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ORIGINAL RESEARCH

Synthesis and larvicidal and adult topical activity of some hydrazide-hydrazone derivatives against *Aedes aegypti*

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ABSTRACT

A series of novel hydrazide-hydrazone derivatives were synthesized and evaluated for their larvicidal and adult topical activity against *Aedes aegypti*. The proposed structures of all the synthesized compounds were confirmed using elemental analysis, UV, IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy. Compounds **4a-h** were screened in larval bioassays at concentrations of 100, 50 and 25 ppm in a dose dependent manner and data for their mortality was recorded. Among the tested compounds, 1-(4-nitrophenyl)-3-(4-{2-oxo-2-[2-(2-oxo-1,2-dihydro-3H-ylidene)hydrazinyl] ethyl} phenyl)urea (**4b**) showed noteworthy larvacidal activity against *Aedes aegypti*. Dose-response data of compound **4b** showed LC_{50} and LC_{90} values of 30.5 (15.4 – 22.7) and 95.9 (73.8 – 139.4) ppm, respectively. Screening of compounds **4a-h** at four doses by topical bioassay indicated a range of activity between 10000 and 1000 ppm.

Keywords: Hydrazide-hydrazone, mosquito control, *Aedes aegypti,* larvicidal activity, adult topical activity

INTRODUCTION

Mosquitoes are vectors of serious human pathogens that cause malaria, Dengue Fever, Yellow Fever, Rift Valley Fever, and Chikungunya. All of these diseases can lead to explosive outbreaks in humans which can cause high rates of morbidity and mortality [1-3]. These mosquito vector-borne diseases are ecologically sensitive; continue to be endemic in regions with human interactions leading to introductions in new geographical regions and potential epidemics in the future [2]. Currently, the development of naturally occurring insecticides and repellents are under exploration to increase and improve our ability to protect humans from mosquito bites, and ultimately to reduce the incidence of mosquito-borne illnesses. Personal protection and control mosquitoes in larval stages are the general accomplishments for the mosquito control [4-5]. Larvicides play significant role in controlling mosquitoes at their breeding and immature stages. Hydrazone derivatives possessed good larvicidal activity in our previous study [6-8]. In recent years, the chemistry of carbon-nitrogen double bond of hydrazone is fast becoming the backbone of condensation reaction in benzo-fused N-heterocycles. Hydrazone containing azomethine –NHN=CH protons

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constitute an important class of compounds for new drug development [9-10].

Hydrazones are present in many of the bioactive heterocyclic compounds because of their various biological and clinical applications such as antimicrobial, antiplatelet, anticancer, antifungal, antiviral, antitumoral, antibacterial and antimalarial activities [11-13]. Recently, our group has been investigating the possible pharmacological potential of new molecules that contain a hydrazide-hydrazone scaffold [14-15].

Many hydrazone derivatives have been reported to possess broad spectrum insecticidal activity and are used as active ingredients for controlling agricultural and horticultural pests [16-18]. For example, the first hydrazone type insecticide, hydramethylnon, was registered for use in the United States by the Environmental Protection Agency in 1980 to control ants and cockroaches [18]. Aggarwal et al. [19] found that nalidixic hyrazide derivatives demonstrated 70-100% mortality against *Spodoptera litura*. Yang et al. [20] reported that cholesterol-based hydrazone derivatives showed better insecticide activity than their precursor cholesterol against pre-third larvae of *Mythimma separata in vivo*.

As part of our current project to discovering new insecticides for control of these vectors and to explore the bioactivity of hydrazone derivatives, 4-{[(substitutedphenyl) carbamoyl]amino}phenyl)acetic acid derivatives were synthesized and tested for their larvicidal activity against 1-day old and adulticidal activity against 3-5 day old adult female *Aedes aegypti* L.

MATERIALS AND METHODS

Reactions were monitored by thin layer chromatography (TLC) and purity of the products was checked by High Performance Liquid Chromatography (HPLC). TLC was performed on 60 F-254 silica gel plates with visualization by UV-light using chloroform and methanol as solvent system. Melting points were determined on a SMP II apparatus (Gehrden, Germany). The IR spectra were recorded on a Schimadzu FTIR 8400S spectrometer (Kyoto, Japan). ^{1}H NMR spectra were recorded on Bruker Avance-DPX-400 spectrometer (Brillerica, MA, USA) in d_6-DMSO. Chemical shifts were recorded in parts per million downfield from TMS. The splitting patterns of ^{1}H-NMR were designed as follows: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet. Mass spectra were recorded on LC–MS-Waters 2695 Alliance Micromass ZQ (Milford, USA). Elemental analysis was performed on Leco CHNS-932 analyzer (Michigan, USA).

All chemicals and solvents were procured from Merck and Aldrich (Darmstad and Steinheim, Germany).

CHEMISTRY

The synthesis of some isatin hydrazide-hydrazones of (4–{[(substitutedphenyl) carbamoyl]amino}phenyl)acetic acid is illustrated and outlined in Scheme 1.

General procedure for synthesis of urea derivatives of 4-aminophenylacetic acid [1a-h]

0.500 g (3.3 mmol) 4-(aminophenyl)acetic acid was solved in acetone at 100ºC. Then, a solution of corresponding isocyanate (3.3 mmol) in 5 mL acetone was added as three parts per 30 minutes. After 6-8 hours, reaction was finalized by TLC control. Solid material was filtered and recrystallized with a suitable solvent (**1a-h**). Spectroscopic characterisation of **1a-h** have been previously described [8].

General procedure for synthesis of hydrazide-hydrazones of (4–{[(substitutedphenyl) carbamoyl]amino}phenyl) acetic acid

Urea derivatives of 4-aminophenylacetic acid [**1a-h**] were esterified with ethanol using sulfuric acid as catalyst and the resulting ester [**2a-h**] was refluxed with hydrazine hydrate in ethanol to give phenylacetyl hydrazines [**3a-h**]. Equimolar amounts of phenylacetyl hydrazines and isatin were refluxed in absolute ethanol for 4-6 hours. The reaction mixture was concentrated and left to cool. The solid product obtained was filtered and recrystallized with ethanol to give as yellow crystals [**4a-h**].

1-(4-Methoxyphenyl)-3-(4-{2-oxo-2-[2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazinyl]ethyl}phenyl)urea (**4a**)

IR ν, cm^{-1}: 3318 (NH), 1692, 1633 (C=O), 1430 (C=N). ^{1}H-NMR (400 MHz, DMSO-d6, TMS): δ 3.48 (2H, s, $-CH_2$), 3.70 (3H, s, -OCH3), 6.81-7.50 (12H, m, Ar-H) 7.86 (s, 1H, N=CH), 8.43 (1H, s, urea NH), 8.53, (1H, s, urea NH), 11.15 (bs, 1H, hydrazone NH), 13.98 (1H, s, indole NH). ^{13}C-NMR (100 MHz, DMSO-d_6, TMS) δ (ppm): 165.0 (indole C=O), 161.1 (hydrazide-hydrazone C=O) 154.9 (urea C=O), 114.4, 125.0, 126.4, 129.4, 131.0, 133.2 (aromatic C), 55.60 (CH_3), 36.60 (CH_2). LC/MS (APCI, DMSO-d_6): [M+H] = m/z 444 (%100). Anal. Calcd. for $C_{24}H_{21}N_5O_4$: C, 65.00; H, 4.77; N, 15.79. Found: C, 65.04; H, 5.22; N, 15.10.

1-(4-Nitrophenyl)-3-(4-{2-oxo-2-[2-(2-oxo-1,2-dihydro-3H-ylidene)hydrazinyl] ethyl}phenyl)urea (**4b**)

IR ν, cm^{-1}: 3100, (NH); 1688, 1630 (C=O), 1410 (C=N). ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 3.25 (2H, s, -CH_2), 7.11-8.00 (12H, m, Ar-H) 8.10 (s, 1H, N=CH), 8.70 (1H, s, urea NH), 9.33 (1H, s, urea NH), 11.15 (s, 1H, hydrazone NH), 13.90 (1H, s, indole NH). ^{13}C-NMR (100 MHz, DMSO-d6, TMS) δ (ppm): 166.1 (indole C=O), 161.0 (hydrazide-hydrazone C=O), 156.1 (urea C=O), 118.2, 123.89, 126.62, 126.75, 126.79, 127.93, 128.99, 131.14, 131.46 (aromatic C), 36.61 (CH_2). LC/MS (APCI, DMSO-d_6): [M+H] = m/z 459 (%100). Anal. Calcd. for $C_{23}H_{18}N_6O_5$: C, 60.26; H, 3.96; N, 18.33. Found: C, 60.04; H, 3.69; N, 18.10.

1-(4-Trifluoromethylphenyl)-3-(4-{2-oxo-2-[2-(2-oxo-1,2-dihydro-3H-ylidene) hydrazinyl]ethyl}phenyl)urea (**4c**)

IR ν, cm^{-1}: 3106, (NH); 1670, 1635 (C=O), 1425 (C=N). ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 3.26 (2H, s, -CH_2), 6.70-7.80 (12H, m, Ar-H), 7.90 (s, 1H, N=CH), 8.25 (1H, s, urea NH), 8.90, (1H, s, urea NH), 12.13 (s, 1H, hydrazone NH), 13.95 (1H, s, indole NH). ^{13}C-NMR (100 MHz, DMSO-d6, TMS) δ (ppm): 169.4 (indole C=O), 164.0 (hydrazide-hydrazone C=O), 159.68 (CF_3), 153.0 (urea C=O), 115.00, 123.89 126.62, 126.75, 126.79, 127.93, 128.99, 131.14, 131.46, 136.20, 136.29, (aromatic C), 36.60 (CH_2). LC/MS (APCI, DMSO-d_6): [M+H] = m/z 482 (%100.0). Anal. Calcd. for $C_{24}H_{18}F_3N_5O_3$: C, 59.88; H, 3.77; N, 14.55. Found: C, 60.02; H, 3.60; N, 14.70.

1-(4-Methylphenyl)-3-(4-{2-oxo-2-[2-(2-oxo-1,2-dihydro-3H-ylidene)hydrazinyl]ethyl} phenyl)urea (**4d**)

IR ν, cm^{-1}: 3106, (NH); 1670, 1635 (C=O), 1425 (C=N). ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 2.23 (3H, s, -CH_3), 3.40 (2H, s, -CH_2), 6.70-7.85 (12H, m, Ar-H), 8.05 (s, 1H, N=CH), 8.25 (1H, s, urea NH), 8.90, (1H, s, urea NH), 12.13 (s, 1H, hydrazone NH), 13.95 (1H, s, indole NH). ^{13}C-NMR (100 MHz, DMSO-d_6, TMS) δ (ppm): 163.0 (indole C=O), 158.6 (hydrazide-hydrazone C=O), 153.0 (urea C=O), 118.1, 125.0, 126.4, 126.70, 126.81, 127.93, 129.4, 131.0, 133.2 (aromatic C), 36.60 (CH_2), 22.40 (CH_3). LC/MS (APCI, DMSO-d_6): [M+H] = m/z 428 (%100.0). Anal. Calcd. for $C_{24}H_{21}N_5O_3$: C, 67.44; H, 4.95; N, 16.38. Found: C, 68.02; H, 4.75; N, 16.40.

1-(4-Chlorophenyl)-3-(4-{2-oxo-2-[2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)hydrazinyl]ethyl}phenyl)urea (**4e**)

IR ν, cm^{-1}: 3210 (NH); 1684, 1630 (C=O), 1440 (C=N). ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 3.48 (2H, s, -CH_2), 6.70-7.80 (12H, m, Ar-H), 7.95 (s, 1H, N=CH), 8.20 (1H, s, urea NH), 8.95 (1H, s, urea NH), 12.00 (s, 1H, hydrazone NH), 13.90 (1H, s, indole NH). ^{13}C-NMR (100 MHz, DMSO-d_6, TMS) δ (ppm): 174.0 **(** indole C=O**),** 166.2 (hydrazide-hydrazone C=O) 159.2 (C=O urea), 120.0, 122.3, 126.4, 126.9, 127.1, 129.5, 130.2, 132.0 (aromatic C), 36.00 (CH_2). LC/MS (APCI, DMSO-d_6): [M+H] = m/z 448 (%100.0). Anal. Calcd. for $C_{23}H_{18}ClN_5O_3$: C, 61.68; H, 4.05; N, 15.64. Found: C, 61.02; H, 3.95; N, 15.70.

1-(2,6-Dichlorophenyl)-3-(4-{2-oxo-2-[2-(2-oxo-1,2-dihydro-3H-ylidene)hydrazinyl] ethyl}phenyl)urea (**4f**)

IR ν, cm^{-1}: 3100 (NH); 1688, 1640 (C=O), 1410 (C=N). ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 3.49 (2H, s, -CH_2), 7.09-7.60 (11H, m, Ar-H), 7.85 (s, 1H, N=CH), 8.10 (1H, s, urea NH), 8.90 (1H, s, urea NH), 12.00 (s, 1H, hydrazone NH), 13.50 (1H, s, indole NH). ^{13}C-NMR (100 MHz, DMSO-d_6, TMS) δ (ppm): 167.20 **(** indole C=O**),** 165.00 (hydrazide-hydrazone C=O) 158.60 (urea C=O), 128.76, 129.14, 129.85, 130.58, 130.75, 131.35, 133.30, 134.26, 135.61, 137.14 (Aromatic C), 35.00 (CH_2). LC/MS (APCI, DMSO-d_6): [M+H] = m/z 483 (%100.0). Anal. Calcd. for $C_{23}H_{17}Cl_2N_5O_3$: C, 57.27; H, 3.55; N, 14.52. Found: C, 58.10; H, 3.65; N, 14.40.

1-(3,5-Dichlorophenyl)-3-(4-{2-oxo-2-[2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)hydrazinyl]ethyl}phenyl)urea (**4g**)

IR ν, cm^{-1}: 3150 (NH); 1670, 1640 (C=O), 1410 (C=N). ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 3.48 (2H, s, -CH_2), 6.99-8.03 (12H, m, Ar-H and N=CH), 8.20 (1H, s, urea NH), 8.80 (1H, s, urea NH), 12.10 (s, 1H, hydrazone NH), 13.60 (1H, s, indole NH). ^{13}C-NMR (100 MHz, DMSO-d_6, TMS) δ (ppm): 168.80 **(**indole C=O), 163.00 (hydrazide-hydrazone C=O) 154.00 (urea C=O), 121.00, 127.96, 128.31, 129.15, 129.91, 130.59, 133.40 (aromatic C), 36.00 (CH_2). LC/MS (APCI, DMSO-d_6): [M+H] = m/z 483 (%100.0). Anal. Calcd. for $C_{23}H_{17}Cl_2N_5O_3$: C, 57.27; H, 3.55; N, 14.52. Found: C, 57.20; H, 3.60; N, 14.50.

1-(4-{2-Oxo-2-[2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazinyl]ethyl}phenyl)-3-(2,4,6-trichlorophenyl)urea (**4h**)

IR ν, cm^{-1}: 3150 (NH); 1670, 1640 (C=O), 1410 (C=N). ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 3.48 (2H, s, -CH_2), 6.99-7.83 (10H, m, Ar-H), 8.10 (s, 1H, N=CH), 8.22 (1H, s, urea NH), 8.94 (1H, s, urea NH), 12.00 (s, 1H, hydrazone NH), 13.40 (1H, s, indole NH). ^{13}C-NMR (100

MHz, DMSO-d_6, TMS) δ (ppm): 165.90 (indole C=O), 164.00 (hydrazide-hydrazone C=O) 152.00 (urea C=O), 121.10, 128.28, 129.73, 130.17, 131.66, 133.0, 133.91, 134.01, 136.21, 137.62 (aromatic C), 36.00 (CH_2). LC/MS (APCI, DMSO-d_6): [M+H] = m/z 517 (%100). Anal. Calcd. for $C_{23}H_{16}Cl_3N_5O_3$: C, 53.46; H, 3.12; N, 13.55. Found: C, 54.10; H, 3.20; N, 13.50.

Larvicidal activity

Larvae of *Ae. aegypti* (Orlando strain) used in these bioassays were hatched from the eggs obtained from a laboratory colony maintained at the Mosquito and Fly Research Unit at the Center for Medical, Agricultural and Veterinary Entomology, USDA-ARS, Gainesville, Florida. The eggs were hatched and the larvae were maintained at a temperature of 27 ± 2˚C and 60 ± 10 % RH in a photoperiod regimen of 12:12 h (L: D). Bioassays were conducted using the system described by Pridgeon et al. [21] to determine the larvicidal activity of these compounds against *Ae. aegypti*. Five 1-d-old larvae were transferred to individual wells of a 24-well tissue culture plates in a 30-40 µL droplet of water. Fifty µL of larval diet of 2% slurry of 3:2 beef liver powder (Now Foods, Bloomingdale, Illinois) and Brewer's yeast (Lewis Laboratories Ltd., Westport, CT) and 1 mL of deionized water were added to each well by using a Finnpipette stepper (Thermo Fisher, Vantaa, Finland). Compounds were dissolved and diluted in DMSO. Eleven microliters of the test chemical was added to the labeled wells, while 11 µL of DMSO was added to the control treatments. After treatment application, the plates were swirled in clock-wise and counter clockwise motions and front and back and side to side five times to ensure even mixing of the tested compounds. Permethrin (46.1% *cis* – 53.2% *trans*, Chemical Service, West Chester, PA) at 0.025 ppm was used as positive control. Larval mortality was recorded 24 h post treatment. For dose response study, a series of 5 dosages of 4-{[(substitutedphenyl) carbamoyl]amino}phenyl)acetic acid derivatives were used to get a range of mortality between 0 and 100%. Treatments were replicated 10 times. LC_{50} values for larvicidal data were calculated by using SAS, Proc Probit [22] (Version 9.2, 2007) Control mortality was corrected by using Abbott's formula [23].

Adulticidal activity

Pupae from the *Aedes aegypti* "Orlando" strain were allowed to emerge into a screen cage with access to 10% sucrose soaked cotton balls. Three to five day old adults were aspirated and cold anesthetized by holding in a 4C refrigerator. Cohorts of ten female mosquitoes were sorted into 3.5 oz (TK35, Solo) cups and kept on ice until topical application of 0.5ul of test solution. The adult topical assay follows the method described previously [24]. Mortality was recorded after 24 hours for all dilutions as well as the controls. Negative controls consisted of untreated mosquitoes and acetone only treated cohorts. The positive control in this assay was permethrin, with four doses of 1000, 100, 10, and 1 ppm. For the hydrazide-hydrazone derivatives, **4a-h**, a ten-fold dilution series of 10000, 1000, 100, and 10 ppm was made in acetone from a 100000 ppm stock of each compound. Replicates of the same assay were performed on three successive days. Mortality was converted to percentage for each replicate and the three percentage values were used to determine the mean and standard error.

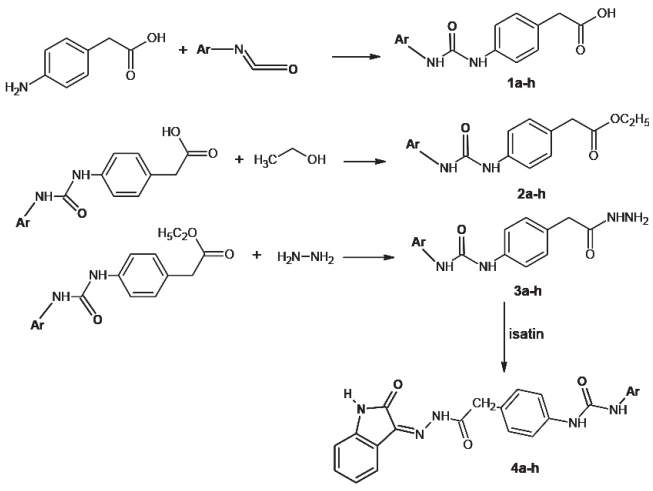
Table 1. Some properties of compounds **4a-h**

Comp.	Ar	Molecular Formula	Melting point (ºC)	Yield (%)	Molecular weight
4a	4-OCH_3-C_6H	$C_{24}H_{21}N_5O_4$	258-260	78	443
4b	4-NO_2-C_6H_4	$C_{23}H_{18}N_6O_5$	250-252	65	458
4c	4-CF_3-C_6H_4	$C_{24}H_{18}F_3N_5O_3$	212-214	64	481
4d	4-CH_3-C_6H_4	$C_{24}H_{21}N_5O_3$	228-230	71	427
4e	4-Cl-C_6H_4	$C_{23}H_{18}ClN_5O_3$	200-202	64	448
4f	2,6-Cl_2-C_6H_3	$C_{23}H_{17}Cl_2N_5O_3$	249-251	75	482
4g	3,5-Cl_2-C_6H_3	$C_{23}H_{17}Cl_2N_5O_3$	236-238	78	482
4h	2,4,6-Cl_3-C_6H_2	$C_{23}H_{16}Cl_3N_5O_3$	240-242	73	516

RESULTS AND DISCUSSION

A series of new isatin hydrazide-hydrazone derivatives were prepared according to Scheme 1. The structures of the target compounds **4a-h** were elucidated using UV, IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopic methods besides elemental analysis. All compounds were isolated in satisfactory yields (64-78%) and purified by recrystallization from ethanol. The purity of the compounds was checked by TLC and elemental analysis. The chemical structures of all compounds were characterized by various spectroscopic methods and elemental analysis. Both analytical and spectral data of all the synthesized compounds were in full agreement with the proposed structures.

The IR spectra of **4a-h** showed hydrazone N-H bands in 3318-3100 cm^{-1}, C=O bands in 1692-1630 cm^{-1} and C=N bands in 1440-1410 cm^{-1}. ^{1}HNMR spectra of **4a-h** showed



Scheme 1. Synthetic route of the targeted compounds

two signals in the 8.10-7.85 ppm and 12.13-11.15 ppm which are attributed to the N=CH and hydrazone NH protons, respectively. In addition, the N-H peak of indole and urea were observed at 13.98-13.40 ppm and 9.33-7.90 ppm respectively. The signal of aromatic protons was also found in the expected field.

The hydrazide-hydrazone derivatives **4a-h** were evaluated for the first time against yellow fever mosquito, *Ae. aegypti* for their larvicidal activity. Compounds **4a-h** were screened in larval bioassays at concentrations of 100, 50 and 25 ppm in a dose dependent manner and data for the mortality was recorded. Only compound **4b,** having nitrophenyl ring, showed the activity whereas all the other compounds were inactive at the highest dose of 100 ppm. Dose-response data of compound **4b** showed LC_{50} and LC_{90} values of 30.5 (15.4-22.7) and 95.9 (73.8-139.4) ppm, respectively.

To further evaluate the efficacy of **4a-h,** we performed adult topical bioassays using 3-5 day old *Aedes aegypti* females. The permethrin positive control was tested at 1000, 100, 10, and 1 ppm which produced greater than 95% mortality at the three highest doses and 33.3% (Table 2) mortality at 1 ppm. Based on the much larger body mass of the adult as compared to first instar larva, we started with higher doses of 10000,1000, 100, and 10 ppm for **4a-h**. All compounds, with the exception of **4f** and **4g**, showed greater than 50% mortality at the highest dose of 10000 ppm. At this same dose, treatment with **4a** and **4b** resulted in 80% mortality while **4d** produced complete mortality. However the mortality of **4a-h** titered quickly and at 1000 ppm was less than 25% for all compounds. Mortality in the untreated and acetone treated negative controls was 6.67% and 10% respectively.

Table 2. 24 hour mortality of compounds **4a-h** on 3-5 day old female *Aedes aegypti*

Comp.	10000 ppm	1000 ppm	100 ppm	10 ppm	1 ppm
4a	80.0±10.0	20.0±15.3	13.3±6.7	20±10.0	Not tested
4b	80.0±20.0	16.7±3.3	3.3±3.3	10.0±5.8	Not tested
4c	70.0±10.0	20.0±5.8	10.0±10.0	16.7±12.0	Not tested
4d	100.0	3.3±3.3	25.0±5.0	6.7±3.3	Not tested
4e	66.7±14.5	10.0±5.8	6.7±6.7	13.3±3.3	Not tested
4f	26.7±14.5	23.2±12.0	10.0±5.8	16.67±12.0	Not tested
4g	40.0±15.3	20.0±15.3	3.3±3.3	6.7±3.3	Not tested
4h	76.7±6.7	20.0±15.3	46.7±23.3	6.7±3.3	Not tested
Permethrin*	Not tested	100	96.7±3.3	96.7±3.3	33.3±17.6

*The permethrin positive control was tested at 1000, 100, 10, and 1 ppm which produced greater than 95% mortality at the three highest doses and 33.3% mortality at 1 ppm.

CONCLUSION

A series of novel isatin hydrazide-hydrazone derivatives were synthesized and evaluated for their larvicidal activity against *Ae. aegypti*. Among the tested compounds, compound **4b**, showed larvicidal activity whereas all the other compounds were inactive at the highest screening dose of 100 ppm. Adult topical bioassays showed greater than 80% mortality at 10000 ppm for compounds **4a, 4b,** and **4d,** however, these same compounds were relatively inactive at lower doses. These data indicate that compound **4b** may be designed for the new hydrazone derivatives to increase the bioefficacy of these compounds against *Ae. aegypti* larvae.

CONFLICT OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Bazı Hidrazit-Hidrazon Türevlerinin Sentezi ve Larvasidal Etkileri

ÖZET

Bir seri hidrazit-hidrazon türevi bileşik sentezlenmiş ve bunların larvisidal ve yüzeyel etkisi *Aedes aegypti* türüne karşı ölçülmüştür. Sentezlenen tüm bileşiklerin yapıları elementel analiz, UV, IR, ^{1}H-NMR, ^{13}C-NMR ve kütle spektroskopisi kullanılarak doğrulanmıştır. **4a-h** bileşiklerinin biyolojik analizleri 100, 50 and 25 ppm konsantrasyonlarında taranmış ve mortalite oranları kaydedilmiştir. Test edilen bileşikler arasında 1-(4-nitrofenil)-3-(4-{2-okso-2-[2-(2-okso-1,2-dihidro-3H-iliden)hidrazinil] etil} fenil)üre (**4b**) *Aedes aegypti* türüne karşı kaydadeğer larvisidal aktivite göstermiştir. **4b** bileşiğinin doz yanıt verileri, LC_{50} ve LC_{90} değerlerini sırasıyla 30.5 (15.4 – 22.7) ve 95.9 (73.8 – 139.4) ppm olarak göstermiştir. Taranan **4a-h** bileşiklerinin dört dozla yapılan biyolojik analizinde aktivite aralığının 10000 ve 1000 ppm arasında olduğu belirlenmiştir.

Anahtar kelimeler: Hidrazit-hidrazon, sivrisinek kontrolü, *Aedes aegypti,* larvasidal etki, yüzeyel etkinlik

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