small cell lung cancer (NSCLC) have EGFR amplification and overexpression, which is common in many cancer types. Usually, mutations occur in exons 18–21, which include the EGFR gene's kinase domain. About 90% of these mutations show up as deletions inside exon 21 or as exon 21 L858R point mutations. Because of these genetic changes, EGFR kinase activity is elevated, which raises downstream signalling. On the other hand, decreased susceptibility to EGFR TKIs is linked to the majority of exon 20 insertion mutations. Therefore, it is imperative to find new ligands that act as EGFR inhibitors in order to combat resistance [5-7].

Compounds comprising quinazoline and piperazine have been shown in the literature to suppress a variety of cancer forms [8]. In non-small cell lung cancer (NSCLC) and other carcinomas, quinazoline derivatives are known to inhibit EGFR tyrosine kinase (TK) and other kinases. One quinazoline derivative that has been exploited for its anticancer properties, particularly in lung cancer, is gefitinib. Unfortunately, quinazoline compound resistance appears quickly after use [9]. A prominent scaffold for improving a compound's druggability is piperazine, either as a precursor or as a linker. More than 300 therapeutic medications now on the market contain piperazine, which is helpful for addressing a variety of pharmacological activities. The piperazine ring's disubstituted nitrogen is crucial for its efficacy and selectivity against a range of biological targets. [10, 11] Bioactive compounds with dopaminergic, antiviral, anticancer, and antihistaminic effects contain benzohydryl piperazine groups. [12, 13] Antimicrobial inhibition has been documented [14–17] and is anticipated to boost anti-TB efficacy, most likely by making compounds more lipophilic. [18] Furthermore, molecular refractivity may be reduced by a minor substituent, such as hydrogen or fluorine, at the aromatic diphenyl ring's fourth position. [19, 20] But benzhydrylpiperazines, including cetirizine, flunarizine, cyclizine, and chlorcyclizine, can block calcium channels and are being utilised as clinical medications. Substituted benzhydrylpiperazines produced a novel T-type calcium channel blocker that was effective as an analgesic in our previous work. [21, 22]

2. MATERIALS AND METHODS

Materials: S.D. Fine Chemicals, TCI, and Sigma-Aldrich were the suppliers of all the anhydrous solvents and reagents. A syringe was used to transfer solvents during all reactions, which were conducted in an atmosphere. The Barnstead Electrothermal digital melting point device was used to determine the uncorrected melting points. A Thermo Nicolet Nexus 670 FTIR spectrometer was used to record the infrared spectra. Using TMS as an internal standard (chemical shifts in d values, J in Hz), 1H and 13C NMR spectra were captured using a Varian Inova 400 MHz FT spectrometer or a Bruker Avance 300 MHz spectrometer.

Experimental work:

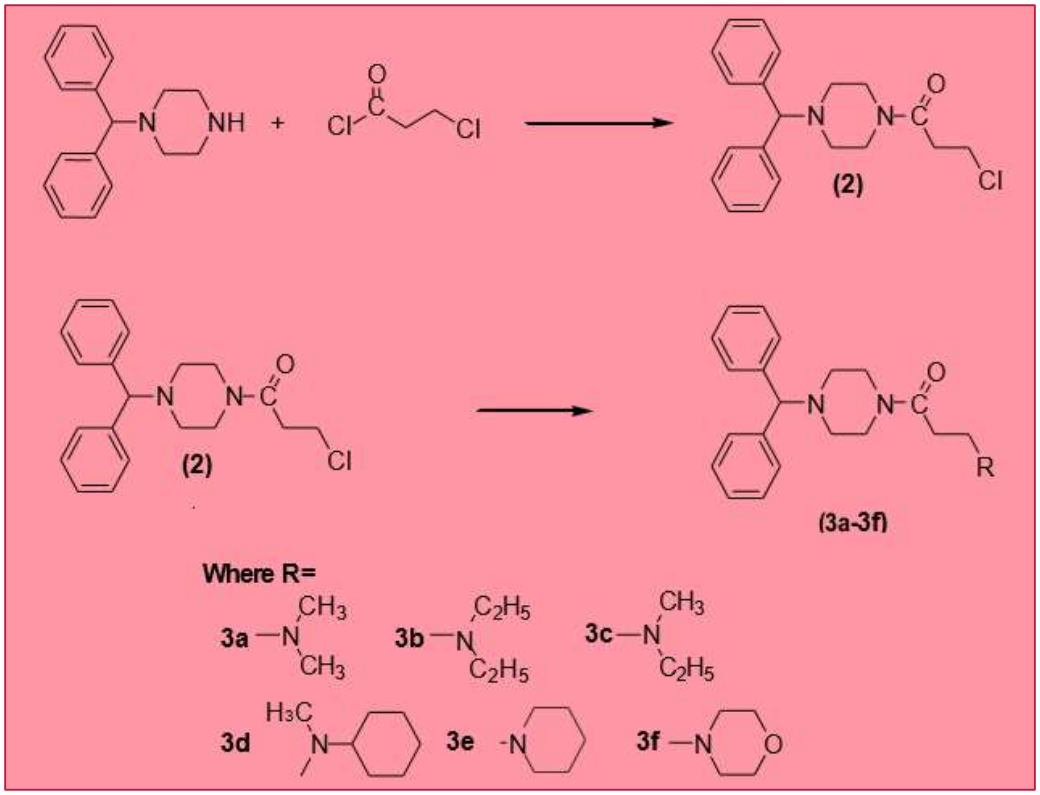
Synthesis of Benzhydryl Piperazine (1): Dichloromethane (100 mL) was used to dissolve benzohydrol (0.31 mol, 52.56 g). After adding 50 mL (0.54 mol) of thionyl chloride, the reaction liquid was agitated for three hours at 40°C. 90% of the dry residue after solvent evaporation was dissolved in 20 millilitres of acetonitrile. Piperazine (1.44g, 0.31 mol) was refluxed with benzohydryl chloride (0.31 mol, 50.78g) for 12 hours. [23] After the solvent was vacuum-evaporated, the residue was dissolved in ethyl acetate and periodically washed with 100 millilitres of water and 100 millilitres of 1N HCl, respectively. The aq was disposed of together with the organic layer. After neutralising the layer with 2N NaOH until the pH was greater than 10, DCM was used to remove the layer. To get the chemical, the DCM was cleaned with brine, dried over sodium sulphate, and then evaporated under vacuum. [24]

Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-1-one (2): After 10 minutes of heating and cooling at 0–5°C in an ice bath, a stirred solution of benzhydryl piperazine (10 mmol, 2.75g) in dioxane was added, and it was stirred for 4–6 hours at room temperature. Ethyl acetate was used to remove the aqueous layer, and water and a 10% ammonium chloride solution were used for washing. After drying the organic layer, the solvent was extracted using less pressure. [25, 26].

Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-(diethyl amino) propan-1-one (3a-d): For 12 hours at 25°C, compound (2), diethylamine, and dry K2CO3 were mixed in benzene. The solvent was extracted under low pressure after the ethyl acetate or DCM layer was roughly three times distilled with water. [27-29]

Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-(piperidin-1-yl) propan-1-one (3e): K2CO3 was utilised as a base in the synthesis of chemical 3e, and a comparable process was applied. Lower pressure was used to evaporate the solvent. Ethyl acetate was used to extract the residue, which was then rinsed with water and dried on sodium sulphate. [30]

Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-morpholinopropan-1-one (3f): In this instance, morpholine was favoured over piperidine, and the result was synthesised using the same process as previously mentioned for other chemicals. [31]



Scheme 1: Derivatives of benzhydrylpiperazine

One-(4-benzhydrylpiperazin-1-yl)-3-(diethyl amino) propan-1-one was synthesised in six different derivatives. To ascertain their molecular weight, all of the synthesised analogues were characterised by means of mass spectrometry (MS), nuclear magnetic resonance spectroscopy (1H NMR and 13C NMR), and infrared spectroscopy (IR).

Biological evaluation: cell viability/MTT assay: Tetrazolium salt reduction was utilised to investigate growth inhibition and cell proliferation. The IC50 (the concentration that caused cytotoxicity in 50% of cells) values are the average of three separate tests, with gefitinib serving as the positive control [32, 33].

All substances were evaluated in vitro using MTT assays against three cell lines: MIAPaCa-2 human pancreatic carcinoma, A-549 human lung carcinoma, and HCT-116 human colon cancer. The A-549 human lung carcinoma, HCT-116 colon cancer, and pancreatic MIAPaCa-2 cell lines were cultured in DMEM, RPMI-1640, and DMEM-F12, respectively. In 96-well plates, 104 cells per well were cultured, and for 48 hours, they were exposed to varying doses of different test chemicals. [34, 35] Following a 44-hour treatment, each well received 20 µl of MTT solution (2.5 mg/ml), which was then incubated for 4 hours at 37 °C in a humidified environment with 5% CO2. For adherent cell lines, the media was extracted without spinning, but for suspension cell lines, the plates were centrifuged for 15 minutes at 1500 r.p.m., and the supernatant was disposed of. 150 µl of dimethyl sulfoxide was used to dissolve the MTT-formazan crystals. [36] In the microplate reader, the absorbance was measured at 570 nm, and the percentage of cell growth inhibition that resulted from cytotoxicity was computed.

% Cell survival = {(At-Ab) / (Ac-Ab)} x 100

where At, Ab and Ac are absorbance of test, blank and control, respectively. Concentrations 1 µM, 10 µM, 20 µM, 30 µM, and 50 µM were used for assay.

3. RESULTS AND DISCUSSION

Chemistry: As shown in the scheme, the synthesis of chemicals (3a, 3b, 3c, 3d, 3e, and 3f) has been completed. These compounds were created by reacting 1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-1-one with piperidine and morpholine, two different disubstituted amines.

Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-(diethyl amino) propan-1-one (3a): % yield 67.3; Yellowish White solid; M.P. 145-149 C; IR: 3026, 3122, 2917, 1933, 1524, 1230 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.99 (d, J = 7.67 Hz, 2H), 8.23 (d, J = 7.67 Hz, 2H), 7.62 (s, 1H), 7.42–7.67 (m, 5H), 6.68–7.13 (m, 3H), 5.28 (s, 1H), 3.57-3.61 (t, 2H, J=6 Hz, pip),

2.71-2.77 (q, 4H, of –N-(CH2)-CH3), 1.36 (t, J = 7.43 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 175.34 (C=O), 161.59 (C11), 145.23 (C19), 139.54 (C9), 132.75 (C7), 127.67 (C15), 118.46 (C17, C20), 113.42 (C10, C13), 60.38 (OCH_2), 51.56 (C3, C5), 34.86 (C3, C5), 16.75 (CH_3); ESIMS (m/z) 456 $[M^+H]^+$; Elemental analysis calculated for C24H32N3O, C 64.23, H 7.23, N 8.64, O 1.97; found C 65.33; H 6.68; N 8.43, 1.86.

Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-(dimethyl amino) propan-1-one (3b): % yield 62.54; Cream yellowish solid; mp 135–138 °C; IR: 3045, 2916, 2587, 2134, 1696, 1509, 1465, 1324, 765 cm^{-1}; ^{1}H NMR (300 MHz, CDCl3): 8.87 (s, 1H), 7.23–7.48 (d, J = 7.56 Hz, 10H), 6.45–6.43 (m, 4H), 5.27 (s, 1H of benzhydryl moiety), 3.57-3.65 (t, 2H,J= 7.5 Hz piperazine), 3.65 (s, 2H), 2.75–2.84 (t, 4H, J=7.5 Hz pip), 2.28 (s, 6H, N-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.43 (C=O), 168.64 (C12), 145.11 (C9, C9'), 138.58 (C17), 128.56 (C16), 124.53 (C8, C11), 114.34 (C10, C12), 113.54 (C10', C12'), 75.75 (C8), 54.75 (C14), 50.11 (OCH_3), 23.54 (CH_3); ESIMS (m/z) 411 $[M+H]^+$; Elemental analysis calculated for C22H29N3O, C 73.34, H 6.56, N 5.75; found C 73.11; H 6.64; N 5.45.

Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-(ethyl (methyl) amino) propan-1-one (3c): % yield 56.56;Yellow solid; mp 187–191 °C; IR: 2918, 2389, 1945, 1723, 1667, 1534, 1325, 1198, 1086, 976 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.17–7.39 (m, 10H, Ar-H), 4.27 (s, 1H, of benzhydryl moiety), 4. 54 (s, 1H), 3.53-3.65 (t, 2H, J= 4.65 Hz piperazine), 2.59–2.68 (m, 8H), 2.22 (s, 3H, N-CH3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.46 (C=O), 163.21 (C21), 159.63 (C11), 141.57 (C9, C9'), 133.56 (C16), 128.65 (C15, C19), 115.52 (C11, C13), 75.64 (C7), 58.65 (OCH_2), 50.52 (C3, C5), 24.33 (CH_3); ESIMS (m/z) 355 $[M+H]^+$; Elemental analysis calculated for C20H18N, C 73.37, H 17.64, N 8.66; found C 72.64, H 15.89, N 7.63.

Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-(cyclohexyl (methyl) amino) propan-1-one (3d): % yield 60.23; Yellowish White solid; MP 132–133 C; IR: 3024, 2175, 1765, 1554, 1423, 1298, 987 cm^{-1} ; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54-7.38 (m, 10H, Ar-H), 7.54 (d, J = 7.37 Hz, 4H), 6.56 (s, 1H), 5.27 (s, 1H, of benzhydryl moiety), 4.43 (s, 1H), 3.53 (s, 2H), 3.59-3.65 (t, 2H, J= 6 Hz -CO-CH_2-(CH_2), 1.47-1.79 (m, 10H of cyclohexane); ^{13}C NMR (75 MHz, $CDCl_3$): 165.56 (C13), 154.53 (C11'), 142.11 (C17), 134.65 (C8, C8'), 128.64 (C19), 127.23 (C18, C22), 116.53 (CN), 116.6 (C11, C13), 50.63 (C3, C5), 21.53 (CH_3); ESIMS (m/z) 346 $[M+H]^+$; Elemental analysis calculated for C15H20N3, C 74.54, H 8.64, N 10.23; found C 73.98; H 8.44; N 10.03.

Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-(piperidin-1-yl) propan-1-one (3e): % yield 71.645; White solid, m.p. 134–137 C; IR: 3024, 2997, 2811, 1723, 1431, 1365, 1143, 1043, 962 cm^{-1}; ^{1}H NMR (300 MHz, CDCl3): δ ,7.16-7.41 (m,10H, Ar-H), 7.65–7.67 (d, J = 8.88 Hz, 2H), 6.93–6.87 (m, 4H), 6.64 (d, J = 8.65 Hz, 2H), 5.27 (s, 1H, of benzhydryl moiety) 4.16 (s, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 3.31(s, 2H), 3.45-3.48 (t, 2H, J=4.8 Hz, pip); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.54 (C=O), 162.53 (C12), 142.54 (C8, C8'), 137.75 (C16), 131.11 (C15), 128.52 (C9, C13), 115.54 (C10, C12), 112.43 (C19, C21), 53.54 (C20–OCH_3), 50.5 (C2, C6); ESIMS (m/z) 367 $[M+H]^+$; Elemental analysis calculated for C17H22N, C 74.54, H 8.43, N 7.21; found C 73.99; H 7.65; N 6.52.

Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-morpholinopropan-1-one (3f): % yield 71.43; White solid, mp 156–157 °C; IR: 3086, 2911, 1987, 1834, 1764, 1543, 1096, 931 cm^{-1}; H1 NMR (300 MHz, CDCl3): δ,7.13-7.41 (m, 10H, Ar-H), 7.63 (d, J = 8.49 Hz, 2H), 6.97–6.87 (m, 4H), 5.17 (s, 1H, of benzhydryl moiety), 4.23 (s, 1H), 3.75 (s, 3H), 2.53–2.37 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.43 (C=O), 165.23 (C11), 144.56 (C8, C8'), 140.21 (C16), 135.82 (C17), 127.64 (C9', C13'), 115.48 (C1O, C12), 116.64 (C10', C12'),76.54 (C7), 56.18 (C14), 52.53 (C2, C6); ESIMS (m/z) 361 [M+H]+; Elemental analysis calculated for C17H20N2, C 75.23, H 11.64, N 7.48; found C 73.41, H 10.29, N 6.97.

Cell viability/MTT assay

Gefitinib demonstrated an IC50 value of 16.56 µM in the adenocarcinomic human alveolar basal epithelial cell line (Lung cancer, A-549), 10.51 µM in the human colon carcinoma cell line (HCT-116 cell line), and 49.50 µM in the human pancreatic carcinoma MIAPaCa-2 cell line. Table 1 displays the MTT assay results for each drug.

Table 1: Results of MTT/cell viability assay

S. No.	Derivatives	Lung IC_{50} (µM)	Colon IC_{50} (M)	Pancreatic IC^{50} (µM)
1	3a	39.23	6.76	26.43
2	3b	53.64	17.11	28.23
3	3c	5.71	4.63	30.11

4	3d	43.75	10.21	12.76
5	3e	32.54	54.64	6.05
6	3f	7.56	18.80	15.11
7	Std.	14.56	9.86	43.11

Electron-donating substitution on the aniline part demonstrated superior inhibition in the lung cancer cell line. In comparison to compounds 3d and 3e, compound 3f demonstrated superior inhibition with an IC50 of 7.56 µM. Compounds containing electron withdrawing groups (EWGs), like 3a and 3b, were mildly active in this cell line, while meta substitution produced favourable activity. Three substances outperformed gefitinib in the colon cancer line. With an IC50 of 4.63 µM, compound 3c was the most active, whereas compounds 3a and 3d showed IC50 values of 6.76 µM and 10.21 µM, respectively. Once more, compounds with electron withdrawing groups were inactive in this cell line, while compounds with electron donating substitutes showed good inhibition. Compounds 3d, 3e, and 3f demonstrated IC50 values of 12.76, 6.05, and 15.11 µM in the pancreatic cell line, respectively. In two of the three cell lines, compound 3c was discovered to be the most active overall. Compounds with electron-donating substituents on the aniline section also showed stronger inhibition than compounds with electron withdrawing groups, according to the IC50 values of all the compounds.

4. CONCLUSION

The potential of six compounds, which are derivatives of benzhydryl piperazine, as anticancer agents against the human lung cancer cell line A-549, the human colon cancer cell line HCT-116, and the human pancreatic carcinoma cell line MIAPaCa-2 was evaluated. Across the three cell lines, substances with electron-donating groups were shown to be more cytotoxic. Compounds with higher anticancer potential were discovered to interact with MET793 at the EGFR binding region, and prior research has connected hydrogen bond interactions with MET793 to EGFR inhibition. The findings imply that these compounds have anticancer properties; nevertheless, additional research is required to determine their selectivity as EGFR inhibitors

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