Turkiye Parazitol Derg 2024;48(1):39-44
DOI: 10.4274/tpd.galenos.2024.93063

Larvicidal Activity of Some Aromatic Thiosemicarbazone and Metal Complexes [Ni (II), Cu (II), Co (II)] Against *Aedes (Stegomyia) aegypti* (Linnaeus, 1762) and *Aedes albopictus* (Skuse, 1894) (Diptera: Culicidae) Larvae

Aedes (Stegomyia) aegypti (Linnaeus, 1762) ve Aedes albopictus (Skuse, 1894) (Diptera: Culicidae) Larvalarına Karşı Bazı Aromatik Tiyosemikarbazon ve Metal Komplekslerinin [Ni (II), Cu (II), Co (II)] Larvasidal Aktivitesi

Fatma Bursalı[1], İlke Demirkaya[2], İlknur Babahan Bircan[2], Fatih Mehmet Şimşek[1]
[1]Aydın Adnan Menderes University Faculty of Science, Department of Biology, Aydın, Türkiye
[2]Aydın Adnan Menderes University Faculty of Science, Department of Chemistry, Aydın, Türkiye

Cite this article as: Bursalı F, Demirkaya İ, Babahan Bircan İ, Şimşek FM. Larvicidal Activity of Some Aromatic Thiosemicarbazone and Metal Complexes [Ni (II), Cu (II), Co (II)] Against *Aedes (Stegomyia) aegypti* (Linnaeus, 1762) and *Aedes albopictus* (Skuse, 1894) (Diptera: Culicidae) Larvae. Turkiye Parazitol Derg 2024;48(1):39-44.

ABSTRACT

Objective: A series of aromatic thiosemicarbazone-oxime [TP1 and TP2] derivatives and their Ni(II), Cu(II), and Co(II) complexes were synthesized, and their larvicidal activity was evaluated against *Aedes aegypti* and *Aedes albopictus* larvae. The efficacy of these substances to *Aedes albopictus* larvae has been demonstrated for the first time.

Methods: Laboratory colonized *Aedes aegypti* and *Aedes albopictus* larvae were subjected to larvicidal activity tests. Larval mortality rates at 24 and 48 hours were recorded and LC_{50} values were calculated. The study was carried out at Aydın Adnan Menderes University in 2021.

Results: For *Aedes aegypti*, LC_{50} of TP1 and its Co(II) complex were 15.41, 9.75, µg/mL whereas for TP2 and its Co(II) complex, LC_{50} were 21.62, 20.50 µg/mL after 24 and 48 h respectively. For *Aedes albopictus*, TP1 and its Co(II) complex showed an LC_{50} of 12.06, 8.75 µg/mL, whereas TP2 and its Co(II) complex showed an LC_{50} of 32.87, 25.48 µg/mL, for 24, and 48 h respectively.

Conclusion: Both TP1 and TP2 compounds and their Co(II) complexes presented high efficacy against the larvae; it can be said that C=S groups in thiosemicarbazone derivatives are effective in showing activity and for this reason, studies should be continued to make these components effective.

Keywords: Mosquito, larvicidal effect, synthetic compounds, larval control

ÖZ

Amaç: Bir dizi aromatik tiyosemikarbazon-oksim [TP1 ve TP2] türevleri ve bunların Ni(II), Cu(II) ve Co(II) kompleksleri sentezlenmiş ve *Aedes aegypti* ve *Aedes albopictus* larvalarına karşı etkinlikleri değerlendirilmiştir. Bu maddelerin *Aedes albopictus* larvalarındaki etkinlikleri ilk kez belirlenmiştir.

Yöntemler: Laboratuvar kolonisi oluşturulmuş *Aedes aegypti* ve *Aedes albopictus* larvaları maddelerin larvisidal etkinlikleri için test edilmiştir. Yirmi dört ve 48 saat sonar larval ölüm oranları kaydedilmiş ve LC_{50} değerleri hesaplanmıştır. Çalışma Aydın Adnan Menderes Üniversitesi'nde 2021 yılında gerçekleştirilmiştir.

Bulgular: *Aedes aegypti* için, TP1 ve Co(II) komplekslerinden 24 ve 48 saat için elde edilen LC_{50} değerleri sırayla 15,41, 9,75, µg/mL iken TP2 ve Co(II) kompleksleri için elde edilen değerler 21,62, 20,50 µg/mL olarak belirlenmiştir. *Aedes albopictus* için, TP1 ve Co(II) komplekslerinden 24 ve 48 saat için elde edilen LC_{50} değerleri sırayla 12,06, 8,75 µg/mL iken TP2 ve Co(II) kompleksleri için elde edilen değerler 32,87, 25,48 µg/mL olarak belirlenmiştir.

Received/Geliş Tarihi: 18.01.2023 **Accepted/Kabul Tarihi:** 25.01.2024

Address for Correspondence/Yazar Adresi: Fatma Bursalı, Aydın Adnan Menderes University Faculty of Science, Department of Biology, Aydın, Türkiye
Phone/Tel: +90 507 772 97 93 **E-mail/E-Posta:** fatma.gunerkan@adu.edu.tr **ORCID ID:** orcid.org/0000-0003-3559-3849

Türkiye PARAZİTOLOJİ Dergisi

Sonuç: Hem TP1 hem de TP2 bileşikleri ve bunların Co(II) kompleksleri, larvalara karşı yüksek etkinlik göstermiştir; tiyosemikarbazon türevlerindeki C=S gruplarının aktivite göstermede etkili olduğu söylenebilir ve bu nedenle bu bileşenlerin etkin hale getirilmesi için çalışmalara devam edilmelidir.
Anahtar Kelimeler: Sivrisinek, larvisidal etki, sentetik bileşikler, larva kontrolü

INTRODUCTION

Mosquitoes (Diptera: Culicidae), insects at the center of entomological research worldwide, are vectors of important diseases. Species such as *Aedes aegypti* (Linnaeus, 1762) and *Aedes albopictus* (Skuse, 1895) play important roles in the transmission of Chikungunya, Zika and Dengue infections (1). The incidence of Dengue, which causes the most death and illness among all other arthropod-borne viral diseases, has increased dramatically over the years with ≥350 million cases and nearly half a million deaths reported annually worldwide (2).

These *Aedes* mosquito species are spreading from their native areas to higher latitudes in North America and Europe (3,4). In Europe *Ae. aegypti* has been detected in Greece, Cyprus, Croatia, Italy, Spain, France, Türkiye, and Portugal; in countries south of the Sahara Desert, Western Morocco and Western Sahara, Northern Algeria and Tunisia, Egypt and Sudan in Africa; as well as in countries in Central and Southern Asia (5-8). *Ae. albopictus,* likewise, has spread from southern Asia to several countries in Africa, Europe, and America (9-11). The existence of *Ae. albopictus* was first recorded in Türkiye in 2011 (12). Then, respectively reported in Black Sea, Marmara and Aegean region in Türkiye (8,13-15).

Control of mosquito-transmitted diseases remains a big challenge. No vaccine is available for most of them, so the mainstay of disease management is vector control. Personal protection and chemical insecticides are also used extensively to control mosquitoes. Although chemical insecticides are efficacious to a certain degree, they are costly, pose serious risks to humans and the environment, and mosquitoes continue to develop resistance against most extant insecticides (16). Scientist across the globe continue to advocate the use of insect bio-pathogens such as *Bacillus thuringiensis* subsp. *israelensis*, *Metarhizium anisopliae* (Sorokin 1883) (Hypocreales: Clavicipitaceae) etc. against larvae and adults (17) as well as the search for safer alternatives.

Hydrazones are a class of organic compounds which are characterized by the presence of an azomethine-NHN=CH group, whereas thiosemicarbazones have the formula H2NC(S) NHN=CR2 (18). These functional groups play a major role in their biological activities (19-21). Hydrazones have various biological and clinical properties such as antituberculosis, anticonvulsant, anticancer, anti-inflammatory, antiviral, antiplatelet, antitumour, antimicrobial, antimalarial and antioxidant activity (22-26). Some thiosemicarbazones derivatives possess good larvicidal/ insecticidal activity against various insects like *Culex pipiens pallens* (Linnaeus, 1758) (Diptera: Culicidae), *Plutella xylostella* (Lepidoptera: Plutellidae), *Laphygma exigua* (Hübner, 1808) (Lepidoptera: Noctuidae), *Rhopalosiphum maidis* (Fitch, 1856) (Homoptera: Aphididae), *Nilaparvata lugens* (Stal, 1854) (Hemiptera: Delphacidae) (27-31). Despite the availability of many insecticides, there has been a search for novel and more efficient agents with less bio-toxicity. The goal of developing new agents is valuable because currently very limited chemical classes are available for vector control.

In this study, we assessed a series of new aromatic thiosemicarbazone-oxime derivatives and their metalic complexes for their larvicidal effects against *Ae. aegypti* and *Ae. albopictus* larvae.

METHODS

Chemistry

The heteroaromatic thiosemicarbazone-oxime derivatives [TP1 and TP2], and their metal complexes [Ni(II), Cu(II) and Co(II)] were synthesized (32,33). The synthesis of these groups and their complexes is illustrated and outlined in Figure 1a, b. [TP1; 3-acetylthiosemicarbazone glyoxime; TP2:4-acetylthiosemicarbazone glyoxime]. Aromatic thiosemicarbazone derivatives consist of pyridine rings.

Compounds structures were determined using mass spectroscopy, UV, H-NMR, IR, C-NMR methods. All compounds obtained were purified by recrystallization from ethanol and verified by TLC and elemental analysis (34). Both analytical and spectral data of compounds were the same as proposed structures. These compounds were diluted to concentrations of 100, 75, 50 and 25 ppm in dimethyl sulfoxide (DMSO) and used in larvicidal activity bioassays (35).

Larvicidal Activity Assays

Aedes aegypti, Bora Bora strain was obtained from Hacettepe University Biology Department and has been reared in insectarium in the Vector Control Laboratory, Aydın Adnan Menderes University, Türkiye. *Aedes albopictus* larvae were sampled from Muğla populations in the Aegean Region and adult laboratory colonies were obtained from these larvae and reared in the insectarium. This species are susceptible strains that have no insecticide resistance. Both species are reared in an insectarium at 25±2 °C, 70±10 relative humidity, and 12 h light-dark photoperiod. Eggs collected were hatched in distilled water in plastic containers and larvae were provided ground fish food (Tetramin). Emerged adults fed on soaked cotton balls containing 10% sucrose.

Bioassays on the larvicidal activity of the compounds were carried out with some modifications using described by World Health Organization in 24-well plates (Corning Falcon microplates) against *Ae. aegypti* and *Ae. albopictus* larvae (36). Four different concentrations [100, 75, 50, 25 ppm (mg/L)] were tested against late 3rd-4th stage larvae of *Ae. aegypti* and *Ae. albopictus* mosquito.

Required concentrations of the compounds were dissolved and diluted in DMSO and used in larvicidal activity bioassays. Experiments were done under laboratory conditions in an incubator maintained at a constant temperature of 28 °C and 80% RH under light and dark conditions for 12 h each. Three independent replicates were carried out. Negative control had DMSO (1%) and the commercial *Bti* (0.05 g/L), (*Bacillus thuringiensis var. israelensis*), (VectoBac 12AS, Valent Biosciences, USA) was used as positive control. After treatment application, contents were evenly mixed by swirling plates. Larvae that failed to move after probing with a brush were recorded as dead. Larval

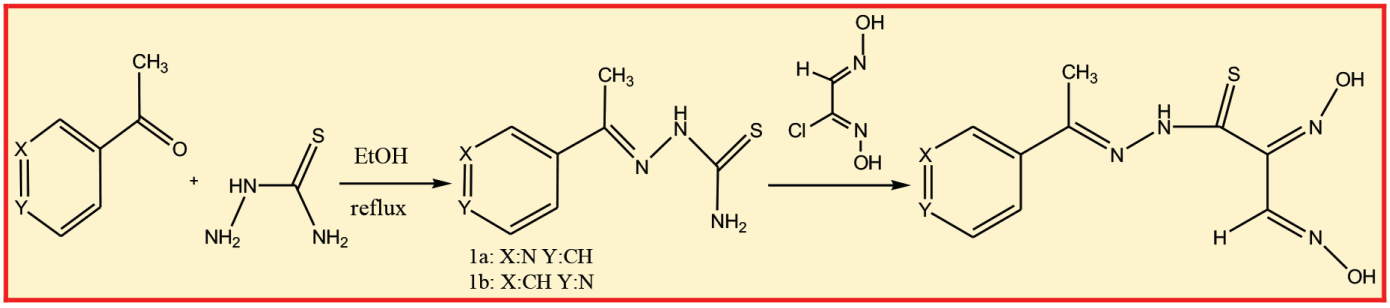

Figure 1a. Synthesis of heteroaromatic thiosemicarbazone-oxime derivatives (TP_1 ve TP_2) [TP_1; 3-acetyl thiosemicarbazone glyoxime (X: N, Y:C); TP_2: 4-acetyl thiosemicarbazone glyoxime (X:C, Y: N)]

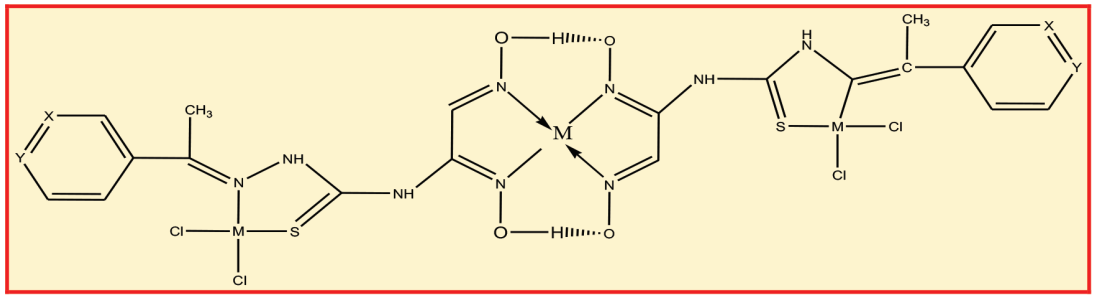

Figure 1b. Structure of metal complexes of thiosemicarbazone-oxime derivatives [M: Ni(II), Cu(II) ve Co(II); X: N, Y: C (TP_1); X:C, Y: N (TP_2)]

mortality was calculated for each concentration and after 24 h and 48 h, larval mortality was recorded and the lethal concentration LC_{50} was calculated.

Statistical Analysis

Larval mortality data was adjusted (37) and analysed using SAS, Proc Probit (Version 9.2) to obtain LC_{50} (the lethal concentration median) value and chi-square values. We used SPSS 23.0 software and a 95% confidence level; results with $p<0.05$ were considered significant. Analysis was done if control mortality was <10%.

RESULTS

Aromatic thiosemicarbazone derivatives and their Ni(II), Cu(II) and Co(II) complexes were synthesized and evaluated for *Ae. aegypti* and *Ae. albopictus* mosquitoes for their larvicidal activity.

Aedes albopictus

The LC_{50} for aromatic thiosemicarbazone (TP_1) and its Ni(II), Cu(II) and Co(II) complexes were 22.717, 26.265, 13.806 and 12.065 µg/mL respectively after 24 h of exposure. The LC_{50} values were recorded as 21.125, 23.308, 12.004, 8.755 µg/mL after 48 h of exposure (Table 1). *Ae. albopictus* larvae were more susceptible to the TP_1-Co complex than the other metal complexes [Ni (II), Cu (II)] of thiosemicarbazone oxime derivatives.

The LC_{50} for TP_2 and its Ni (II), Cu (II) and Co (II) complexes were 51.594, 44.913, 35.719, 32.875 µg/mL after 24 h of exposure while the values were found to be 48.764, 39.037, 27.516, 25.489 µg/mL after 48 h of exposure (Table 1).

Aedes aegypti

Against *Ae. aegypti*, the LC_{50} for aromatic thiosemicarbazone (TP_1) was 44.919 µg/mL and its Ni (II), Cu (II) and Co (II) complexes LC_{50} were 40.644,18.514,15.417 µg/mL after 24 h of exposure. After 48 h these values decline to 31.059, 32.038, 13.665, 9.755 µg/mL respectively (Table 2).

For aromatic thiosemicarbazone (TP_2) and its Ni(II), Cu(II) and Co(II) complexes, LC_{50} values were found to be 44.913, 42.308, 32.875, 21.612 µg/mL after 24 h of exposure, while the values were found to be 42.494, 33.683, 25.489, 20.504 µg/mL after 48 h of exposure, respectively.

DISCUSSION

We observed that TP_1-Co complex (II) and TP_2-Co complex (II) presented higher toxicity against both species than the other compounds named TP_1, TP_1-Ni complex (II), TP_1-Cu complex (II), TP_2, TP_2-Ni complex (II), TP_2-Cu complex (II) after 24 and 48 h of exposure and these compounds were found more effective for *Ae. albopictus* than *Ae. aegypti* larvae.

According to Rayms-Keller et al. (38) showed that copper edetate in nanostructures and chitosan microcapsules exhibited larvicidal activity against *Ae. aegypti* larvae with LC_{90} of 60 and 20 mg/L, respectively. Also, Tabanca et al. (29) tested ten hydrazone derivatives against *Ae. aegypti* larvae. They showed that compound 9 [$CH(CH_3)_2$] exhibited larvicidal activity with LD_{50} values of 57.4 ppm and LD_{90} of 297.8 ppm after 24 h treatment. Similarly, Rochelly et al. (39), showed that tested *Aedes aegypti* and *Anopheles darlingi* larvae were sensitive to

Table 1. Larvicidal bioassays of aromatic thiosemicarbazone (TP_1), (TP2) and Ni(II), Cu(II) and Co(II) complexes against *Ae. albopictus* larvae

Substances	Number of larvae	LC_{50} µg/mL (95% Cl) 24 h	X^2	LC_{50} µg/mL (95% Cl) 48 h	X^2
TP_1	200	22.717 (0.259, 64.251)	2.454	21.125 (0.200, 60.557)	3.159
TP_1-Ni complex (II)	200	26.265 (0.433, 72.596)	1.295	23.308 (0.654, 91.930)	1.610
TP_1-Cu complex (II)	200	13.806 (0.006, 46.463)	1.653	12.004 (0.001, 43.177)	1.545
TP_1-Co complex (II	200	12.065 (0.013, 40.377)	1.414	8.755 (0.006, 31.612)	1.972
TP_2	200	51.594 (8.959, 214.471)	2.101	48.764 (7.762, 116.181)	2.868
TP_2-Ni complex (II)	200	44.913 (8.091, 101.472)	2.436	39.037 (5.432, 89.966)	3.189
TP_2-Cu complex (II)	200	35.719 (5.186, 80.429)	2.409	27.516 (1.944, 67.125)	2.718
TP_2-Co complex (II)	200	32.875 (3.889, 75.811)	2.391	25.489 (2.034, 31.006)	2.048
DMSO		0.00±0.00			
Bti		93.91±0.002			

LC values are expressed in ppm (mg/L) values are means ± SD, X^2: chi-square, CI: Confidence interval, SD: Standard deviation

Table 2. Larvicidal bioassays of aromatic thiosemicarbazone (TP_1), (TP_2) and Ni(II), Cu(II) and Co(II) complexes against *Ae. aegypti* larvae

Substances	Number of larvae	LC_{50} µg/mL (95% Cl) 24 h	X^2	LC_{50} µg/mL (95% Cl) 48 h	X^2
TP_1	200	44.919 (5.736, 108.879)	2.75	31.059 (0.707, 78.654)	2.349
TP_1-Ni complex (II)	200	40.644 (5.358, 95.379)	2.078	32.038 (3.251, 75.392)	2.061
TP_1-Cu complex (II)	200	18.514 (0.003, 61.450)	3.036	13.665 (0.001, 48.173)	3.045
TP_1-Co complex (II	200	15.417 (0.047, 47.888)	2.707	9.755 (0.002, 35.678)	2.161
TP_2	200	44.913 (8.091, 101.472)	2.436	42.494 (9.319, 90.443)	2.898
TP_2-Ni complex (II)	200	42.308 (7.126, 95.572)	3.246	33.683 (4.569, 76.185)	3.225
TP_2-Cu complex (II)	200	32.875 (3.889, 75.811)	2.391	25.489 (2.034, 61.006)	2.048
TP_2-Co complex (II)	200	21.612 (0.769, 56.280)	1.063	20.504 (1.330, 50.283)	2.039
DMSO		0.00±0.00			
Bti		94.60±0.011			

LC values are expressed in ppm (mg/L) values are means ± SD, X^2: chi-square, Cl: Confidence interval, SD: Standard deviation

benzoyl thiosemicarbazone and to the metal nickel complex; benzoyl thiosemicarbazone was more toxic than nickel complex. Kaplancikli et al. (40) showed that hydrazide-hydrazone derivates namely 4-Fluorobenzoic acid [(2-furanyl) methylene] hydrazide), 11(3-Acetyl-5-(4-fluorophenyl)-2-phenyl-2,3-dihydro-1,3,4-oxadiazole), 12(3-Acetyl-5-(4-fluorophenyl)-2-(4-bromophenyl)-2,3-dihydro-1,3,4-oxadiazole) and 17 (3-Acetyl-5-(4-fluorophenyl)-2-[4-(dimethyl amino) phenyl]-2,3-dihydro-1,3,4-oxadiazole at a concentration of 100 ppm caused 100% mortality against *Ae. aegypti* larvae. In contrast, our benzaldehyde derivative and hydrazones carrying oxime group were not effective against the mosquitoes in our study. Bursalı et al. (35) investigated the larvicidal effects of Co(II) complexes with barbiturate derivatives against *Ae. aegypti* and demonstrated that bis[(2-phenoxyphenyl)(2,4,6-trioxotetrahydropyrimidin-5(2H)-ylidene)methyl]amidocopper(II) showed high larvicidal activity with LC50 of 37.91 ppm.

Aromatic thiosemicarbazone and derivatives displayed high toxicity against mosquito larvae so have the potential to be used as larvicides against important mosquito species. However, more studies are needed to elucidate their mode of action as well as to assess the impacts such metals will have on the other organism and the environment and other insects. Insecticide resistance has necessitated the development new compounds, but this is challenging (41). Integrated management programmers aimed at mosquito larvae serves as one of the most efficacious means to control populations and reduce vector-borne disease incidence in endemic areas.

Aromatic thiosemicarbazone derivatives and their Ni(II), Cu(II) and Co(II) complexes were synthesized and evaluated for their larvicidal activity against *Aedes* mosquitoes. This is the first study done with *Aedes albopictus* with these substances. The data results indicating that the aromatic thiosemicarbazone complex has insecticidal potential against *Ae. aegypti* and *Ae. albopictus* larvae and may be used to design new derivatives.

CONCLUSION

The search for new active compounds continues as resistance develops to pesticides used to combat existing vectors. Mosquito management programs targeting larvae serve as one of the most effective ways to control insect populations and reduce the number of vector-borne diseases. A series of aromatic thiosemicarbazone and hydrazone derivatives their Ni(II), Cu(II) and Co(II) complexes were synthesized and evaluated for their larvicidal activity against *Ae. aegypti* and

Ae. albopictus. The data results indicated that the aromatic thiosemicarbazone complex has insecticidal potential and may be used to design new derivatives to increase the bioefficacy of these compounds against *Ae. aegypti* and *Ae. albopictus* larvae. However, elucidating the mode of action of these compounds in larvae and developing new compounds with pharmalogical potential are necessary.

* Ethics

Ethics Committee Approval: This article does not contain any studies with animals performed by any of the authors.

Informed Consent: This article does not contain any studies with animals performed by any of the authors.

* Authorship Contributions

Concept: F.B., İ.B.B., F.M.Ş., İ.D., Design: F.B., İ.B.B., F.M.Ş., Data Collection or Processing: F.B., Analysis or Interpretation: F.B., Literature Search: F.B., Writing: F.B., İ.B.B., F.M.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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