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Original Article

SYNTHESIS AND *IN-VITRO* STUDY OF NOVEL (*Z*)-1-BENZHYDRYL-4-CINNAMYLPIPERAZINE DERIVATIVES AS POTENTIAL ANTICANCER AGENTS

S. SHIVAPRAKASH, K. R. KIRAN, LATHA DIWAKAR, G. CHANDRASEKARA REDDY*

Vittal Mallya Scientific Research Foundation, # 94/3 & 94/5, 23rd Cross, 29th Main, BTM II Stage, Bangalore 560076, India.
Email: gcreddy@vmsrf.org

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ABSTRACT

Objective: The objective of this study was to synthesize *Z*- 1-benzhydryl-4-cinnamylpiperazines by novel stereo selective synthetic method and evaluation of their anticancer properties.

Methods: A series of novel (*Z*)-1-benzhydryl-4-cinnamylpiperazine derivatives (**9a-j)** were synthesized, starting from benzophenones in six steps. Wittig condensation of appropriate benzyltriphenyl phosphonium halides with various 1-benzhydryl- 4-(2-ethanal) piperazines (**3a-j),** and column purification over silica gel afforded pure *Z*- 1-benzhydryl-4-cinnamylpiperazines.

Results: The structures of newly synthesized compounds **9a-j** were established by ^{1}H & ^{13}C NMR and mass spectral analysis. The anticancer potential (MTT assay) of synthesized compounds was tested against human cervical cancer (HeLa) and murine microglial (BV-2) cell lines. Results indicated that the most of the *Z*-derivatives exhibited moderate to good anticancer activity on both the cell lines over their *E*- antipodes.

Conclusion: Compound **9i** (*cis*- flunarizine) exhibited exceptionally superior activity against both HeLa and BV-2 cell lines with IC_{50} value of 13.23±3.51 µM and 23.1±4.12 µM respectively. Hence, this compound may be considered to be a potential lead molecule for further development

Keywords: Benzophenones, Cinnamylpiperazine derivatives, Wittig reaction, Cinnarizine, Anticancer activity.

INTRODUCTION

In spite of considerable progress in recent years, cancer remains one of the most difficult diseases to treat and is responsible for about 13% of deaths all over the world. This incidence is increasing due to the ageing of the population in most countries, especially in the developed countries. Further metastasis that sets in may cause about 90% of cancer deaths. Currently, surgery and radiotherapy are the methods used in the treatment of cancer. Another effective way frequently preferred for the treatment of cancer is the systemic chemotherapy. In general, 5-fluorouracil (5-FU) in combination with other anti-cancer agents is used in the treatment of the aerodigestive tract, breast, head, and neck, especially in colorectal cancers therapies with oxaliplatin and irinotecan [1-3]. Cytotoxic and anti- hormonal drugs are the main chemotherapeutics used to reduce the proliferation of malignant cells. On the other hand, significant side-effects along with growth of tumor-cell population are often encountered during chemotherapy [4-7]. Strategies have been working out in many laboratories to look for newer chemical agents, one such example is piperazine and piperazine related compounds which displayed the wide variety of biological activities [8, 9] including apoptosis inducing effects on some cancer cells[10]. In addition, some piperazine compounds with substituent group at position 3 on the piperazine ring can strongly act as a selective κ-opioid receptor agonists [11, 12].

Many piperazine sulfonamide derivatives exhibit MMP-3 enzyme inhibition and carbonic anhydrase inhibition activities [13, 14]. In many cases, piperazine derivatives reduce growth inhibition in human erythroleukemia K562 cells and myeloid leukemia HL-60 cells [15]. Also, inhibit topoisomarase II activity [16].Sampson J. J. *et al.* reported that, some piperazine derivatives induce apoptosis in U937 cells [17]. The *N*-Alkyl, *N*-sulfonyl and *N*-benzoyl substitution of benzhydrylpiperazine derivatives showed antimicrobial and anticancer properties[18-20]. In few occasions' compounds with cinnamoyl group often employed in the design of anticancer drugs [21, 22].Encouraged by these literature data and therapeutic value of the piperazine scaffolds prompted us to synthesize some novel piperazine compounds having 1, 4-disubstitutions. Herein, we synthesized various (*Z*)-1-benzhydryl-4-cinnamylpiperazine derivatives and studied their *in-vitro* anticancer activity.

MATERIALS AND METHODS

Chemistry

All chemicals purchased were of LR grade from Sigma-Aldrich, Merck, and Loba-chemie; solvents used were of the commercial grade. Melting points were determined on Acro melting point apparatus (using a calibrated thermometer). Thin-layer chromatography (TLC) was run on silica gel pre-coated on aluminium sheet (silica gel 60 F_{254}. Merck). Chromatographic separation of mixtures was performed in open glass columns packed with silica gel (Merck Grade 7734, 70-230 mesh) and eluted with ethyl acetate/hexane solvent mixture. Analytical HPLC was recorded with Shimadzu (CLASS-VP) equipped with LC-10AT VP high-pressure pumps, a SPD-M10A VP photodiode array detector, a CTO-10AS VP oven and a SCL-10A VP controller (RP column: Atlantis-T3, 5.0 µm, 4.6x150 mm; Mobile phase: 1% ammonium acetate and 0.2% acetic acid in acetonitrile- gradient elution; UV detector: 230 nm). The Mass spectra were recorded on GCMS-QP2010S (direct probe) instrument and high-resolution mass spectral (HRMS) data were obtained on the Micromass Q-Tof micro instrument using electrospray ionization (ESI). ^{1}H and [13]C NMR spectra were recorded on a Bruker spectrometer 400 MHz and 100 MHz respectively using $CDCl_3$ as solvent and TMS as an internal reference.

General procedure for the synthesis of benzyl triphenyl phosphonium salts (4-8)

A mixture of appropriate benzyl halides (1.0 equiv) and triphenylphosphine (1.0 equiv) in toluene was heated under reflux for 10-12 h. the reaction mixture was cooled slowly to room temperature; the precipitated solid were filtered under suction. Finally, be washed with toluene and air dried to afford corresponding benzyltriphenyl phosphonium halides **4-8** as white to off- white solid.

General procedure for the synthesis of *(Z)*-1-[Bis-(4-chlorophenyl)-methyl]-4-(cinnamyl) piperazine (9a)

Compound **1a** (3 g, 9.3 mmol) in DMF (6 mL) was added into a mixture of chloroacetaldehyde dimethylacetal (1.28 g, 10.3 mmol), anhydrous K_2CO_3 (1.42 g, 10.3 mmol) and KI (0.08 g, 0.46 mmol) at

room temperature. The reaction mixture was then heated under stirring at 85-90 °C for 6-7 h. Progress of the reaction was monitored by TLC. After the completion of reaction, the mixture was quenched into ice water, and extracted with hexane at room temperature. Organic layer was separated, dried over anhydrous sodium sulphate and concentrated under vacuum. The pure viscous oily material **2a,** thus obtained after column purification was taken in 48% aq. HBr (15 mL) and stirred at room temperature for 1-1.5 h. The reaction mixture was then quenched into ice water, basified with dilute NaOH solution and extracted with dichloromethane. The compound **3a** present in dichloromethane (30 mL) was dried over anhydrous sodium sulfate, benzyltriphenyl phosphonium chloride (**4)** (4.0 g, 10.4 mmol) was added. The mixture was cooled to 5 °C; *t*-BuOK (2.6 g, 23.3 mmol) was added under N_2 atmosphere with continuous stirring. After completion of reaction, the mixture was quenched into water. Organic layer was separated, dried over anhydrous sodium sulphate and concentrated under vacuum. The crude was then subjected to column purification over SiO_2 using EtOAc / hexane as an eluent to afford **9a** as a viscous liquid. Overall Yield: 2.10 g (51%). ^{1}H NMR: δ 7.16 - 7.54 (m, 13 H, Ar-H), 6.56 (d, *J* =11.8 Hz, 1 H), 5.75 (dt, *J* =11.8, 6.6 Hz, 1 H), 4.17 (s, 1 H), 3.27 (dd, *J* = 6.6, 1.8 Hz, 2 H), 2.47 (bs, 4 H), 2.39 (bs, 4 H). [13]C NMR: δ 140.79, 137.10, 131.84, 129.30, 129.14, 128.91, 128.79, 128.59, 128.16, 126.91, 74.67, 56.10, 53.38, 51.75. HRMS calculated for $C_{26}H_{27}Cl_2N_2$ $[M+H]^+$ 437.1551; found 437.1551.

***(Z)*-1-[Bis-(4-methylphenyl)-methyl]-4-(cinnamyl) piperazine (9b)**

The procedure was similar to the one as described for **9a,** but compound **1b** (3 g, 10.7 mmol) was taken as starting material and the benzyltriphenyl phosphonium chloride (**4**) was used during Wittig reaction. The compound **9b** obtained as a viscous liquid. Overall Yield: 2.20 g (52%). ^{1}H NMR: δ 7.02 - 7.42 (m, 13 H, Ar-H), 6.55 (d, *J* =11.8 Hz, 1 H), 5.77 (dt, *J* =11.8, 6.6 Hz, 1 H), 4.13 (s, 1 H), 3.27 (dd, *J* = 6.6, 1.8 Hz, 2 H), 2.45 (bs, 4 H), 2.42 (bs, 4 H), 2.25 (s, 6 H, Ar-CH_3). [13]C NMR: δ 140.09, 136.36, 131.34, 130.22, 129.45, 129.15, 128.90, 128.14, 127.74, 126.86, 75.65, 56.17, 53.52, 51.89, 21.03. HRMS calculated for $C_{28}H_{33}N_2$ $[M+H]^+$ 397.2644; found 397.2641.

***(Z)*-1-[(4-Bromophenyl) phenyl methyl]-4-(cinnamyl) piperazine (9c)**

The procedure was similar to the one as described for **9a,** but compound **1c** (3 g, 9.1 mmol) was taken as starting material and the benzyltriphenyl phosphonium chloride (**4**) was used during Wittig reaction. The compound **9c** obtained as a viscous liquid. Overall Yield: 2.0 g (49%). ^{1}H NMR: δ 7.19 - 7.46 (m, 14 H, Ar-H), 6.56 (d, *J* =11.8 Hz, 1 H), 5.76 (dt, *J* =11.8, 6.5 Hz, 1 H), 4.18 (s, 1 H), 3.27 (dd, *J* = 6.5, 1.8 Hz, 2 H), 2.46 (bs, 4 H), 2.42 (bs, 4 H). [13]C NMR: δ 142.06, 141.90, 137.07, 131.57, 131.42, 129.56, 129.27, 128.86, 128.56, 128.11, 127.82, 127.13, 126.85, 120.62, 75.45, 56.08, 53.38, 51.75. HRMS calculated for $C_{26}H_{28}BrN_2$ $[M+H]^+$ 447.1436; found 447.1433.

***(Z)*-1-(Diphenylmethyl)-4-(4'-methoxycinnamyl) piperazine (9d)**

The procedure was similar to the one as described for **9a,** but compound **1d** (3 g, 11.9 mmol) was taken as starting material and the benzyltriphenyl phosphonium halide (**5**) was used during Wittig reaction. The compound **9d** obtained as a viscous liquid. Overall Yield: 2.20 g (46%). ^{1}H NMR: δ 7.38 - 7.40 (m, 4 H, Ar-H), 7.22 - 7.25 (m, 4 H, Ar-H), 7.13 - 7.19 (m, 4 H, Ar-H), 6.85 – 6.88 (m, 2 H, Ar-H), 6.48 (d, *J* =11.6 Hz, 1 H), 5.67 (dt, *J* =11.6, 3.2 Hz, 1 H), 4.21 (s, 1 H), 3.80 (s, 3 H, Ar-OCH_3), 3.26 (dd, *J* = 2.4, 0.8 Hz, 2 H), 2.49 (bs, 4 H), 2.43 (bs, 4 H). [13]C NMR: δ 158.45, 142.75, 130.69, 130.12, 129.79, 128.40, 127.90, 127.80, 126.83, 113.52, 76.16, 56.20, 55.21, 53.47, 51.86. HRMS calculated for $C_{27}H_{31}N_2O$ $[M+H]^+$ 399.2436; found 399.2437.

***(Z)*-1-(Diphenylmethyl)-4-(3', 5'-dimethoxycinnamyl) piperazine (9e)**

The procedure was similar to the one as described for **9a,** but compound **1e** (3 g, 11.9 mmol) was taken as starting material and the benzyltriphenyl phosphonium halide (**6**) was used during Wittig reaction. The compound **9e** obtained as a viscous liquid. Overall Yield: 2.28 g (44%). ^{1}H NMR: δ 7.39 (d, *J* =8.0 Hz, 4 H, Ar-H), 7.23 (t, *J* =3.6 Hz, 4 H, Ar-H), 7.14 (t, *J* =6.8 Hz, 2 H, Ar-H), 6.49 (d, *J* =11.6 Hz, 1 H), 6.41 (s, 2 H, Ar-H), 6.36 (s, 1 H, Ar-H), 5.76 (dt, *J* =11.6, 6.8 Hz, 1 H), 4.21 (s, 1 H), 3.77 (s, 6 H, Ar-OCH_3), 3.26 (d, *J* = 6.4Hz, 2 H), 2.49 (bs, 4 H), 2.43 (bs, 4 H). [13]C NMR: δ 160.46, 142.72, 138.97, 131.44, 129.73, 128.38, 127.87, 126.82, 107.02, 99.04, 76.13, 56.12, 55.25, 55.23, 53.42, 51.85. HRMS calculated for $C_{28}H_{33}N_2O_2$ $[M+H]^+$ 429.2542; found 429.2539.

***(Z)*-1-(Diphenylmethyl)-4-(3', 4'-dimethoxycinnamyl) piperazine (9f)**

The procedure was similar to the one as described for **9a,** but compound **1f** (3 g, 11.9 mmol) was taken as starting material and the benzyltriphenyl phosphonium halide (**7**) was used during Wittig reaction. The compound **9f** obtained as a white solid, mp 104-06 °C. Overall Yield: 2.38 g (46%). ^{1}H NMR: δ 7.39 (d, *J* =7.2 Hz, 4 H, Ar-H), 7.22 - 7.26 (m, 4 H, Ar-H), 7.13 - 7.17 (m, 2 H, Ar-H), 6.79 – 6.87 (m, 3 H), 5.69 (dt, *J* =11.6, 6.8 Hz, 1 H), 4.21 (s, 1 H), 3.88 (s, 3 H, Ar-OCH_3), 3.86 (s, 3 H, Ar-OCH_3), 3.26 (dd, *J* = 6.8, 1.6 Hz, 2 H), 2.52 (bs, 4 H), 2.43 (bs, 4 H). [13]C NMR: δ 148.50, 148.03, 142.75, 131.27, 130.11, 128.40, 127.89, 127.85, 126.85, 121.54, 112.37, 110.83, 76.16, 56.18, 55.86, 55.83, 53.48, 51.89. HRMS calculated for $C_{28}H_{33}N_2O_2$ $[M+H]^+$ 429.2542; found 429.2544.

***(Z)*-1-(Diphenylmethyl)-4-(3', 4'-methylenedioxycinnamyl) piperazine (9g)**

The procedure was similar to the one as described for **9a,** but compound **1g** (3 g, 11.9 mmol) was taken as starting material and the benzyltriphenyl phosphonium halide (**8**) was used during Wittig reaction. The compound **9g** obtained as a viscous liquid. Overall Yield: 2.47 g (40%). ^{1}H NMR: δ 7.39 (d, *J* =6.8 Hz, 4 H, Ar-H), 7.24 (t, *J* =7.2 Hz, 4 H, Ar-H), 7.14 (t, *J* =7.2 Hz, 2 H, Ar-H), 6.68 - 6.78 (m, 3 H, Ar-H), 6.44 (d, *J* =12.0 Hz, 1 H), 5.94 (s, 2 H), 5.67 (dt, *J* =12.0, 6.4 Hz, 1 H), 4.21 (s, 1 H), 3.24 (dd, *J* = 6.4, 1.6 Hz, 2 H), 2.49 (bs, 4 H), 2.43 (bs, 4 H). [13]C NMR: δ 147.40, 146.38, 142.75, 131.25, 130.87, 128.40, 128.33, 127.90, 126.84, 122.70, 109.13, 108.01, 100.94, 76.17, 56.16, 53.48, 51.87. HRMS calculated for $C_{27}H_{29}N_2O_2$ $[M+H]^+$ 413.2229; found 413.2230.

***(Z)*-1-(Diphenylmethyl)-4-(cinnamyl) piperazine (9h)**

The procedure was similar to the one as described for **9a,** but compound **1h** (3 g, 11.9 mmol) was taken as starting material and the benzyltriphenyl phosphonium halide (**4**) was used during Wittig reaction.

The compound **9h** obtained as a white solid, mp 90-92 °C. Overall Yield: 2.30 g (52%). ^{1}H NMR: δ 7.10 - 7.42 (m, 15 H, Ar-H), 6.55 (d, *J* =12.0 Hz, 1 H), 5.77 (dt, *J* =12.0, 6.6 Hz, 1 H), 4.22 (s, 1 H), 3.28 (dd, *J* = 6.6, 1.80 Hz, 2 H), 2.46 (bs, 8 H). [13]C NMR: δ 142.8, 137.1, 131.6, 129.5, 128.9, 128.4, 128.1, 127.9, 126.9, 126.8, 76.2, 56.2, 53.5, 51.9. HRMS calculated for $C_{26}H_{29}N_2$ $[M+H]^+$ 369.2331; found 369.2335.

***(Z)*-1-[Bis-(4-fluorophenyl)-methyl]-4-(cinnamyl) piperazine (9i)**

The procedure was similar to the one as described for **9a,** but compound **1i** (3 g, 10.4 mmol) was taken as starting material and the benzyltriphenyl phosphonium halide (**4**) was used during Wittig reaction. The compound **9i** obtained as a pale yellow viscous liquid. Overall Yield: 2. 0 g (46%). ^{1}H NMR: δ 7.20 - 7.35(m, 9 H, Ar-H), 6.87-6.98 (m, 4 H, Ar-H), 6.50 (d, *J* =12 Hz, 1 H), 5.76 (dt, *J* =12.0, 6.6 Hz, 1 H), 4.20(s, 1 H), 3.27 (dd, *J* = 6.6, 1.8 Hz, 2 H), 2.47 (bs, 4 H), 2.40 (bs, 4 H). [13]C NMR: δ 163.1, 160.6, 138.3, 137.1, 132.6, 132.5, 131.5, 129.3, 129.2, 128.9, 128.2, 126.9, 115.5, 115.3, 74.5, 56.1, 53.4, 51.7. HRMS calculated for $C_{26}H_{27}F_2N_2$ $[M+H]^+$ 405.2142; found 405.2145.

***(Z)*-1-[(4-Chlorophenyl) phenyl methyl]-4-(cinnamyl) piperazine (9j)**

The procedure was similar to the one as described for **9a,** but compound **1j** (3 g, 10.4 mmol) was taken as starting material and the benzyltriphenyl phosphonium halide (**4**) was used during Wittig reaction. The compound **9j** obtained as a viscous liquid. Overall Yield: 1. 9 g (45%). ^{1}H NMR: δ 7.13 - 7.37 (m, 14 H, Ar-H), 6.56 (d, *J* =12.0 Hz, 1 H), 5.76 (dt, *J* = 12.0, 6.6Hz, 1 H), 4.20 (s, 1 H), 3.27 (dd, *J* =6.6, 1.8 Hz, 2 H), 2.48 (bs, 4 H), 2.43 (bs, 4 H). [13]C NMR: δ 142.1,

141.4, 137.1, 132.5, 131.4, 129.3, 129.2, 128.9, 128.6, 128.5, 128.1, 127.8, 127.1, 126.8, 75.4, 56.1, 53.4, 51.8. HRMS calculated for $C_{26}H_{28}ClN_2$ $[M+H]^+$ 403.194; found 403.1940.

Anticancer assay

Cell lines were maintained in Dulbecco's Modified Eagle's Medium (Sigma- Aldrich Inc., USA) supplemented with 10% fetal bovine serum (Gibco BRL., USA) in a CO_2 incubator at 37 °C. The cytotoxicity of the compounds was measured by MTT assay. Two human cancer cell lines HeLa (cervical) and BV-2 (murine microglial) were placed in a 96-well plate at the density of 10,000 cells per well. After 24 h, cells were treated with various concentrations of compounds from 100 µM serially diluted up to 3.13 µM using cinnarizine, flunarizine and clocinizine as positive controls. The cells were further incubated for 48 h, 20 µl of MTT (5 mg/ml stock, Sigma- Aldrich Inc., USA) was added to each well and incubated for another three hours. The purple formazan crystals formed were dissolved by adding 100 µl of DMSO to each well and absorbance was read at 570 nm in a spectrophotometer [Spectra Max 340]. The cell death was calculated as follows:

Cell death =100- [(test absorbance/ control absorbance) x100]

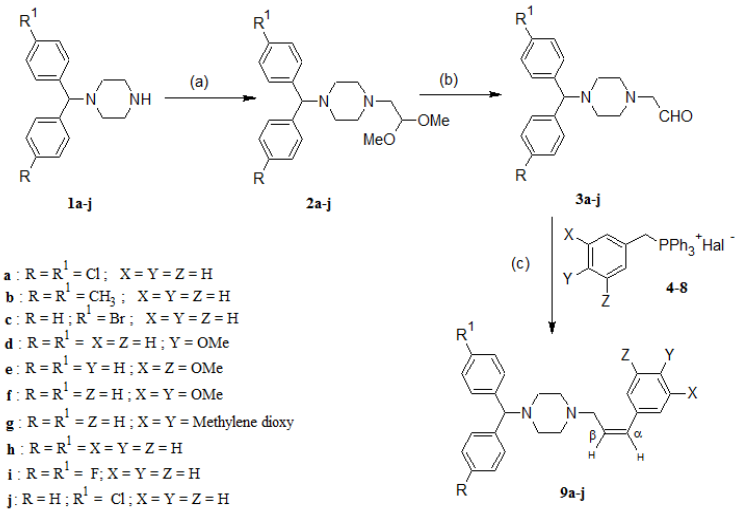
The test result is expressed as the concentration of a test compound which inhibits the cell growth 50% (IC_{50}).

RESULTS AND DISCUSSION

Chemistry

The procedure outlined in Scheme 1 illustrates the synthesis of (*Z*)-1-diphenylmethyl-4-cinnamylpiperazine derivatives **9a-j** starting from the corresponding benzhydrylpiperazines **1a-j.** This in turn obtained from appropriate benzophenones in three steps as described in our earlier procedure [23]. The process comprises the reduction of benzophenone with $NaBH_4$, conversion of alcohol obtained into benzhydryl chlorides using conc. HCl in toluene and finally treatment with anhydrous piperazine gave compounds **1a-j**, which are key intermediates for many known drugs. Further, reaction with equimolar amounts of chloroacetaldehyde dimethylacetal and anhydrous K_2CO_3 in DMF gave compounds **(2a-j)** which on treatment with aq. HBr (48%) at room temperature afforded the corresponding aldehydes **(3a-j)**.

Finally, Wittig reaction of these aldehydes with appropriate benzyltriphenyl phosphonium halides **4-8** (Table 1) in presence of t-BuOK in dichloromethane followed by column purification over silica gel using EtOAc/hexane (1:9) mixture as eluent, afforded mainly *(Z)*-1-benzhydryl-4-cinnamylpiperazines **(9a-j)**. All the newly synthesized compounds were characterized by ^1H & ^{13}C NMR and mass spectral analysis.



Scheme 1: Synthesis of (*Z*)-1-benzhydryl-4-cinnamylpiperazine derivatives (9a-j). Reagents and conditions: (a) Chloroacetaldehyde dimethylacetal, K_2CO_3, DMF, 85-90 °C, 6-7 h; (b) HBr 48% in water, rt, 1-1.5 h; (c) Wittig salts (4-8); *t*-BuOK, CH_2Cl_2, 5 °C, ~3-4 h or till completion of reaction by TLC

Table 1: Benzyltriphenyl phosphonium halides 4-8

Compound	Hal	X	Y	Z	Yield# (%)
4	Cl	H	H	H	95
5	Br	H	OMe	H	88
6	Br	OMe	H	OMe	92
7	Cl	OMe	OMe	H	78
8	Cl	3, 4-Methylene dioxy		H	72

#isolated yield.

Biological studies: Anticancer activity

Further, compounds (**9a-j**) were subjected for their *in vitro* anticancer activity against human cervical cancer (HeLa) and murine microglial (BV-2) cell lines using MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide] assay as per standard protocol [24]. The IC_{50} value of each compound was calculated by the excel curve software and the results are summarized in table 2. Cinnarizine, Flunarizine and Clocinizine drugs which are (*E*) – geometrical isomers were taken as internal reference standards and camptothecin (CPT) as positive control. Results from the table indicated that all the *Z*-derivatives displayed moderate to good anticancer activity on both the cell lines. Against HeLa cell line, the compounds **9f** and **9g** with vicinal dioxy system (*meta*-, *para*-position) on cinnamyl ring displayed poor anticancer activity.

However, these compounds showed good anticancer effect on BV-2 cell line. Similarly, compounds **9d** and **9e** exhibited moderate to good inhibitory effect on both the cell lines. In the case of compounds **9h**, **9i** and **9j**, which are antipodes of cinnarizine, flunarizine and clocinizine drugs showed good inhibition against both cell lines. Further, compounds **9a**, **9b** and **9c** with no substitution on cinnamyl ring

exhibited moderate to good anticancer activity on both the cell lines. It is noteworthy to mention that of all compounds, the difluoro derivative (**9i)** found to exhibit significant activity against both the cell lines with IC_{50} values were very close to the standard drug camptothecin.

Table 2: IC_{50} values of compounds 9a-j on HeLa and BV-2 cell lines

Compound	IC_{50} (µM)^ ± SD*	
	HeLa cell line	BV-2 cell line
9a	42.68 ±4.91	53.14 ±2.92
9b	32.25 ±4.54	40.84 ±3.82
9c	40.15 ±3.73	26.3 ±7.56
9d	42.72 ±3.61	33.81 ±1.65
9e	41.17 ±2.69	36.0 ±3.79
9f	>200	29.35 ±6.7
9g	>200	34.03 ±1.89
9h (*cis*-Cinnarizine)[23]	34.54 ±5.57	41.62 ±0.58
9i (*cis*-Flunarizine)[23]	13.23 ±3.51	23.1 ±4.12
9j (*cis*-Clocinizine)[23]	14.97 ±5.40	37.28 ±0.3
Cinnarizine#	>200	64.99 ±3.09
Flunarizine#	>200	45.7 ±0.27
Clocinizine#	>200	56.0 ±3.14
CPT	9.57±1.17	14.9±1.21

* The values obtained in at least three separate assays done in triplicate **±**SD – Standard deviation, ^ The IC_{50} value defined as the concentration at which 50% survival of cells was observed, # Internal reference drugs.

CONCLUSION

In summary, we have synthesized series of novel (*Z*)-1-benzhydryl-4-cinnamylpiperazine derivatives (**9a-j**) and evaluated for their *in vitro* anticancer potential against HeLa and BV-2 cell lines. The preliminary study indicated that newly synthesized *Z*- derivatives exhibited moderate to good anticancer activity at micro molar level against selected cancer cell lines. Compounds **9h**, **9i** and **9j**, which are antipodes of cinnarizine, flunarizine and clocinizine exhibited good inhibition against both cell lines. Significant finding is that compound **9i** (*cis*-flunarizine) exhibited potent anticancer effect against both HeLa (IC_{50} = 13.23±3.51 µM) and BV-2 (IC_{50} = 23.1 ±4.12 µM) cell lines and stands in close proximity with camptothecin. Hence, compound **9i** would stand out as a lead molecule for further study.

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CONFLICT OF INTERESTS

Declared None

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