Indian Journal of Heterocyclic Chemistry
Vol. 33 - Number 01 (Jan-Mar 2023) 57-62
DocID: https://connectjournals.com/01951.2023.33.57

ISSN (Print) : 0971-1627
ISSN (Online) : 2456-4311

New Dihydrobenzoindolydene Schiff Bases with an Aromatic Core as Potential Anticancer Agents

Israa Nadim Hamdi[1], Salih Mahdi Salman[2]*, Luma Salman Abd[1]

[1]Department of Chemistry, University of Diyala, College of Sciences, Diyala, Iraq
[2]Department of Chemistry, University of Diyala, College of Medicine, Diyala, Iraq

ABSTRACT There are many heterocyclic molecules used in the field of medical application as anticancer agents, but unfortunately cancer cells can be familiar with known agents day by day. There is a continuous demand to develop or synthesis new analogs. This work aims to synthesize new heterocyclic molecules able to overcome this problem using a simply accessible methodology, economic resources, and chemically stable products. 1,1,2-trimethyl-1*H*-benzo[e]indole (**1**) was chosen as starting material which was easily modified by treatment with phosphoryl chloride to reach the synthon 2-(1,1-dimethyl-1*H*-benzo[e]indol-2(3*H*)-ylidene) malonaldehyde (**2**). Schiff's reaction was applied on the latter to yield a series of three monosubstituted and two di-substituted malonaldehyde derivatives. The structures and purities of the target compounds were confirmed by spectroscopy. The synthesized compounds showed good activity in a human liver cancer cell line HepG2 inhibition at 37°C within 24 h using two concentrations which make them suitable for medical application.

KEYWORDS Schiff bases, Indoles, Anti-cancer agents, Dihydrobenzoindolydenes.

How to cite this article: Hamdi, I.N., Salman, S.M., Abd, L.S. New Dihydrobenzoindolydene Schiff Bases with an Aromatic Core as Potential Anticancer Agents, *Indian J. Heterocycl. Chem.*, **2023**, *33*, 57–62.*(DocID: https://connectjournals.com/01951.2023.33.57)*

INTRODUCTION

In general, heterocyclic compounds are an important class of organic chemistry, which can define as compounds that have other atoms besides carbon and hydrogen such as oxygen, nitrogen, and sulfur. Dihydrobenzoindolydene(1,1,2-Trimethyl-1*H*-benzo[e]indole, **1)** is an important heterocyclic derivative that was converted and modified to many others compounds used in a lot of applications in all fields of life including medical and industrials applications. (1) was used as starting materials for the synthesis of fluorescent probes for imaging tumors *in vivo*,[1-5] and in the synthesis of ahemicyanine-based near-infrared (NIR) fluorescent probe which is used for the detection of exogenous and endogenous CO in various biological samples such as cells, tissue, and *in vivo*.[6-8] The conjugation of coumarin with indole form an intramolecular charge transfer (ICT) platform is an effective method to construct new fluorescent pH probes for acidic microenvironments.[9-11] Three conjugated pyrazole-indole hybrids have been reported which serve as an interesting source of photosensitizing compounds with anticancer activity.[12] Chun-Lin and his coworker used designed a novel benzoindolicsquaraine (BIS) dye molecule that exhibits a high-performance NIR emission and two-photon excited fluorescence are both desirable features for bioimaging. Treatment of the dihydrobenzoindolydene synthon with electrophilic counterparts has led to many applications for the development of NIR fluorescent probes.[13-15] Organic squaraine dyes based 1,1,2-Trimethyl-1*H*-benzo[e]indolium salts have been synthesized and applied as dye-sensitized solar cells.[16,17] Squaraine dyes derived from (1) with some combinations of barbituric groups joined to the central ring, having ester groups and alkyl chains in the nitrogen atoms of heterocyclic rings were reported and show antifungal properties against the yeast Saccharomyces cerevisiae.[18] Treatment of 1,1,2-trimethyl-1*H*-benzo[e]indole with acrylic acid, acrylamide or tert-butyl acrylate in an autoclave or a microwave reactor at 180–200°C afforded benzo[e]pyrido[1,2-a]indole derivatives, various chemical transformations of the latter

*Corresponding author: Email: waamrs@yahoo.com

Published & Hosted by :
Journal Homepage :
www.connectjournals.com/ijhc
www.connectjournals.com

in ppm): δ = 14.22 (d, 1H, NH), 9.45 (s, 2H, -CH=N-), 7. 24–8.94 (m, 16H, Ar-H), and 1,79, 1.83 (s, 6H, 2× CH_3). The ^{13}C-NMR spectra for compound **4** show the signals (400 MHz, DMSO, δ in ppm): δ = 157.53 for N-C, 148.37 for NH-CH=C, 139.93 for -C=NH-, 138.10 for -N-C= (aromatic), 108.74 for (-C=C-), 118.48–132.52 for Ar-C, 114.12 for O=C-C=C, 56.71 for CH_3-C-CH_3, and 20.82 for 2× CH_3.

(N,N'E,N,N'E)-N,N'-(2-(1,1-Dimethyl-1H-benzo[e] indol-2(3H)-ylidene)propane-1,3-diylidene) bis(1-phenylmethanamine) (6)

Compound **5 (**0.20 g, 0.000564 mmole) was reacted with benzylamine according to second Schiff's procedure to yield red crystals of **6 (**0.13 g, mmole, 66%) m.p. (140°C). ^{1}H NMR chemical shifts at (400 MHz, DMSO, δ in ppm): δ = 12.27 (d, 1H, NH), 9.23 (s, 1H, -CH=N-), 7. 24-8.52 (m, 16H, Ar-H), 4.478 for (2H, -NH-CH_2-C), 4.24 for (2H, =N-CH_2-C-), and 1,78,1.87 (s, 6H, 2× CH_3). The ^{13}C-NMR spectra for compound 6 show the signals (400 MHz, DMSO, δ in ppm): δ = 169.59 for C=CH, 156.41 for N-, 149.23 for NH-CH=C, 142.15 for -C=NH-, 140.08 for -N-C= (aromatic), 106.58 for (-C=C-), 117. 69- 1321.25 for Ar-C, 114.10 for O=C-C=C, 45.23 for CH_3-C-CH_3, 42.45 for CH_2 benzyl and 23.03 for 2× CH_3.

HepG2 Cell Line Investigation

Solutions used in this experiment (Culture Media RPMI-1640, Trypsin–Version solution, Crystal Violet Stain, and Trypan blue stain) were prepared according to the Giuliano method.[29] The HepG2 cell line and normal cell line (Rhabdomyosarcoma) (RD) were grown in RPMI-1640 medium equipped with 10% calf fetal serum according to the Freshney method.[27,30] The cytotoxicity assay was carried out using the crystal violate stain according to the method of Freshney.[31] The target compounds were dissolved in DMSO and diluted by serum-free media (SFM) to prepare different concentrations range of (50, 100) µg/mL. Two types of cell lines were used human liver cancer (HepG2), and normal human (RD) (RPMI-1640) cell lines. The tumor cells (1×10^5 cell/mL) were seeded in a 96-well microplate and incubated for 24 h at 37°C, and then the old media was changed with new SFM containing concentrations of each compound. The plate was incubated for 24 h in a humidified incubator at 37°C containing 5% CO_2. After incubation, the culture medium was discarded and 100 µL of crystal violate was added to each and reincubated for 20 min at 37°C. The results were read using the ELISA with a wavelength of 492 nm. The inhibiting ratio was calculated according to the equation:

Percentage of cell inhibition = (Absorbance reading of control cells − Absorbance reading of treated cells for each concentration/absorbance reading of control cells) × 100

CONCLUSION

Five new derivatives of dihydrobenzoindolydene were synthesized from 1,1,2-trimethyl-1H-benzo[e]indole after functionalization with POC_l3 and coupling with three aromatic molecules including aniline, benzylamine, and 4-methyl-o-phenylenediamine through Schiff reaction. This reaction subjected stearic hindrance and property already overcame by controlling the time of reactions (The later was easily modified by treatment with phosphoryl chloride to reach the synthon 2-(1,1-dimethyl-1H-benzo[e]indol-2(3H)-ylidene)malonaldehyde. Schiff's reaction was applied on the synthon to yield a series of mono-substituted and di-substituted malonaldehyde derivatives). This property is directed and used to synthesize both mono and disubstituted derivatives. The synthesized compounds show a good ability to inhibit of HepG2 cancer cell line, which make them useful as potential anticancer agents.

ACKNOWLEDGMENTS

We are thankful to the University of Diyala, and the Faculty of Sciences for providing the facilities required for this research.

REFERENCES

[1] Sathya, V., Deepa, A., Sangeetha, L.K., Srinivasadesikan, V., Lee, S.L., Padminim, V. Development of optical biosensor for the detection of glutamine in human biofluids using merocyanine dye, *J. Fluoresc.,* **2022**, *32,* 1389–1396.

[2] Menéndez, G.O., Pichel, M.E., Spagnuolo, C.C., Jares-Erijman, E.A. NIR fluorescent biotinylated cyanine dye: Optical properties and combination with quantum dots as a potential sensing device, *Photochem. Photobiol. Sci.*, **2013**, *12*, 236–240.

[3] Zhang, K., Meng, J., Bao, W., Liu, M., Wang, X., Tian, Z. Mitochondrion-targeting near-infrared fluorescent probe for detecting intracellular nanomolar level hydrogen sulfide with high recognition rate, *Anal. Bioanal. Chem.*, **2021**, *413*, 1215–1224.

[4] Miki, K., Oride, K., Kimura, A., Kuramochi, Y., Matsuoka, H., Harada, H., Hiraoka, M., Ohe, K. High-contrast fluorescence imaging of tumors *in vivo* using nanoparticles of amphiphilic brush-like copolymers produced by ROMP, *Angew. Chem. Int. ED.,* **2011**, *50,* 6567–6570.

[5] Onoe, S., Temma, T., Kanazaki, K., Ono, M., Saji, H. Development of photostabilized asymmetrical cyanine dyes for *in vivo* photoacoustic imaging of tumors, *J. Biomed. Opt.,* **2015**, *20*, 096006.

[6] Li, S.J., Zhou, D.Y., Li, Y.F., Yang, B., Ou-Yang, J., Jie, J., Liu, J., Li, C.Y. Mitochondria-targeted near-infrared fluorescent probe for the detection of carbon monoxide *in vivo*, *Talanta,* **2018**, *1*, 691–700.

[7] Kiyose, K., Hanaoka, K., Oushiki, D., Nakamura, T., Kajimura, M., Suematsu, M., Nishimatsu, H., Yamane, T., Terai, T., Hirata, Y., Nagano, T. Hypoxia-sensitive fluorescent probes for *in vivo* real-time fluorescence imaging of acute ischemia, *J. Am. Chem. Soc.,* **2010**, *132*, 15846–15848.

[8] Wang, H., Wang, X., Li, P., Dong, M., Yao, S.Q., Tang, B. Fluorescent probes for visualizing ROS-associated proteins in disease, *Chem. Sci.*, **2021**, *12*, 11620–11646.

[9] Niu, W., Nan, M., Fan, L., Wong, M.S., Shuang, S., Dong, C. A novel pH fluorescent probe based on indocyanine for imaging of living cells, *Dyes Pigm.*, **2015**, *126*, 224–231.

[10] Liu, X.D., Xu, Y., Sun, R., Xu, Y.J., Lu, J.M., Ge, J.F. A coumarin-indole-based near-infrared ratiometric pH probe for intracellular fluorescence imaging. *Analyst*, **2013**, *138*, 6542–6550.

[11] Wen, Y., Jing, N., Huo, F., Yin, C. Recent progress of organic small molecule-based fluorescent probes for intracellular pH sensing, *Analyst*, **2021**, *146*, 7450–7463.

[12] Varvuolytė, G., Malina, L., Bieliauskas, A., Hošíková, B., Simerská, H., Kolářová, H., Kleizienė, N., Kryštof, V., Šačkus, A., Žukauskaitė, A Synthesis and photodynamic properties of pyrazole-indole hybrids in the human skin melanoma cell line G361, *Dyes Pigm.*, **2020**,*183*,108666.

[13] Sun, C.L., Lv, S.K., Liu, Y.P., Liao, Q., Zhang, H.L., Fu, H., Yao, J. Benzoindolic squaraine dyes with a large two-photon absorption cross-section, *J. Mater. Chem. C.*, **2017**, *5*, 1224–1230.

[14] Gong, X., Yang, X.F., Zhong, Y., Chen, Y., Li, J. A mitochondria-targetable near-infrared fluorescent probe for imaging nitroxyl (HNO) in living cells. *Dyes Pigm.*, **2016**, *131*, 24–32.

[15] Han, C., Yang, H., Chen, M., Su, Q., Feng, W., Li, F. Mitochondria-targeted near-infrared fluorescent off-on probe for selective detection of cysteine in living cells and *in vivo*, *ACS Appl. Mater. Interf.*, **2015**, *7*, 27968–27975.

[16] Connell, A., Holliman, P.J., Davies, M.L., Gwenin, C.D., Weiss, S., Pitak, M.B., Horton, P.N., Coles, S.J., Cooke, G. A study of dye anchoring points in half-squarylium dyes for dye-sensitized solar cells, *J. Mater. Chem. A.*, **2014**, *2*, 4055–4066.

[17] Khopkar, S., Jachak, M., Shankarling, G. Viscosity sensitive semisquaraines based on 1, 1, 2-trimethyl-1H-benzo[e]indole: Photophysical properties, intramolecular charge transfer, solvatochromism, electrochemical and DFT study, *J. Mol. Liq.*, **2019**, *285*, 123–135.

[18] Gomes, V.S.D., Ferreira, J.C.C., Boto, R.E.F., Almeida, P., Fernandes, J.R., Sousa, M.J., Gonçalves, M.S.T., Reis, L.V. Squaraine dyes derived from indolenine and benzo[e]indole as potential fluorescent probes for HSA detection and antifungal agents, *Photochem. Photobiol. B.*, **2022**, *98*, 1402–1417.

[19] Steponavičiūtė, R., Martynaitis, V., Bieliauskas, A., Šačkus, A. Synthesis of new fluorescent building blocks via the microwave-assisted annulation reaction of 1, 1, 2-trimethyl-1H-benzo[e]indole with acrylic acid and its derivatives, *Tetrahedron*, **2014**, *70*, 1967–1974.

[20] Rothan, H.A., Amini, E., Faraj, F.L., Golpich, M., Teoh, T.C., Gholami, K., Yusof, R. NMDA receptor antagonism with novel indolyl, 2-(1,1-Dimethyl-1,3-dihydro-benzo[e]indol-2-ylidene)-malonaldehyde, reduces seizures duration in a rat model of epilepsy, *Sci. Rep.*, **2017**, *7*, 45540.

[21] Simakov, S., Kartsev, V., Petrou, A., Nicolaou, I., Geronikaki, A., Ivanov, M., Kostic,M., Glamočlija,J., Soković, M., Talea, D., Vizirianakis, I.S. 4-(Indol-3-yl)thiazole-2-amines and 4-ιndol-3-yl)thiazole acylamines as νovel antimicrobial agents: Synthesis, *in silico* and *in vitro* evaluation, *Pharmaceuticals (Basel)*, **2021**, *14*, 1096.

[22] Salih, S.M., Alkubaisi, H.M., Faraj, F.L. Synthesis and characterization of novel pyrazole derivatives from 4-florophenylhydrazine and study their cytotoxicityas anti-cancer agent, *Egypt. J. Chem.*, **2021**, *64*, 6473–6480.

[23] Mekheimer, R.A., Al-Sheikh, M.A., Medrasi, H.Y. Sadek, K.U. Advancements in the synthesis of fused tetracyclic quinoline derivatives, *RSC Adv.*, **2020**, *10*, 19867.

[24] Essam, Z.M., Ozmen, G.E., Setiawan, D., Hamid, R.R., Abd El-Aal, R.M., Aneja, R., Hamelberg, D., Henary, M. Donor acceptor fluorophores: Synthesis, optical properties, TD-DFT and cytotoxicity studies, *Org. Biomol. Chem.*, **2021**, *19*, 1835–1846.

[25] Berber, N., Arslan, M. Preparation and characterization of some Schiff base compounds, *Adıyaman Univ. J. Sci.*, **2020**, *10*, 179–188.

[26] Calvaruso, G., Giuliano, M., Portanova, P., Pellerito, O., Vento, R., Tesoriere, G. Hsp72 controls bortezomib-induced HepG2 cell death via interaction with pro-apoptotic factors, *Oncol. Rep.*, **2007**, *18*, 447–450.

[27] Hinson, A.R.P., Jones, R., Crose, L.E.S., Belyea, B.C., Barr, F.G., Linardic, C.M. Human rhabdomyosarcoma cell lines for rhabdomyosarcoma research: Utility and pitfalls, *Front. Oncol.*, **2013**, *3*, 183.

[28] Chandrakar, T.R., Singh, A.P., Sarkhel, B.C., Bagchi, S.N. *In vitro* cytotoxicity and genotoxicity assessments of carbofuran and malathion pesticides on cat (*Felis catus*) fibroblast cells. *Biomed. Pharmacol. J.*, **2020**, *13*, 1157–1168.

[29] Naji, A.M., Abdula, A.M., Nief, O.A., Abdullah, E.K. Synthesis, characterization, antimicrobial and molecular docking study of benzooxadiazole derivatives, *Chem. Chem. Technol.*, **2022**, *16*, 25–33.

[30] Zozulya, Z., Kuntyi, O., Mnykh, R., Sozanskyi, M. Synthesis of antibacterially active silver nanoparticles by galvanic replacement on magnesium in solutions of sodium polyacrylate in an ultrasound, *Chem. Chem. Technol.*, **2021**, *15*, 493–499.

[31] Rahman, H., Qasim, M., Schultze, F.C., Oellerich, M., Asif, A.R. Fetal calf serum heat inactivation and lipopolysaccharide contamination influence the human T lymphoblast proteome and phosphoproteome, *Proteome Sci*., **2011**, *9*, 71.

Received: 31 Jul 2022; Accepted: 27 Dec 2022