Original Article

Journal of Pharmaceutical and Medicinal Chemistry
Volume 4 Number 1, January - June 2018
DOI: http://dx.doi.org/10.21088/jpmc.2395.6615.4118.2

Synthesis and Biological Evaluation of Dithiocarbamates of 1-Naphylamine Chalchone

K. Madhavi[1], A. Lakshmana Rao[2], K. Jaya Bharathi[3], J. Subhashini[4], K. Bindu Bhargavi[5], K. Anjaneyulu[6]

[1]Assistant Professor, Dept. of Pharmaceutical Chemistry, [2]Principal & Professor, Dept. of Pharmaceutical Analysis, [3-6]Student, V.V. Institute of Pharmaceutical Sciences, Gudlavalleru, Andhra Pradesh 521356, India.

Abstract

The new dithio carbamate derivatives, 2-(naphthalen-8-ylcarbamoyl)-1-(4-hydroxyphenyl) ethyl diethylcarbamodithioate (IIIa) and 2-(naphthalen-8-ylcarbamoyl)-1-(2,4-dichlorophenyl) ethyl diethylcarbamodithioate (IIIa) were synthesized from 1-naphylamine chalchone. The new molecules were characterized by spectral and elemental analysis data. The synthesized analogues were evaluated for anti-mitotic activity by Bengal gram seed germination model showed strong to moderate activities compared with control. Both the molecules showed good inhibition.

Keywords: Dithiocarbamates; 1-Naphthalamine; Antimitotic Activity.

Introduction

Dithiocarbamates, the half amides of dithiocarbonic acids, were discovered as a class of chemical compounds in the history of organo sulphur chemistry. Dithiocarbamates are a common class of organic molecules that form mono and bidentate coordination with transition metals. Transition metal complexes of dithiocarbamate present a wide range of biological activities and are recently applied in the treatment of cancer. Since brassinin (Fig. 1), a phytoalexin first isolated from cabbage had cancer preventive activity, structural modification on this compound led to the synthesis of isobrassinin (Fig. 1) and a series of Dithiocarbamates [1], some of these were found to have antitumor activity. On the other side, Chalcones are the bio-genetic precursors of all known flavonoids and isoflavanoids and are abundant in edible plants. They exhibit a broad spectrum of pharmacological activities such as anticancer, anti-inflammatory, anti-malarial, antifungal, anti-lipidemic, antiviral, anti-Leshmanial, anti-ulcer and antioxidant activities. Recently Yong Qian and coworkers reported a series of chalcone derivatives (Fig. 1), with dithiocarbamated moieties which possessed potential anti-proliferative and anti-tubulin properties. Microtubules are among the most important molecular targets for cancer chemo-therapeutic agents. These small molecules bind to the tubulin, interfering with the polymerisation or depolymerisation of micro- tubules and there by inducing cell cycle arrest, resulting in cell death or apoptosis. Based on above information used to

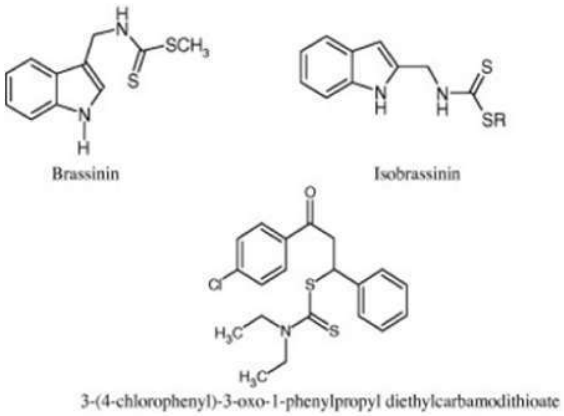


Fig. 1:

Reprint Request: K. Madhavi, Assistant Professor, Department of Pharmaceutical Chemistry, V.V. Institute of Pharmaceutical Sciences, Gudlavalleru, Andhra Pradesh 521356, India.

E-mail: madhavikamma19@gmail.com

design the dithiocarmates of 1-naphtyl amino derivatives via Chalcones route.

Methodology

Step 1: Synthesis of 1-Napthyl Acetamide from 1-Napthyl Amine

Take 5 gm of 1-napthylamine, 2 ml of Acetic Anhydride and 5 ml of Acetyl chloride were stir it continuously for 5 mins. Then a precipitate was form to which added to some small cubes of ice and stir the solution for 2 min then filter the acetylated Product and the residue was thoroughly washed with each 10 ml of warm water and dried it. Finally characterized by M.P and TLC (1:1 n-hexane & ethyl acetate).

Step-2: Synthesis of 3-(2, 4-Dichlorophenyl)-N-(Naphthalen-8-Yl) Acryl amide

1 gm of the above acetylated product, 6 ml of both substituted Benzaldehydes (4- chloro & 4-hydroxy) each were taken individually, and then added to a solution of 5 of NaOH with 20ml of water separately.

To the above both solution, added to each 20ml of ethanol and cooled to at room temperature separately. Mix and Stir it for 15-30 mins individually then filter the naphthylated Chalcones derivatives and were thoroughly washed with each 10 ml of warm water and dried them. Finally characterized by M.P and TLC (1:1 n-hexane & ethyl acetate). There will be formation of 2 products here in this step with each of the 2 taken Benzaldehydes.

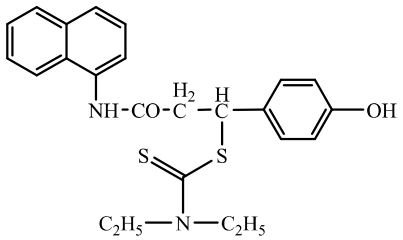
Step 3: Synthesis of 2-(naphthalen-8-ylcarbamoyl)-1-(2,4-dichlorophenyl)ethyl diethylcarbamodithioate

Then, taken 1 gm of each of the above formed product, 6 ml of diethyl amine and 6 ml of carbon disulfide and mix the solution individually. 5 gm of stannous chloride was taken separately and dissolved it in 10 ml of water. And then added this solution to the previous both solutions and mix them for a while.

After that the reaction mixtures were Stir it for 15-30 mins separately by Magnetic stirring process then filter the two dithiocarbamate derivatives. The derivatives were thoroughly washed with each 10 ml of warm water and dried it. Finally characterized by M.P and TLC (1:1 n-hexane & ethyl acetate).

Spectral Data

Compound- IIIA



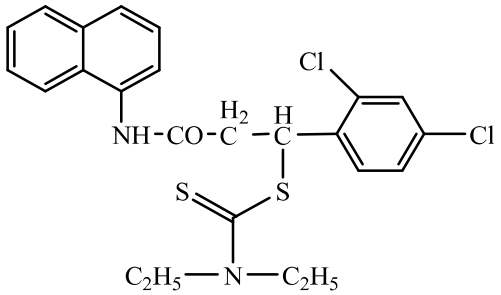
2-(naphthalen-8-ylcarbamoyl)-1-(4-hydroxyphenyl)ethyl diethylcarbamodithioate

(IIIa)

^{1}H NMR (400 MHz, $CDCl_3$): 6.25-7.66(S, 7H, ArH) 7.00-7.23 (m, 3H, ArH) 3.32-3.07 (m 1H, CH2), 8.0 (S 1H –NH).

IR (KBr) (cm^{-1}): 3309 (N-H Str), 2956cm^{-1} (Ar-C-H Str), 2452cm^{-1} (C=S), & 1721cm^{-1} (C=O).

COMPOUND- IIIb



2-(naphthalen-8-ylcarbamoyl)-1-(2,4-dichlorophenyl)ethyl diethylcarbamodithioate

(IIIb)

^{1}H NMR (400 MHz, $CDCl_3$): 6.25-7.66(S, 7H, ArH) 7.00-7.23 (m, 3H, ArH) 3.32-3.07 (m 1H, CH2), 8.0 (S 1H –NH).

IR (KBr) (cm^{-1}): 3389 (N-H Str), 2986cm^{-1} (Ar-C-H Str), 2492cm^{-1} (C=S), & 1733cm^{-1} (C=O)

Biological Evaluation

Antimitotic Activity

Approximately writhingly (40±0.5g) of the Bengal gram (Cicer arietinum) were obtained from the local market. They were soaked in tap water in

the control group or in a drug solution in the test group for 6 hours. The water or the drug solution was drained and the seedlings were kept moist (either with tap water or the drug solutions in covered petridish) until the radicals in the control group had grown to 1.0-1.5 cm (time T0). At T0, the weight of seedlings, %germination, length of radical were recorded both in the control and test group. The seedlings were maintained at room temperature under moist conditions for an additional period of 48 hours. (T48). All the parameters recorded at T0 & T48. The change in weight and gain in radical length & % of germination were measured the seeds that did not germinate were simply weighted and no other parameters could be measured on these seeds.

$$\% \text{ of Germination} = \frac{\text{Total number of dividing cells}}{\text{Total number of cells examined}} \times 100$$

The percentage of the number of dividing cells compared to the control and the percent inhibition of mitosis by anti-mitotic agent at a different concentration such as 2, 4, 5 and 30mg/ml against water were calculated. The results in Table 2 and graphically depicted in Fig.3.

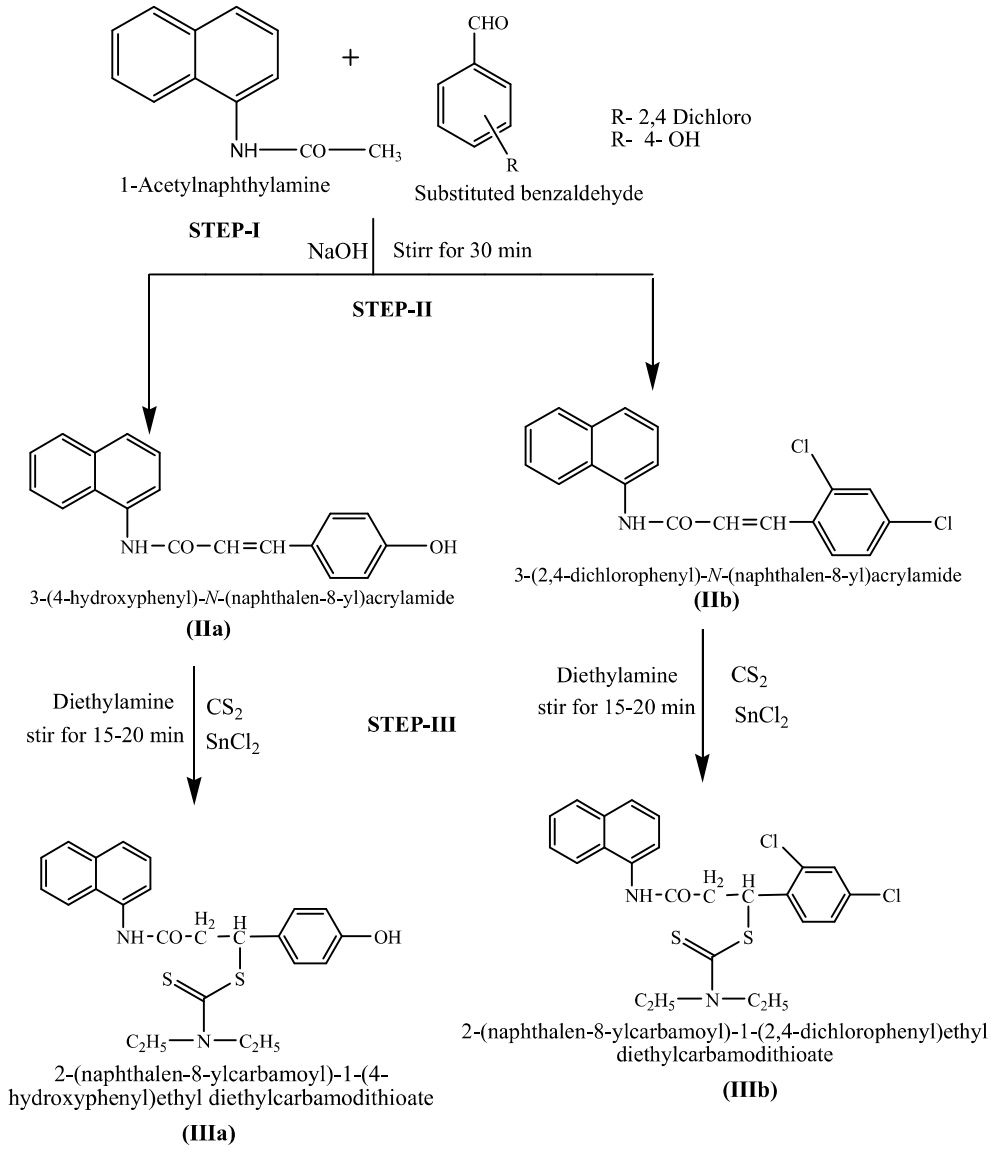


Fig. 2: Scheme of the work

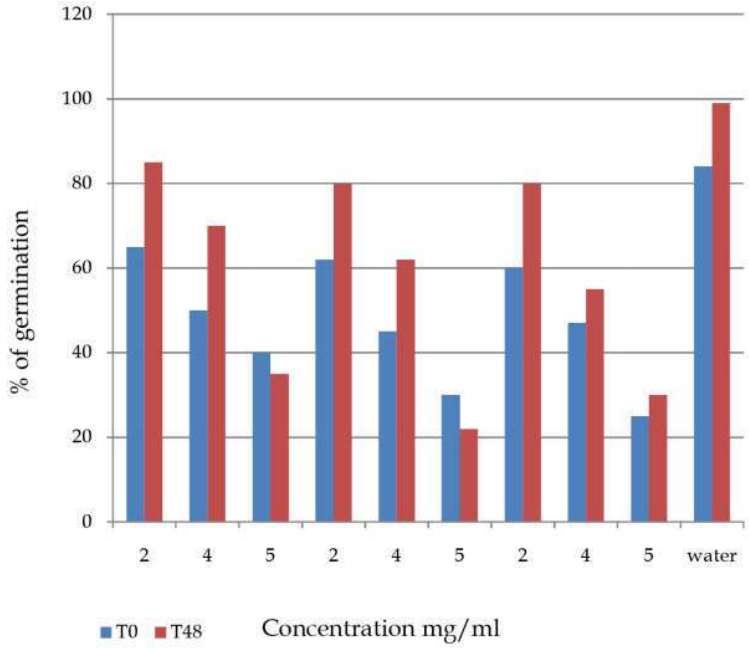


Fig. 3: Data showing Anti mitotic activity of synthesized compounds

Table 1: Physical Characterization data of synthesized compound

Compound code	Molecular formula	Mol. wt (g)	Melting point (^{0}C)	% Yield	Rf Value
STEP-I	$C_{12}H_{11}NO$	185	80	90	1.5
STEP-IIa	$C_{19}H_{18}NO_2$	292	190	60	0.9
STEP-IIb	$C_{19}H_{15}NOCl_2$	344	180	70	0.8
STEP-IIIa	$C_{23}H_{28}N_2O_2S_2$	428	110	40	0.5
STEP-IIIb	$C_{23}H_{26}N_2OCl_2S_2$	481	95	50	0.7

Table 2: Antimitotic activity of Synthesized Compounds

Compound name	Conc. mg/ml	% of germination		Radical length in cm	
		T_0	T_{48}	T_0	T_{48}
IIIa	2.0	65	85	1.5	2.5
	4.0	50	70	1.0	1.8
	5.0	**40**	**35**	**1.0**	**1.2**
IIIb	2.0	62	80	1.5	2.5
	4.0	45	62	1.0	1.6
	5.0	**30**	**22**	**1.0**	**1.0**
Aspirine	2.0	60	80	1.5	2.5
	4.0	47	55	1.0	1.5
	5.0	**25**	**30**	**1.0**	**1.2**
water	-	84	99	1.5	3.0

Results and Discussion

In the present work the activities of the substituted Dithiocarbamates were synthesized, the structure of synthesized compound was established by their M.P, TLC, IR, and H^1NMR spectral studies. Their RF values are mentioned in the respective table.

The synthesized compounds were evaluated to their Antimitotic activity and at different concentrations by seed germinating method using Aspirin as standard drugs respectively.

Antimitotic Activity

The title compounds were screened for preliminary cytotoxic evaluation on germinating seeds of Bengal gram *(Cicer arietinum)* for rapid and inexpensive screening of drug exhibiting cytotoxic properties. Aspirin was used as a standard references drug. Various parameters measured at T_0& T_{48} % germination & changes in length of radicals were reported in Table 2 for evaluating the cytotoxicity.

The synthesized compounds 2-(naphthalen-8-ylcarbamoyl)-1- (4-hydroxyphenyl) ethyl diethylcarbamodithioate (IIIa) and 2-(naphthalen-8-ylcarbamoyl)-1-(2,4-dichlorophenyl) ethyl diethyl carb modi thiolate (IIIb) showed dose dependent inhibitory effect on seed germination and radical length in Table 2.

Conclusion

From the results one can establish that generally Dithiocarbamates compound can rich source of exploitation. Therefore, the synthesized compounds were shows Antimitotic activity Finally the Antimitotic activity revealed that, the compounds bearing Electronic nature of the substituent's of electron withdrawing groups (NO_2, Cl) and electron donating groups (OH, NH_2). Based on the cytotoxic tests performed for the above product in the Laboratory i.e in -vitro Studies, these studies has shown the promised Antimitotic Activity. And these products can be further tested for the in-vivo studies. Based on these studies may be the synthesized compound shows dose dependant inhibitory effect on seed germination, radical length at different concentration.

Acknowledgement

The authors are thank full to management of V.V. Institute of Pharmaceutical Sciences, Gudlavalleru for providing necessary facilities for carry out the research work.

References

1. Keerthana Bacharaju , Swathi Reddy Jambula , Sreekanth Sivan , Saritha Jyostna T and Vijjulatha M. Design, synthesis, molecular dockin and biological evaluation of new dithiocarbamates substituted Benzimmidazole and Chalcones as possible chemotherapeutic agents. Bio organic and Medical chemistry is letters. 2012;22:3274-3277.
2. Hemakumar K H, Sathisha A D and Y B Basavaraju Synthesis And Anti-Mitotic Activity Study Of New Tetralone Ester Intermidiates Of Anti - Cancer Agent Beta-Apopicropodophyllin. Indo American Journal of Pharmaceutical Research. 2016;2231-6876.
3. Singh Shachi. Antimitotic activity of a New Compound Isolated from the Flower of Prosopis juliflora. Research Journal of Recent Science. June 2012;1(6):22-26.
4. A.Thenmozhi, A. Nagalakshmi and U.S Mahadeva Rao. Study of Cytotoxic and Antimitotic Activities of Solanum nigrum by Using Allium cepa Root Tip Assay and Cancer Chemo preventive Activity Using MCF-7-Human Mammary Gland Breast Adenocarcinoma Cell Lines. International Journal of Science & Technology. 2011;1(2):2250-141X.
5. Azim Ziyaei Halimehjani and Katayoun Marjani, the Synthesis of Dithiocarbamate by Markovnikov Addition Reaction, Royal society Chemistry, 2010.
6. H.Nabipour Synthesis of a new dithiocarbamates cobalt complex and its nanoparticle with the study of their biological properties. International Journal of Nano Dimention. Winter 2011;1(3):225-32.
7. Usama abu Mohsen the Synthesis and Antimicrobial Activity of Some Piperazine Dithiocarbamate Derivatives properties. Turkish Journal of Pharmaceutical Sciences. 2014;11(3):347-54.
8. Barahman Movassagh and Bahareh Shokri. A Facile and Efficient One-Pot Regioselective Synthesis of 2-Hydroxyalkyl Dithiocarbamates under Catalyst-Free Conditions. International Journal of Organic Chemistry, 2012;2:248-53.
9. Usama abu mohsen Biological Evaluation of Thiazole derivatives bearing Dithiocarbamate moiety as potential cholinesterase inhibitors. International Journal of Pharmacy and Pharmaceutical Science 2015; (2):0975-1491.
10. Devdutt Chaturvedi and Sadaf Zaidi . The role of Organic Dithiocarbamates in Drug Discovery Research. Research and Reviews: Journal of Chemistry. 2016;5(2):10-12.
11. W. Huang. Lead Structure of Chalcone Dithiocarbamates with Broad Spectrum Anti Cancer activity. Chemistry and Biology Interface, 2014;4(6): 321-340.
12. T. Lavanya. Rapid Synthesis of Evaluation of new 1, 4-Dihydropyridines as possible Anti-Mitotic agents. International Journal of Research in Pharmacy and Chemistry. 2011;1(4):2231-81.
13. L. Srividya, G. Kiran and A. Rama Narsimha Reddy. Evaluation of Antimitotic Activity of Indole Derivative on Germinating Bengal Gram Seeds, World Journal of Pharmaceutical and life sciences. 2017;3(7):278-81.