

IN VITRO ANTI-PROLIFERATIVE ACTIVITY OF NOVEL ANALOGUES OF (E)-2-BENZYLIDENE-N-(3-(3-OXO-2,3-DIHYDRO-4H-BENZO[B][1,4]OXAZIN-4-YL)PROPYL) HYDRAZINE-1-CARBOTHIOAMIDE

Palla Sai Lakshmi, Puligilla Shankaraiah✉

Department of Pharmacy, Chaitanya Deemed to be University, Hanamakonda-506001,
Telangana State, India.

✉Corresponding Author: drspuligilla@gmail.com

ABSTRACT

A novel analog of substituted-(*E*)-2-benzylidene-*N*-(3-(3-oxo-2,3-dihydro-4*H*-benzo[*b*] [1,4] oxazin-4-yl)propyl) hydrazine-1-carbothioamides (9a-j) appeared to be assess being anti-proliferative activity in vitro environment some of the newly derived derivatives have shown sufficiently great to modest suppression in the number of cells in cancer among GrowthInhibition₅₀ was (0.180-4.20 μ M). Compounds 9a, 9b, 9d, 9g, 9i, and 9j showed promising acts contrarily 4 human being tumor cell lines. Out of 9a and 9g displayed heartening cancer act in opposition to IMR-32 (Human being neuroblastoma cells) at 0.23 μ M and MIAPACA(human pancreatic carcinoma cells) at 0.18 μ M respectively. Notably, compound 9g showed significant activity at 0.18 μ M against the MIAPACA cell line respectively.

Keywords: Human Cervical Malignant Cells, Pancreatic Carcinoma, Breast Adenocarcinoma, Human Neuroblastoma Cells, DMEM, Doxorubicin, Paclitaxel.

RASAYAN J. Chem., Vol. 16, No. 2, 2023

INTRODUCTION

Scaffolds of (2*H*)-1,4-Benzoxazin-3(4*H*)-one gained much attentiveness from research workers of phytochemistry afterward 2,4-dihydroxy-(2*H*)-1,4-benzoxazin-3(4*H*)-one(I-DIBOA)&2,4-dihydroxy-7-methoxy-(2*H*)-1,4-benzoxazin-3(4*H*)-one (II-DIMBOA) be extracted from grasses, which belongs Gramineae. Phytotoxic, antifeedant, antimicrobial, insecticidal, and antifungal biological properties have been exhibited interestingly.¹ Figure-I indicates that analogues of fluconazole containing 2*H*-1,4-benzoxazine-3 3(4*H*)-one moiety (III) exhibited good antifungal activity² and antimicrobial activity³ were found in some of the derivatives of benz oxazinones (IV). Oxazinones act contrarily on corona pathogens.⁴ Cx-614 has oxazinone highly latent in dealing with the cognitive malady.⁵ Benz oxazinone is a pivotal actinic in ATL-962 to handle obesity.⁶ Stocrin is an NNRTI distinctly probable in handling human immunodeficiency pathogens.⁷

EXPERIMENTAL

Materials and Methods

The cultures of animal cells, HeLa (Human cervical cancer cells); MIAPACA (pancreatic carcinoma cells); MDA-MB-231 (breast adenocarcinoma cells); IMR-32 (neuroblastoma cells) acquired from the global biological resource centre (ATCC), US.

Detection Methods

Cultured Cells, Conservation, and Cancer Act Assessment

Newly synthesized test compounds 9a-j⁸ were estimated to identify anti-neoplastic action in vitro environment in 4 cancerous types. Cultured cancerous cells are continuously exposed to the drug for 48 hr and Sulfo-rhodamine B assay⁹ is applied for identification of viability. The sulforhodamine B checks for the ability whether binds basic AA residues of CCl₃COOH fixed cells electrostatically. DMEM acts as a growing medium. Cell lines be bedded in 96-well plates in 100 μ L fractional having 10%FBS and incubated for about 24hr under 5% CO₂ at 37°C for attachment.¹⁰

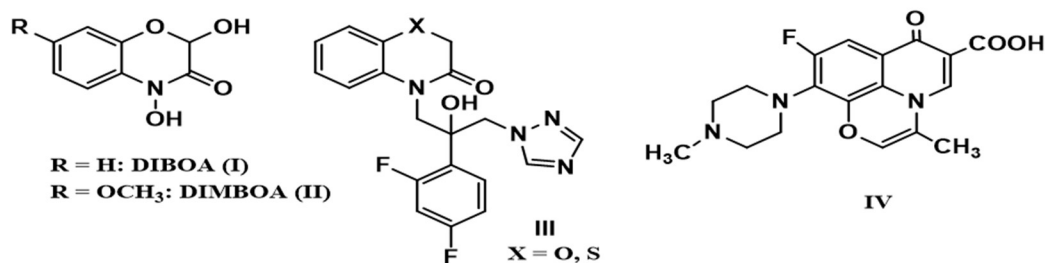
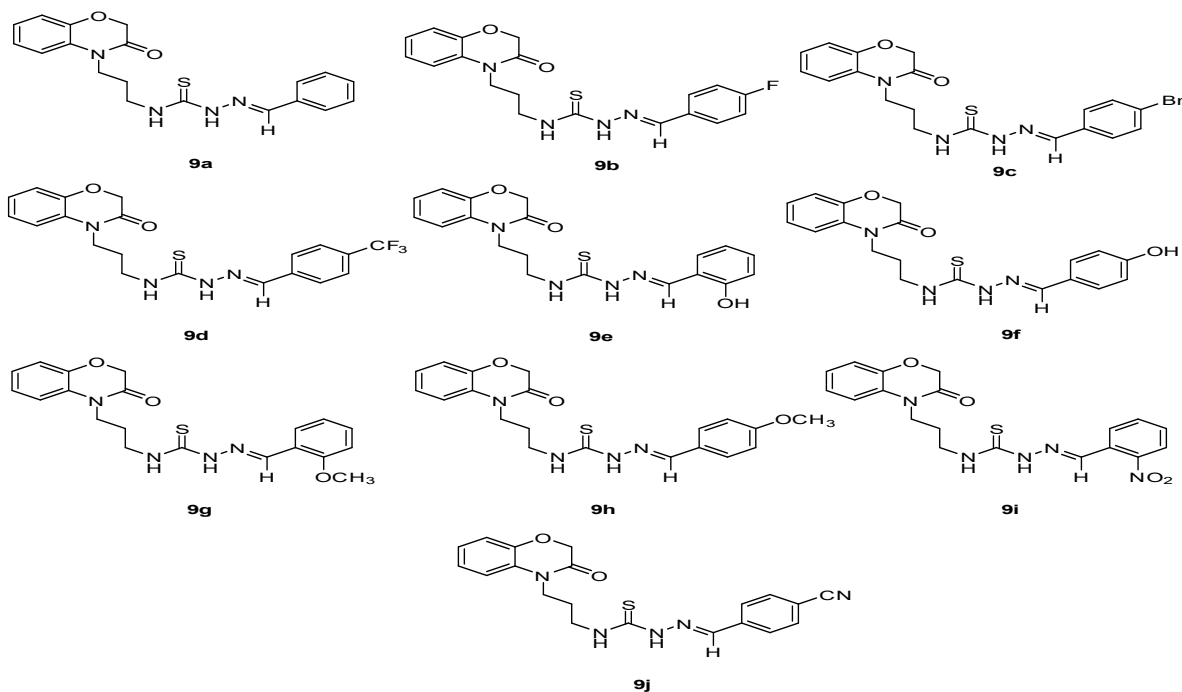


Fig.-1: Biologically Active 1,4-benzoxazines

RESULTS AND DISCUSSION

The Compound's Action on the Ability to Live Human Cancer Cells

The chemotherapeutic action of outlined compounds 9a-j be appraised as opposed to 4 human malignant cell types HeLa, MIAPACA, MDA-mb-231, and IMR-32 summarised in Table-1. 5 concentrations (0.01, 0.1, 1, 10, 100 μ M) of designed ligands were prepared as opposed to 4 cancerous cell lines. GI₅₀ values showed half of the decrease in cell amelioration to standard doxorubicin and paclitaxel. Determining each one of the parameters if the concerned activity is achieved. If the concerned has not attained the values described as < or > the max or min concentration tested. Entrenched Table-1, synthesized series of ligands 9a-j have shown notable to modest cancer cell amelioration inhibition. GrowthInhibition₅₀ values (0.18-4.20 μ M). The consequence of different substitutable carbosulfonamides was scrutinized. The outcome of ligands flashed appreciable cytotoxicity to these cell lines and laid out the proportional act to the control of doxorubicin and paclitaxel.

Table-1: (GrowthInhibition₅₀)^a Values of the Experimented Ligands 9a-j against 4 Human Malignant Types

S. No.	Ligands	HeLa	MIAPaCa	MDA-mb-231	IMR-32
1	9a	2.01±0.3	4.0±0.2	3.4±0.4	0.23±0.04
2	9b	2.8 ±0.65	8.0±0.6	>100	3.6 ±0.06
3	9c	>100	12.0±0.5	6.0±0.4	>100
4	9d	2.3 ±0.05	2.8 ±0.63	18.0±0.6	21.8±0.65
5	9e	>100	26.4±0.83	>100	>100
6	9f	4.2±0.2	>100	21.5±0.1	>100
7	9g	0.30±0.2	0.18±0.09	1.6±0.06	0.41±0.04

8	9h	14.0±0.8	16.0±0.9	14.8±0.5	22.6±0.06
9	9i	1.3±0.2	3.2±0.5	3.0±0.7	0.36±0.04
10	9j	1.1±0.5	1.02±0.3	1.7±0.2	1.5±0.3
	Doxorubicin ^b	0.074±0.001	0.092±0.002	0.086±0.001	0.026±0.002
	Paclitaxel ^b	0.033±0.001	0.056±0.002	0.094±0.005	0.074±0.003

^aGI₅₀: 50% amelioration suppression, drug in μM resulting in a 50% depletion of protein build-up proportional to control cells.

^b Positive controls.

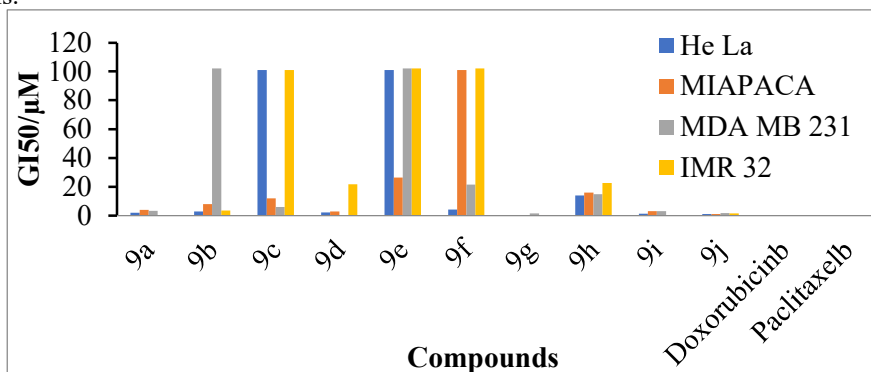


Fig.-1: (GI₅₀/μM) of Experimented Ligands (9a-j) Opposed to 4 Cell Lines

CONCLUSION

In conclusion a newly prepared succession of ligands 9a-j have shown notable to modest cancer cell amelioration suppression with growth inhibition₅₀ values (0.18-4.20 μM). The consequence of different substitutable carbothioamides were scrutinized. Compounds 9a, 9b, 9d, 9g, 9i, and 9j showed promising acts as opposed to 4 human cancer cell lines. Amid 9a and 9g flashed impressive anti-cancer act against IMR-32 (Human neuroblastoma cells) at 0.23 μM and MIAPACA (human pancreatic carcinoma cells) at 0.18 μM respectively. Notably, compound 9g showed significant activity at 0.18 μM against the MIAPACA cell line respectively. Besides, attempts are in head way to amend the anti-cancer activity of the above probable ligands.

ACKNOWLEDGMENTS

Authors are grateful to the Department of Pharmacy, Chaitanya Deemed to be University, Hanamakonda, India.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

P. Sai Lakshmi  <https://orcid.org/0000-0001-9819-3311>

P. Shankaraiah  <https://orcid.org/0000-0001-6747-5674>

Open Access: This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

REFERENCES

1. A. Macias Francisco, D. Marin, A. Oliveros-Bastidas, D. Chinchilla, M. Simonet, G. Molinillo Jose, *Journal of Agriculture and Food Chemistry*, **54**, 991(2006), <https://doi.org/10.1021/jf050896x>

2. B. Borate Hanumant, R. Maujan Suleman, P. Sawargave Sangmeshwer, A. Chandavarkar Mohan, R. Vaiude Sharangi, A. Joshi Vinay, D. Wakharkar Radhika, Iyer Ramki, G. Kelkar Ramesh, P. Chavan Subhash, S. Kunte Sunita, *Bioorganic and Medicinal Chemistry Letters*, **20**, 722(2010), <https://doi.org/10.1016/j.bmcl.2009.11.071>
3. S. A. Hayta, E. A. Sener, B. T. Gulbas, I. Yildiz, O. T. Arpaci, I. Yalcin, N. Altanlar, *European Journal of Medicinal Chemistry*, **41**, 1398(2006), <https://doi.org/10.1016/j.ejmech.2006.06.011>
4. P. W. Hsieh, F. R. Chang, C. H. Chang, P. W. Cheng, L. C. Chiang, F. L. Zeng, K. H. Lin, Y. C. Wu, *Bioorganic and Medicinal Chemistry Letters*, **14**, 4751(2004), <https://doi.org/10.1016/j.bmcl.2004.06.083>
5. B. Gao, K. Chen, X. Bi, J. Wang, *Tetrahedron Letters*, **73**, 7005(2017), <https://doi.org/10.1016/j.tet.2017.09.001>
6. Y. Yamada, T. Kato, H. Ogino, H. Ashina, K. Kato, *Hormone and Metabolic Research*, **40**, 539(2008), <https://doi.org/10.1055/s-2008-1076699>
7. M. Patel, R. J. McHugh, B. C. Cordova, R. M. Klabe, S. Erickson-viitanen, G. L. Trainor, S. Soo. Ko, *Bioorganic and Medicinal Chemistry Letters*, **9**, 3221(1999), [https://doi.org/10.1016/S0960-894X\(99\)00565-X](https://doi.org/10.1016/S0960-894X(99)00565-X)
8. P. Sailakshmi and P. Shankaraiah. Synthesis of (*E*)-2-benzylidene-*N*-(3-(3-oxo-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)propyl)hydrazine-1-carbothioamide (*Manuscript under preparation*).
9. P. S. Kehan, R. Storeng, D. Scudiero, A. Monks, J. McMahon, D. Vistica, J. Warren, H. Bokesch, S. Kenney, M. R. Boyd *Journal of National Cancer Institute*, **82**, 1107(1990), <https://doi.org/10.1093/jnci/82.13.1107>
10. A. Rajini, M. Nooka Raju, I. Ajithkumar Reddy, N. Venkatathri, *Journal of Saudi Chemical Society*, **21**, 77(2017), <https://doi.org/10.1016/j.jscs.2013.10.005>

[RJC- 8154/2022]