ORIGINAL ARTICLE

FUTURE JOURNAL OF PHARMACEUTICALS AND HEALTH SCIENCES

Published by Pharma Springs Publication Journal Home Page: https://pharmasprings.com/fjphs

In vitro anti-proliferative activity of newly synthesized compounds of substituted-(3-phenyl-1,2,4-oxadiazol-5yl)-methyl-9-chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carboxylates

Gomedhika P M, Subhashini NJP*

Department of Chemistry, Osmania University, Hyderabad-500 007, Telangana, India

Article History:

Received on: 23 Feb 2022
Revised on: 10 Mar 2022
Accepted on: 12 Mar 2022

Keywords:

American Type Culture Collection,
MDA MB 231,
PANC-1

ABSTRACT

A series of the newly synthesized substituted-(3-phenyl-1,2,4-oxadiazol-5yl)-methyl-9-chloro-2,3-dimethyl-6,7-dihydro-5*H*-benzocyclohepten-8-carboxylates 13a-h have been assessed for their anti-proliferative activity *in vitro* and shown negative effect with GI_{50} values 0.320-4.750 μM towards cancer cell growth. The compounds 13d, 13e, 13f, 13g showed significant activity towards three cancer cell lines of human. Among them 13 gm showed strong anti-cancer activity towards PANC-1 at 0.312 *m*M respectively. Notably, compound 13e showed significant activity at 0.320 *m*M against MDA MB-231 respectively.

*Corresponding Author

Name: Subhashini NJP
Phone:
Email: njsubhashini@yahoo.co.in

eISSN: 2583-116X pISSN:

DOI: https://doi.org/10.26452/fjphs.v2i2.237

Production and Hosted by

Pharmasprings.com

INTRODUCTION

With the discovery of Colchicine [1, 2] (I), the anti-cancer effect of benzosuberone has been raised since 1984. In drug discovery program Benzosuberone, which contain the core structure take a different role, particularly in natural products. The associated components of benzosuberone have been marvellous agents for therapeutic purpose as cytotoxic [3–5], anticancer [6, 7], CB1 (high) receptors [8], anti-malarial [9] and strong activity of antagonistic [8]. Here, few new analogues of benzosuberone [10, 11], (II-IV) represent in Figure 1 are proved to be effective as tubulin (polymerization inhibitors).

MATERIALS AND METHODS

Required human cancer cell lines (MDA MB 231, He La, and IMR 32, MIAPACA, and SIHA, PANC-1) procured from American Type Culture Collection (ATCC), US.

Methodology

The newly synthesized compounds 13a-h [12] were analysed according to usual reported method for their anti-proliferative activity for three various cancer cell lines of human as SIHA, MDA MB 231, PANC-1 *in vitro*. A protocol of drug exposure for 48h continuously and SRB cell proliferation assay was used for estimation viability or growth of cell. In a humidified atmosphere containing 10% FBS and 5% CO_2 at 37 °C for growth of cell lines (Dulbecco's modified Eagle's medium). Cells were trypsinized and aliquots at plating densities based on the individual cell lines doubling time, from T25 flasks/60 mm dishes sub-confluent and 96-well plates in 100 μL were seeded.

RESULTS AND DISCUSSION

Compounds Effects on the Viability of Human Cancer Cells

The anti cancer activity *in vitro* of the compounds 13a-h was observed against three various cancer cell lines of human SIHA (uterus), MDA-MB-231

Table 1: ($GI_{50}/\mu M$) Values of the Tested Compounds (13a-h)

S. No	Compound	SIHA	MDAMB-231	PANC-1
1	13a	4.750 ±0.07	2.800 ±0.02	2.155 ±0.02
2	13b	3.530 ±0.01	2.500 ±0.03	1.290 ±0.04
3	13c	2.650 ±0.02	4.280 ±0.07	2.421 ±0.03
4	13d	1.140 ±0.05	1.475 ±0.05	0.612 ±0.05
5	13e	1.411 ±0.06	0.320 ±0.01	0.670 ±0.07
6	13f	0.972 ±0.02	0.860 ±0.06	0.633 ±0.01
7	13g	1.109 ±0.02	0.370 ±0.02	0.312 ±0.04
8	13h	0.650 ±0.04	0.660 ±0.05	0.950 ±0.08
9	Cambretostatin(CA4)[b]	0.05 ±0.001	0.019 ±0.001	<0.01

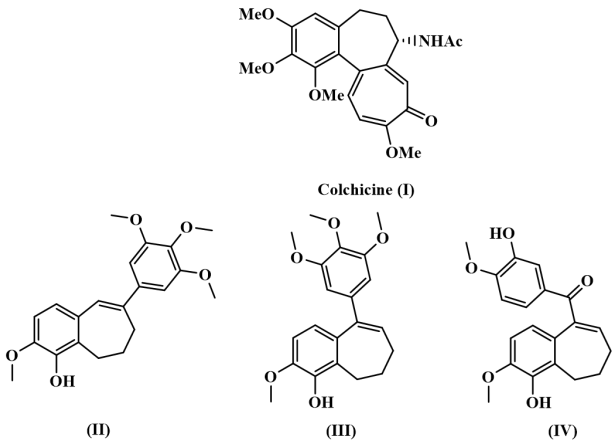

Figure 1: Benzocycloheptenone Core Structure with Biological Importance

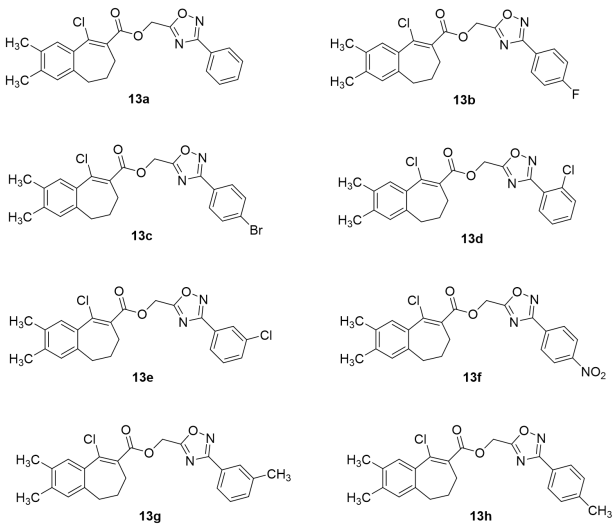

Figure 2: Schemes of the Tested Compounds (13a-h)

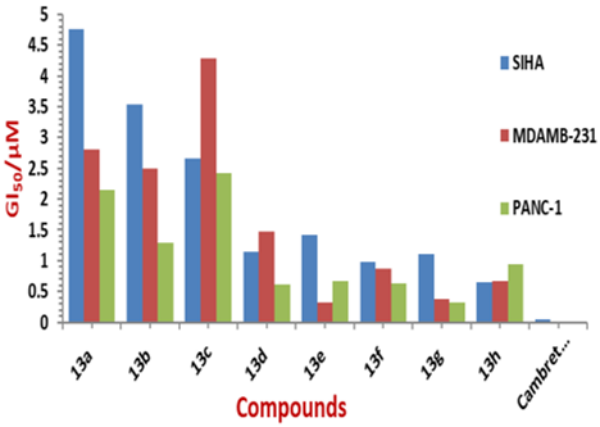

Figure 3: ($GI_{50}/\mu M$)[a] Values of the Tested Compounds (13a-h)

(breast), PANC-1(pancreatic) summarised in the Table 1 (Figure 2, Figure 3). Compounds were chosen for an advanced assay against four cancer cell lines of human at five different concentrations (0.01, 0.1, 1, 10, 100 μM). GI_{50} was calculated. As compared with standard Combretostatin these values in arrangement to concentration of the compound causing 50% net cell growth decrease. For each one of these parameters results were calculated.

According to Table 1, 13a-h the synthesised series of compounds have shown negative towards the growth of cancer cell with GI_{50} values (0.312-4.750 μM). Benzocycloheptenone of various substituents activity was examined. Based on demonstration many of the compounds show moderate cytotoxicities to the cell lines and can be compared with the activity to the +ve control of Combretostatin.

CONCLUSION

In conclusion, with subject to Table above, the newly synthesized a series of compounds 13a-h with GI_{50} values (0.320-4.750 μM) have shown effect on cancer cell growth inhibition. On dimethyl-

benzocycloheptenone the effect of various substituents was analysed. The compounds 13d, 13e, 13f, 13g showed good activity towards three cancer cell lines of human. Among them 28k showed strong anti-cancer activity towards PANC-1 at 0.312 *m*M respectively. Notably, compound 13e showed significant activity at 0.320 *m*M against MDA MB-231 respectively.

ACKNOWLEDGEMENT

Authors are grateful to the Head, Department of Chemistry, Osmania University, Hyderabad, India.

Conflict of Interest

The authors attest that they have no conflict of interest in this study.

Funding Support

The authors declare that they have no funding support for this study.

Future Perspectives

Benzosuberone based compounds form an important class of benzofused heterocycles with a wide spectrum of biological activities such as anti-cancer. Many compounds are in development phase as potential new drugs acting against different targets. A literature survey revealed that modification on benzosuberone pharmacophore may results in increase in its biological potencies.

REFERENCES

[1] H G Capraro and A Brossi. Tropolonic colchicum alkaloids. 1984. In The Alkaloids: Chemistry and Pharmacology, Academic Press, Vol. 23, pp. 1-70.

[2] O. Boye. A. Brossi in The Alkaloids. 1992. A. Brossi, G. A. Cordell, Eds.; Academic Press; Newyork, Vol.41: p125.

[3] Jonathan R. Dimmock, Gordon A. Zello, Eliud O. Oloo, J. Wilson Quail, Heinz-Bernhard Kraatz, Pál Perjési, Ferenc Aradi, Krisztina Takács-Novák, Theresa M. Allen, Cheryl L. Santos, Jan Balzarini, Erik De Clercq, and James P. Stables. Correlations between Cytotoxicity and Topography of Some 2-Arylidenebenzocycloalkanones Determined by X-ray Crystallography. *Journal of Medicinal Chemistry*, 45(14):3103–3111, 2002.

[4] A. E. G. Hammam, N. A. Abdel-Hafez, W. H. Midura, and M. Z. Mikolajczyk. Chemistry of Seven-Membered Heterocycles, VI. Synthesis of Novel Bicyclic Heterocyclic Compounds as Potential Anticancer and Anti-HIV Agents. *Naturforsch*, 55b:417–424, 2000.

[5] Abdel-Galil E. Amr, Ashraf M. Mohamed, Salwa F. Mohamed, Nagla A. Abdel-Hafez, and Abu El-Fotooh G. Hammam. Anticancer activities of some newly synthesized pyridine, pyrane, and pyrimidine derivatives. *Bioorganic and Medicinal Chemistry*, 14(16):5481–5488, 2006.

[6] Naesoa Hafez and A G Hammam. 5 Synthesis of some F-heterocyclic compounds of potential anticancer activity using 8-fluoro-1-benzosuberone as a synthon. *Egyptian Journal of Chemistry*, 49(1):63–72, 2006.

[7] L S Boulos, H A Abdel-Malek, and N F El-Sayed. Synthesis of Novel Benzosuberone Derivatives using Organophosphorus Reagents and their Antitumor Activities. *Zeitschrift Für Naturforschung B*, 67(3):243–252, 2012.

[8] A R Stoit, J H M Lange, A P Hartog, E Ronken, K Tipker, H H Van Stuivenberg, J A R Dijksman, H C Wals, and C G Kruse. Design, synthesis and biological activity of rigid cannabinoid CB 1 receptor antagonists. *Chemical and Pharmaceutical Bulletin*, 2002.

[9] L Bounaadja, M Schmitt, S Albrecht, E Mouray, C Tarnus, and I Florent. Selective inhibition of PfA-M1, over PfA-M17, by an aminobenzosuberone derivative blocks malaria parasites development in vitro and in vivo. *Malaria Journal*, 16(1), 2017.

[10] Z Chen, A Maderna, S K Sukuru, M Wagenaar, J Christopher, M H Lam, and F Loganzo. Design, Synthesis, and Biological Evaluation of Water-Soluble Amino Acid Prodrug Conjugates Derived from Combretastatin, Dihydronaphthalene, and Benzosuberene-Based Parent Vascular Disrupting Agents. *Bioorg. Med. Chem. Lett*, 23:6688, 2013.

[11] S Bhat, J S Shim, and J O Liu. Tricyclic thiazoles are a new class of angiogenesis inhibitors. *Bioorganic & Medicinal Chemistry Letters*, 23(9):2733–2737, 2013.

[12] P M Gomedhika and N J P Subhashini. Synthesis of substituted-(3-phenyl-1,2,4- oxadiazol-5yl)-methyl-9-chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8- carboxylates. *Indian Journal of Advances in Chemical Sciences*, 10(1):18–21, 2022.

Cite this article: Gomedhika P M, Subhashini NJP. *In vitro* anti-proliferative activity of newly synthesized compounds of substituted-(3-phenyl-1,2,4-oxadiazol-5yl)-methyl-9-chloro-2,3-dimethyl-6,7-dihydro-5H-benzocyclohepten-8-carboxylates. Future J. Pharm. Health. Sci. 2022; 2(2): 91-94.