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SYNTHESIS AND *IN-VITRO* ANTIPROLIFERATIVE ACTIVITY OF SUBSTITUTED-2, 3-DIMETHYL-N-(3-(4-PHENYL PIPERAZIN-1-YL) PROPYL)-6, 7-DIHYDRO-5H-BENZO [7] ANNULENE-8-CARBOXYLIC ACIDS

K. Vijay * and Ch. B. Praveena Devi

Department of Chemistry, University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Nagarjuna Nagar, Guntur - 522510, Andhra Pradesh, India.

Keywords:

Benzocycloheptenones, Benzosuberone, Piperazine derivatives, Antiproliferative activity

Correspondence to Author:
Dr. K. Vijay

Assistant Professor,
Department of Chemistry,
University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Nagarjuna Nagar, Guntur - 522510, Andhra Pradesh, India .

E-mail: vijai.kotra@gmail.com

ABSTRACT: Benzosuberones and phenylpiperazinyl moieties are important heterocyclic compounds which constitute many biological activities which include anti bacterial, anti fungal, anti inflammatory, antioxidant, antitubercular and anti cancer activities. A novel series of 2,3-dimethyl-*N*-(3-(4-phenyl piperazin-1-yl)propyl)-6,7-dihydro-5*H*-benzo[7] annulene-8-carboxylic acids (5a-e) have been synthesized in good to excellent yields by experimental simplicity and milder reaction conditions and evaluated for their anti-proliferative activity. The titled compounds were identified and characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis. The novel derivatives synthesized were evaluated for *in-vitro* anti-proliferative activities on four different human cancer cell lines He La (cervical), MIAPACA (pancreatic), MDA-MB-231 (breast) and IMR32 (neuroblastoma) by sulphorhodamine B assay method. These synthesized novel derivatives which showed excellent anti-proliferative activity. The obtained results suggest that these classes of compounds can be considered as new hits for further structural optimization to obtain better anti-proliferative drug development program.

INTRODUCTION: Benzocycloheptenone and its derivatives are an important class of heterocyclic compounds which constitute the key core of various natural products and play a unique role in drug discovery programme. The benzosuberone nucleus contains a seven membered ring fused to an aromatic ring, is a core structure in several natural products such as colchicines, theaflavin, bussealine E, favaline which was found to possess anticancer activity. Colchicine is the major alkaloid from *Colchicum autumnale*, is one of the oldest known natural products.

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Theaflavin is a promising anti-cancer active compound present in black tea. Yang *et al*., extensively studied about the possible cancer-preventive activity of tea and tea polyphenols [1]. Synthetic benzosuberone derivatives have also showed various biological activities such as anti bacterial [2, 3], anti cancer [4 - 7], anti oxidant [8], anti-inflammatory [9]. Extensive investigations have been focused on natural member of benzosuberone cytoskeleton from anti-proliferative point of view.

Phenylpiperazine moiety is a core structure of many drugs like anti cancer [10], anti convulsant [11]. Kulig [12] *et al*., synthesized some enantiomers of piperazinyl derivatives.

Thus, our interest is to conjugate these two heterocyclic moieties and synthesize novel derivatives of 2, 3-benzocyclohepteneones and to evaluate their biological (anti-proliferative)

properties. Nagarapu *et al*., have synthesized a series of novel analogues of benzosuberones [13 – 15]. The synthesized derivatives were confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis. The compounds were evaluated by *in-vitro* biological tests for their anti-proliferative properties.

MATERIALS AND METHODS: Melting points were determined on Fischer - John's melting point apparatus and are uncorrected. E Merck silica gel plates (60F254) were used for TLC and silica gel 60-120 mesh were used for Column Chromatography. The ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ solution on a Varian Gemini - 200, Brucker Avance 300, Varian unity - 400 with 2-10 nm solutions at 300 (^{1}H), 75 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. Coupling constants (J) are in hertz (Hz). Mass were recorded on Q STAR mass spectrometer at 5 or 7K resolution using polytethylene glycol as internal reference compound.

9-Chloro-2,3-dimethyl-6,7-dihydro-5*H* -benzo[7] annulene - 8 - carbaldehyde (2): 9-Chloro-2,3-di methyl-6,7-dihydro - 5*H* - benzo [7] annulene-8-carbaldehyde was prepared by transferring the dry DMF to RBF followed by addition of $POCl_3$ (2.3 mL) at 0 °C. Then compound 1 was added in inert atmosphere with continuous stirring. Then the reaction was heated with stirring for about 4 h. The reaction mass was then quenched with $NaHCO_3$ and the pure organic layer was and concentrated by evaporation under vacuum using a rotary evaporator. m.p. 52°C. IR(KBr) γ: υ 1665 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$): δ 10.36 (s, 1H, CHO), 7.43 (s, 1H, Ar-H), 7.26 (s, 1H, Ar-H), 2.87 (t, *J*=6.79Hz, 2H, CH_2), 2.54 (t, *J*=6.79Hz, 2H, CH_2), 2.30 (s, 6H, CH_3), 1.79-1.85 (m, 2H, CH_2). MS (ESI) *m/z*: 235[M+1].

9-Chloro-2,3 dimethyl-6,7-dihydro-5*H*-benzo[7] annulene-8-carboxylic acid (3): To a 100 mL RBF, 9-chloro-2,3 dimethyl-6,7-dihydro-5*H*-benzo [7] annulene-8-carbaldehyde (5 g, 0.021 moles) in H_2O-acetonitrile (4:6) (40 mL), NaH_2PO_4 (0.46 g, 0.0034 moles), $NaClO_2$ (3.34 g, 0.036 moles) and 35% H_2O_2 (0.71mL, 0.30 moles) were added and reacted for 6 h at 0 ºC-RT, to give the compound and the contents were extracted with ethyl acetate and the organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure with the rotary evaporator.

General procedure for the synthesis of substituted - 2, 3-dimethyl – *N* - (3-(4-phenyl piperazin-1-yl)propyl)-6,7-dihydro-5*H*-benzo [7] annulene-8-carboxylic acids (5a-e). 9-Chloro-2,3 dimethyl-6,7-dihydro - 5*H* - benzo [7] annulene-8-carboxylic acid was dissolved in tetrahydrofuran (5 mL) and HOBt (1.1 mmol), EDC.HCl (1.1 mmol) were added to it. The reaction mixture was stirred for 5 min, 3-(4-phenylpiperazin-1-yl)propan-1-amine (1.2 mmol) was added in a slow stream and followed by the addition of triethylamine (2 mmol) and refluxed for 24 h. The progress of the reaction was monitored by TLC. After completion of the reaction, distil off the solvent, water (10 mL) was added to the reaction mixer and extracted with ethyl acetate. Organic layer was collected and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the resultant compound was subjected to column chromatography over silica gel to afford the following compounds:

9-Chloro-2,3dimethyl-*N*- (3- (4-phenylpiperazin-1-yl)propyl)-6,7-dihydro-5*H*-benzo[7] annulene-8-carboxylic acid (5a): Pale brown solid, m.p. 148-151 ºC with 62% yield. IR (KBr, u): 3419, 2923, 2853, 1666, 1456, 1375, 1262, 1020, 750, 451 cm^{-1} : ^{1}H NMR (300MHz, $CDCl_3$) : δ 1.81-2.02 (m, 2H, CH_2), 2.14-2.19 (m, 4H, CH_2), 2.22-2.29 (s, 6H, CH_3), 2.57-2.61 (t, *J*=6.56 Hz, 2H, CH_2), 2.73-2.86 (m, 6H, pip- CH_2, CH_2), 3.26 (s, 4H, pip- CH_2), 3.49-3.54 (m, 2H, CH_2), 6.86-6.96 (m, 5H, Ar-H), 7.22-7.25 (m, 1H, Ar-H), 7.33-7.46 (m, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$):δ 19.3,19.5, 21.6, 24.4, 28.8, 29.6, 31.0, 34.4, 38.4, 42.2, 52.5, 56.2, 116.4, 120.4, 128.1, 129.1, 129.2, 129.8, 134.6, 137.6, 137.9, 150.3, 168.6, 175.3; MS (ESI) *m/z*: 452 $[M+H]^+$.

9-Chloro - 2, 3 – dimethyl - *N*-(3-(4-2-methoxy phenylpiperazin-1-yl)propyl) - 6, 7- dihydro-5*H*-benzo[7] annulene-8-carboxamide (5b): Pale brown solid, m.p. 148 - 151 ºC with 62% yield. IR (KBr, u): 3358, 2925, 2854, 1637, 1458, 1377, 1244, 1026, 871, 542 cm^{-1}: ^{1}H NMR (300MHz, $CDCl_3$) : δ 1.88- 1.92 (m, 2H, CH_2), 2.14-2.21 (m, 4H, CH_2), 2.25 (s, 6H, CH_3), 2.62 (t, *J*=6.56 Hz,

2H, CH_2), 2.75 (t, *J*=6.40 Hz, 2H, CH_2), 2.86 (s, 4H, pip- CH_2), 3.14 (s, 4H, pip-CH_2), 3.50-3.54 (m, 2H, CH_2), 3.85 (s, 3H, OCH_3), 6.80-6.87 (m, 2H, Ar-H), 7.28 (s, 1H, Ar-H), 7.61 (s, 1H, Ar-H).^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3,19.5, 21.6, 24.4, 28.8, 29.6, 31.0, 34.4, 38.4, 42.2, 52.5, 56.2, 116.4, 120.4, 128.1, 129.1, 129.2, 129.8, 134.6, 137.6, 137.9, 150.3, 168.6, 175.3; MS (ESI) *m/z*: 482 $[M+H]^+$.

9-Chloro-2,3 dimethyl-*N*-(3-(4-4-triflouromethyl phenylpiperazin-1-yl) propyl) - 6, 7 - dihydro - 5*H*-benzo[7] annulene-8-carboxamide (5c): Pale brown solid, m.p. 148-151 ºC with 62% yield. IR (KBr, u): 3413, 2925, 2855, 1635, 1458, 1381, 1257, 1079, 754 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.71- 1.76 (m, 2H, CH_2), 2.14-2.18 (m, 4H, CH_2), 2.21 (s, 6H, CH_3), 2.54 (t, *J*= 7.32 Hz, 2H, CH_2), 2.64 (t, *J* = 4.88 Hz, 4H, pip-CH_2), 3.27 (t, *J* = 4.88 Hz, 4H, pip-CH_2), 3.33-3.37 (m, 2H, CH_2), 6.71(s, 1H, Ar-H), 6.86-6.93 (m, 3H, Ar-H), 7.0-7.03 (m, 1H, Ar-H), 7.47-7.50 (s, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 19.6, 25.5, 29.5, 29.6, 31.2, 35.1, 36.8, 38.8, 47.8, 52.7, 56.9, 114.5, 120.5, 121.0, 125.6, 126.3, 126.4, 129.4, 129.6, 133.7, 136.2, 139.5, 152.9, 172.8; MS (ESI) m/z: 520 $[M+H]^+$.

9-Chloro-2, 3 dimethyl-*N*-(3-(4-2-flourophenyl piperazin-1-yl)propyl)-6,7-dihydro-5*H*- benzo[7] annulene-8-carboxamide (5d): Pale brown solid, m.p. 148-151 ºC with 62% yield. IR (KBr, u): 3415, 2927, 2856, 1637, 1459, 1382, 1256, 1079, 755 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.87-2.06 (m, 2H, CH_2), 2.13-2.20 (m, 4H, CH_2), 2.24 (s, 6H, CH_3), 2.61 (t, *J*=6.40 Hz, 2H, CH_2), 2.71-2.85 (m, 6H, pip-CH_2, CH_2), 3.16 (s, 4H, pip-CH_2), 3.50-3.56 (m, 2H, CH_2), 6.81-6.87 (m, 1H, Ar-H), 6.92-6.97 (m, 3H, Ar-H), 6.98-7.04 (m, 2H, Ar-H), 7.47-7.50 (s, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$):δ 19.3, 19.5, 24.6, 25.7, 28.9, 29.6, 31.2,34.4, 39.2, 50.0, 53.0, 57.0, 115.9, 116.1, 118.9,122.6, 122.7, 124.3, 124.4, 129.2, 129.9, 134.6, 134.7, 135.0, 137.6, 137.9, 168.4; MS (ESI) m/z: 470 $(M+H)^+$.

9-Chloro-2, 3-dimethyl - *N* - (3-(4-4-nitromethyl phenylpiperazin-1-yl)propyl) - 6, 7-dihydro – 5*H* -benzo[7] annulene-8-carboxamide (5e): Semi solid, with 75% yield. IR (KBr, u): 3415, 2924, 2854, 1660, 1382, 1238, 1053, 724, 469 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ1.87-1.94 (m, 4H, CH_2). 2.14-2.19 (m, 4H, CH_2), 2.22 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.59 (t, 2H, CH_2), 2.77 (t, 2H, CH_2), 2.84 (t, 4H, pip_{-H}), 3.26 (t, 4H, pip_{-H}), 3.50-3.53 (m, 2H, CH_2), 6.87-6.94 (m, 5H, Ar-H), 7.23-7.25 (m, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$):δ 14.01, 22.3, 24.5, 28.9, 29.9, 32.0, 34.5, 37.2, 45.5, 52.0, 55.9, 114.1, 126.0, 126.5, 128.0, 128.2, 128.6, 135.2, 137.2, 139.6, 140.0, 154.0, 169.0; MS (ESI) m/z: 497 $[M+H]^+$.

Biological Activity: A protocol of 48 h continuous drug exposure was used and an SRB cell proliferation assay was used to estimate cell viability or growth. All the cell lines were grown in Dulbecco's modified Eagle's medium (containing 10% FBS in a humidified atmosphere of 5% CO_2 at 37 °C). Cells were trypsinized when sub-confluent from T25 flasks/60 mm dishes and seeded in 96-well plates in 100 µL aliquots at plating densities depending on the doubling time of individual cell lines.

The micro titre plates were incubated at 37 °C, 5% CO_2, 95% air, and 100% relative humidity for 24 h prior to addition of experimental drugs and were incubated for 48 h with different doses (0.01, 0.1, 1, 10, 100 µM) of prepared derivatives**.** After 48 hours incubation at 37 °C, cell mono layers were fixed by the addition of 10% (wt/ vol) cold trichloroacetic acid and incubated at 4 °C for 1h and were then stained with 0.057% SRB dissolved in 1% acetic acid for 30 min at room temperature. Unbound SRB was washed with 1% acetic acid. The protein bound dye was dissolved in 10mM Tris base solution for OD determination at 510 nm using a micro plate reader (Enspire, Perkin Elmer, and USA). Using the seven absorbance measurements [time zero, (Tz), control growth, (C), and test growth in the presence of drug at the five concentration levels (Ti)], the percentage growth was calculated at each of the drug concentrations levels. Percentage growth inhibition was calculated as:

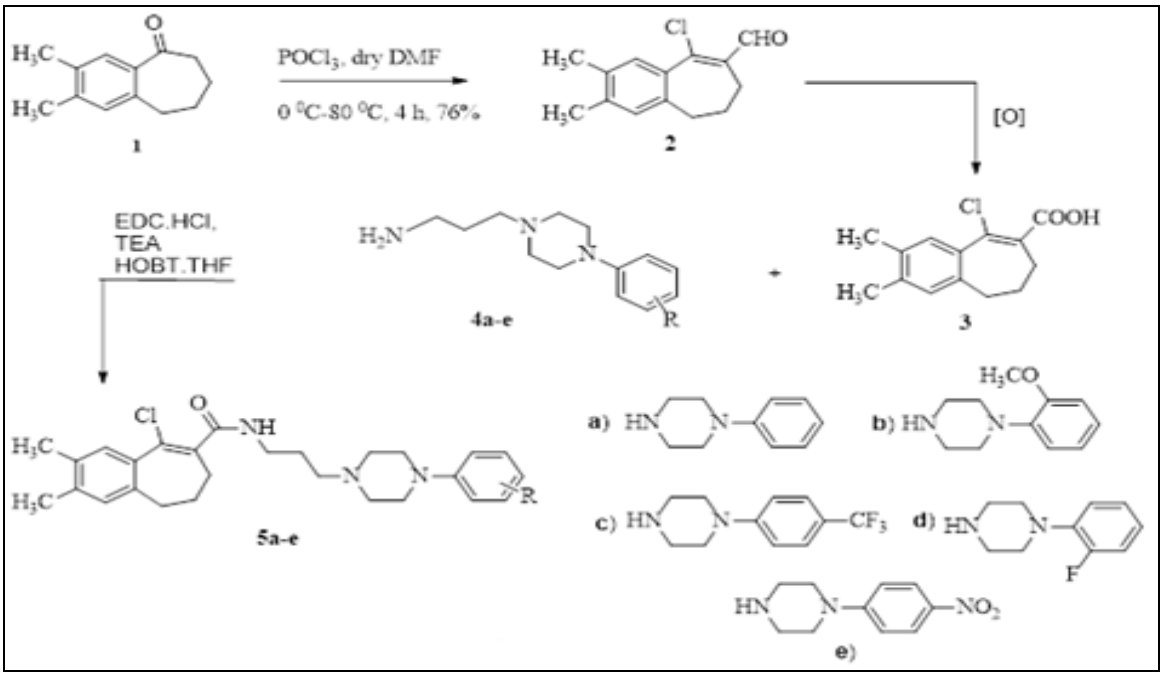
[(Ti-Tz)/(C-Tz)] × 100 for concentrations for which Ti>/=Tz

[(Ti-Tz)/Tz] × 100 for concentrations for which Ti<Tz

The dose response parameter, growth inhibition of 50% (GI_{50}) was calculated from [(Ti-Tz)/(C-Tz)] x 100 = 50, which is the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. Values were calculated for this parameter if the level of activity is reached; however, if the effect is not reached or is exceeded, the value for that parameter was expressed as greater or less than the maximum or minimum concentration tested.

RESULTS AND DISCUSSION: In the present work, we synthesized new benzocycloheptenone derivatives (5a-e) by condensing 9-chloro-2, 3 dimethyl - 6, 7-dihydro-5*H*-benzo [7] annulene-8-carboxylic acid (3) with 3-(4-phenylpiperazin-1-yl) propane-1-amines [16] (4a-e) as shown in Scheme 1. The (*Z*)-9-chloro - 2, 3-dimethyl - 6, 7-dihydro-5*H*-benzo[7]annulene - 8 - carbaldehyde [17] (2) was synthesized from Vilsmeier-Haack-Arnold reaction of 2,3-dimethyl-6,7,8,9-tetrahydro benzocyclo hepten-5-one (11) in presence of $POCl_3$, dimethylformamide in a yield of 84-87%. The structures of all the synthesized compounds were determined by spectral data (IR, Mass, ^{1}H NMR and ^{13}C NMR). In the ^{1}H NMR spectra, the presence of characteristic singlet at 10.36 ppm representing one proton provided evidence for the formation of carbaldehyde (12).

The required starting compounds were synthesized from Friedel-Craft's acylation of aromatic hydrocarbons with glutaric anhydride furnishing arylbutyric acids which on Clemmenson reduction followed by cyclization with excess polyphosphoric acid gave 2,3-dimethyl-6,7, 8, 9-tetrahydrobenzocyclohepten-5-one [17] (11). 9-Chloro - 2, 3 dimethyl-6,7-dihydro-5*H*-benzo[7] annulene-8-carboxylic acid (13) was obtained by oxidation of (*Z*)-9-chloro-2,3-dimethyl-6,7-dihydro - 5*H* - benzo [7] annulene-8-carbaldehyde (12) with sodium chlorite in the presence of 30% H_2O_2 in acetonitrile at 0 ºC in quantitative yield. The targeted 2,3-dimethyl-*N*-(3-(4-phenyl piperazin-1-yl)propyl)-6,7-dihydro-5*H*-benzo[7] annulene-8-carboxylic acids (14a-e) were achieved by treating with 9-chloro-2,3 dimethyl-6,7-dihydro-5*H*-benzo [7] annulene-8-carboxylic acid (13) in presence of peptide coupling reagents EDC. HCl, TEA, HOBT.THF at reflux temperature for 24 h in excellent yields.



The synthesized compounds were confirmed on the basis of spectral data. In ^{1}H NMR spectra the characteristic broad singlet signal appeared for amide proton of compound 5a at δ 7.40 ppm and in ^{13}C NMR appeared at δ 176 ppm, followed by in FT-IR appeared at 3419 cm^{-1}. The structures of all the compounds were further confirmed by ESI-MS analysis. For instance compound 5a displayed molecular ion peak at *m/z* = 452$[M+H]^+$.

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Biological Activity: The *in-vitro* anti-proliferative activities of the compounds prepared were examined on human cancer cell lines was evaluated against four different human cancer cell lines He La (cervical), MIAPACA (pancreatic), MDA-MB-231 (breast) and IMR32 (neuro blastoma) summarized in **Table 1**. The compounds 5a, 5b, 5c, 5d showed promising activity against four human cancer cell lines. Compound 5a showed potent activity against HeLa at 0.97 μM and moderate activity against MDA MB 231 at 2.0 μM. Compound 5b showed significant activity against IMR 32 at 1.4 μM. Compound 5c showed potent activity against HeLa, IMR 32 at 0.3 μM and also potent activity against IMR 32 at 0.71 μM. Compound 5d showed potent activity against MDA MB 231, MIAPACA at 0.29 μM, 0.7 μM respectively.

TABLE 1: (GI_{50}/μM)[a] VALUES OF THE TESTED COMPOUNDS 5a-e AGAINST FOUR HUMAN CANCER CELL LINES

Sample	HeLa	MIAPACA	MDA MB 231	IMR 32
5a	0.97 ± 0.06	59.2 ± 0.5	2.0 ± 0.06	>100
5b	5.7 ± 0.51	>100	20.4 ± 0.1	1.4 ± 0.07
5c	0.3 ± 0.01	10 ± 0.3	0.71 ± 0.02	0.3 ± 0.02
5d	9.2 ± 0.8	0.7 ± 0.01	0.29 ± 0.02	26.5 ± 0.08
5e	9.8 ± 0.25	14.0 ± 0.9	4.8 ± 0.06	3.0 ± 0.09
Doxorubicin[b]	0.09 ± 0.002	0.086 ± 0.003	0.087 ± 0.001	0.03 ± 0.008
Paclitaxel[b]	0.035 ± 0.005	0.09 ± 0.0012	0.084 ± 0.002	0.083 ± 0.003

[a]GI_{50}: 50% Growth inhibition, concentration of drug resulting in a 50% reduction in net protein increase compared with control cells. [b]Positive controls

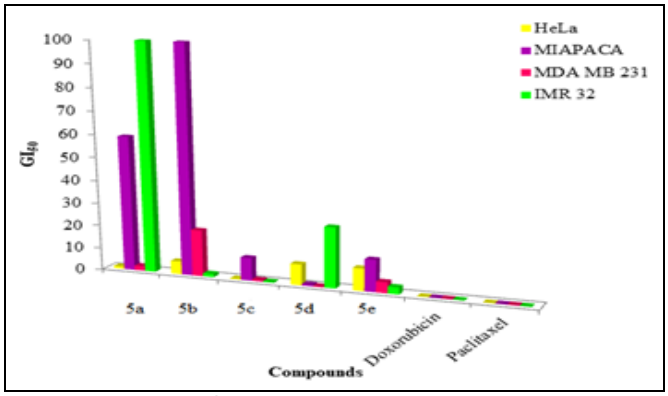

FIG. 1: (GI_{50}/μM)[a] VALUES OF 5a-e, AGAINST FOUR HUMAN CANCER CELL LINES (He La, MIAPACA, MDA MB 231 AND IMR 32)

CONCLUSION: From the research a novel series of 2, 3-dimethyl -N- (3-(4-phenyl piperazin-1-yl) propyl)-6, 7-dihydro-5H-benzo [7] annulene-8-carboxylic acids (5a-e) have been synthesized in good to excellent yields and evaluated for their anti-proliferative activity. The approach can further be applied for the development of benzocyclo heptenone based substituted phenyl piperazines. All the compounds were characterized and confirmed by ^{1}H NMR, ^{13}C NMR, IR and Mass Spectroscopies: The reactions were characterized by experimental simplicity and milder reaction conditions.

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CONFLICT OF INTEREST: The authors confirm that this article content has no conflicts of interest.

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