1. Introduction

Mosquitoes are disreputable as the main vectors for the spread a number of diseases, such as malaria, dengue fever, schistosomiasis Japanese encephalitis, filariasis, and yellow fever (Georges et al., 2013). Odorant-binding proteins were transporting the odorant to olfactory receptors, which plays a major role in major activities of host sensing (Tutin et al., 1911). The control of mosquito has been a big challenge and currently using most effective mosquito larvicidal. Larvicidal activities of benzoquinone (LC50: 9.0 g/mL) against Culex quinquefasciatus (Kim and Ahn, 2017). Naphthalene-1,4-dione (LC50: 0.085 µg/mL) against Estagio larval and isolated from Balsaminaceae (Impatiens glandulifera), (Kim and Ahn, 2017). Naphthalene-1,4-dione (LC50: 1.64 µg/mL) against Culex pipiens pallens, (Jeon et al., 2015), anthracence-9,10-dione (LC50: >25.0 µg/mL) against A. aegypti, tectoquinone LC50: 3.3 µg/mL (A. aegypti), and emodin LC50: 5.3 µg/mL (A. aegypti) (Cheng et al., 2008). However, the above chemicals are problems for usage in biological systems, such as the addition of methyl (—CH3), carboxyl (—COOH), hydroxyl (—OH), and methoxyl (—OCH3) groups of 9,10-anthracenedione outcomes in a broad-spectrum of medicinal properties (Tutin et al., 1911). Fig. 1 shows important larvicidal active compounds that based on structure, relation of target compounds. Larvicidal activities of benzoquinone (LC50: 90 µg/mL) were evaluated on third-instar larvae of A. aegypti (De Sousa et al., 2010). 2-methoxy-1-A-naphthoquinone (LC50: 0.085 µg/mL) against Aedes aegypti (Yang et al., 2013). However, the above drawbacks require the new selective control of mosquito larvae (Yang et al., 2013). Odorant-binding proteins were transporting the odorants to olfactory receptors, which plays in major activities of host-seeking (Bazza et al., 2013; De March and Golebiowski, 2014; Pechlaner and Oostenbrink, 2015). The above scientific information, we have chosen a hydroxyanthraquinone target against Culex quinquefasciatus and using odorant-binding protein (PDB ID: 3OGN) for molecular docking studies. In the present study, synthe-
sis of new hydroxyxanthraquinone Mannich base derivatives for evaluation of larvicidal activity.

2. Materials and methods

2.1. Chemistry

The chemicals were obtained from commercially and fully purified all chemicals before using the reactions. The FT-IR Shimadzu 8201PC (4000–400 cm⁻¹) and ¹H & ¹³C NMR spectra of Bruker DRX-300 MHz were used by analysis all synthesized compounds. Thin layer chromatography (TLC) technique was used by check purity of the compounds with using silica gel plates.

2.1.1. General method for preparation of 4,11-dihydroxy-2-phenyl-2,3-dihydro-1H-naphtho[2,3-f]isoindole-5,10-dione (1a)

A mixture of 1,4-dihydroxy anthraquinone (0.0005 mol, 0.1 mg), benzaldehyde (0.002 mol, 0.5 ml) and aniline (0.001 mol, 0.5 ml) are dissolved in ethanol. The mixture was refluxes by 24 h at 60 °C. The final target compound was monitored by TLC. The product was recrystallized in suitable alcohol. The same experimental method was used for preparation of other compounds 1b-k.

2.1.2. 4,11-dihydroxy-2-phenyl-2,3-dihydro-1H-naphtho[2,3-f]isoindole-5,10-dione (1a)

IR (kBr, cm⁻¹): 1714, 1691, 1462, 822, 752; ¹H NMR (300 MHz): δ ppm 8.37–8.33 (d, J = 13.74 Hz, 2H), 7.82–7.80 (d, J = 13.74 Hz, 2H), 7.21–7.18 (dd, J = 7.72 Hz, J = 7.75 Hz, 2H), 6.95–6.93 (d, J = 7.75 Hz, 2H), 6.91 (d, J = 7.70 Hz, 2H), 6.77–6.75 (d, J = 7.75 Hz, 1H), 6.10 (s, 2H), 5.48–5.46 (q, 2H), 5.36 (s, 2H), 4.49 (s, 2H), 2.12 (d, 6H); ¹³C NMR (75 MHz, DMSO-d₆): 187.5, 151.6, 148.5, 135.9, 133.2, 132.5, 129.5, 128.9, 128.2, 128.0, 126.3, 126.1, 122.3, 113.9, 114.1, 70.6, 27.6, 20.5; El-MS m/z (rel.int): 518.25 (M⁺, 35%); Anal C₃₈H₂₇NO₄: C, 81.27; H, 4.59; Found: C, 81.27; H, 4.48; N, 3.91; 2.1.3. 4,11-dihydroxy-2-phenyl-1,3-dihydro-1H-naphtho[2,3-f]isoindole-5,10-dione (1b)

IR (kBr, cm⁻¹): 1762, 1689, 1452, 812, 741; ¹H NMR (300 MHz): δ ppm 8.38–8.36 (d, J = 13.74 Hz, 2H), 7.82–7.80 (d, J = 13.74 Hz, 2H), 7.21–7.18 (dd, J = 7.72 Hz, J = 7.75 Hz, 2H), 6.95–6.93 (d, J = 7.75 Hz, 2H), 6.77–6.75 (d, J = 7.75 Hz, 1H), 6.10 (s, 2H), 5.48–5.46 (q, 2H), 5.36 (s, 2H), 4.49 (s, 2H), 2.12 (d, 6H); ¹³C NMR (75 MHz, DMSO-d₆): 187.9, 152.5, 149.1, 133.0, 132.9, 129.0, 128.2, 126.1, 114.6, 114.1, 121.4, 54.9; El-MS m/z (rel.int): 562.21 (M⁺, 45%); 44(18); Anal C₃₈H₂₇NO₄: C, 81.27; H, 4.85; N, 2.49; Found: C, 81.25; H, 4.81; N, 2.48.

2.1.4. 4,11-dihydroxy-1-((E)-4-methylpenta-1,3-dien-1-yl)-3-(Z)-4-methylpenta-1,3-dien-1-yl)-2-phenyl-2,3-dihydro-1H-naphtho[2,3-f]isoindole-5,10-dione (1c)

IR (kBr, cm⁻¹): 1744, 1678, 1451, 816, 738; ¹H NMR (300 MHz): δ ppm 8.31–8.28 (d, J = 13.04 Hz, 2H), 7.80–7.78 (d, J = 13.04 Hz, 2H), 7.26–7.22 (dd, J = 7.70 Hz, 2H), 6.95–6.93 (d, J = 7.70 Hz, 2H), 6.76–6.75 (d, J = 7.71 Hz, 1H), 6.20(s, 2H), 6.10(d, 2H), 5.90(d, 2H), 5.34(s, 2H), 4.69 (s, 2H), 2.14(s, 6H), 1.98(s, 6H); ¹³C NMR (75 MHz, DMSO-d₆): δ ppm (ppm)); 187.5, 151.6, 148.5, 135.9, 133.2, 132.5, 129.5, 128.9, 128.2, 128.0, 126.3, 126.1, 122.3, 113.9, 114.1, 70.6, 27.6, 20.5; El-MS m/z (rel.int): 582.25 (M⁺, 35%); Anal C₃₈H₂₇NO₄: C, 81.27; H, 4.85; N, 2.49; Found: C, 81.25; H, 4.81; N, 2.48.

2.1.5. 4,11-dihydroxy-2-phenyl-1,3-dimethylstyryl)-2,3-dihydro-1H-naphtho[2,3-f]isoindole-5,10-dione (1d)

IR (kBr, cm⁻¹): 1769, 1674, 1462, 812, 738; ¹H NMR (300 MHz): δ ppm 8.32–8.30 (d, J = 13.70 Hz, 2H), 7.86–7.84 (d, J = 13.72 Hz, 2H), 7.42–7.44 (m, 8H), 7.26–7.24 (d, J = 7.70 Hz, 2H), 6.92–6.87 (d, J = 7.70 Hz, 2H), 6.69–6.67 (d, J = 7.70 Hz, 1H), 5.32 (s, 2H), 4.59 (s, 2H), 6.69(s, 2H),6.21(s, 2H); ¹³C NMR (75 MHz, DMSO-d₆): δ ppm (ppm)); 187.9, 152.5, 149.1, 138.5, 132.9, 132.7, 129.0, 128.5, 128.2, 126.1, 121.4, 114.6, 114.1, 121.4, 54.9; El-MS m/z (rel.int): 562.21 (M⁺, 45%); 44(18); Anal C₃₈H₂₇NO₄: C, 81.27; H, 4.85; N, 2.49; Found: C, 81.25; H, 4.81; N, 2.48.

2.1.6. 1,3-difuran-2-yl)-4,11-dihydroxy-2-phenyl-2,3-dihydro-1H-naphtho[2,3-f]isoindole-5,10-dione (1e)

IR (kBr, cm⁻¹): 1725, 1681, 1461, 823, 712; ¹H NMR (300 MHz): δ ppm 8.39–8.36 (d, J = 13.74 Hz, 2H), 7.86–7.82 (d, J = 13.74 Hz, 2H), 7.62(d, J = 7.62 Hz, 2H), 7.22–7.20 (dd, J = 7.72 Hz, 2H), 6.94–6.91 (d, J = 7.75 Hz, 2H), 6.71–6.68 (d, J = 7.75 Hz, 1H), 6.25–6.21 (d, J = 7.62 Hz, 2H), 6.45–6.42(d, J = 7.62 Hz, 2H), 5.38(s, 2H), 5.36 (s, 2H); ¹³C NMR (75 MHz, δ ppm)); 187.4, 151.9, 150.6,
147.9, 141.0, 135.6, 131.9, 128.7, 127.9, 126.5, 126.1, 122.9, 121.4, 114.1, 113.9, 68.5; EIMS m/z (rel.int): 600.21 (M* 36%); Anal C34H23NO6O: C, 76.61; H, 5.58; N, 7.05; Found: C, 76.63; H, 5.59; N, 7.09.

2.1.1.1. 1,3-bis(4-dimethylamino)phenyl)-4,11-dihydroxy-2-phenyl-2,3-dihydro-1H-naphtho[2,3-f]isoindole (1f)

IR (kBr, cm⁻¹): 2821, 1742, 1682, 812, 740; ¹H NMR (300 MHz): 6.35–6.34 (d, J = 13.70 Hz, 2H), 7.89–7.86 (d, J = 7.71 Hz, 2H), 7.16 (4H, CH), 6.90–6.88 (d, J = 7.71 Hz, 2H), 6.75–6.73 (d, J = 7.71 Hz, 1H), 114.6 (4H, CH), 5.27 (s, 2H), 5.15 (s, 2H), 3.85 (s, 6H), 3.57 (s, 2H), 1.3% NMR (75 MHz, δ (ppm)): 187.1, 159.8, 153.0, 148.9, 136.8, 133.2, 132.8, 129.3, 128.1, 127.3, 122.2, 111.6, 114.2, 115.6, 70.5, 55.9; EIMS m/z (rel.int): 570.10 (M* 30%); Anal C36H27NO6: C, 75.91; H, 4.78; N, 2.46; Found: C, 75.05; H, 4.77; N, 2.45.

2.2. Biological activity

2.2.1. Larvicidal activity

Larvicidal activities of 10, 25, 50 and 100 µg/mL of compounds (1a-1k) were screened as we previously described in publication [3]. Mortality caused by the compounds was evaluated as ratios (%) of the numbers of dead vs. live larvae. The 50% lethal doses (LD₅₀) values of the compounds were calculated using probit analysis and statistically analyzed using SPSS version 16.0 software.

2.2.2. Statistical analysis

Larvicidal activities results were calculated through 3 independent evaluations and Microsoft Excel was used to analysis the standard deviations (SD) of each compound.

![Scheme 1. Route of synthesis larvicidal active target molecules.](image)
2.2.3. Molecular docking

This study was carried out via Autodock vina 1.1.2. (Trott and Olson, 2010), which using to interpret the binding mode of compounds (1c) and permethrin with mosquito odorant protein. Crystal structure of mosquito odorant binding protein (PDB ID: 3OGN) was collected from protein data bank web link. The 3D association of the compound (1c) and permethrin was accomplished through Chem Draw Ultra 12.0 software. The 3OGN protein was fixed at

![Docked complex](image1)

![Molecular surface](image2)

![3D](image3)

![2D](image4)

Fig. 2. Molecular docked modes of 1c with binding site of 3OGN.

### Table 1
Larvicidal activity of anthraquinone analogues (1a-1k) and permethrin.

| Compounds | Concentration (μg/mL) | Mortality (%) | LD50 (μg/mL) |
|-----------|-----------------------|---------------|--------------|
|           | 10                    | 25            | 50           | 100          |
| 1a        | –                     | 0 ± 0.00      | 16 ± 0.27    | 36 ± 0.97    | >100         |
| 1b        | 7 ± 0.89              | 23 ± 1.25     | 36 ± 0.96    | 55 ± 0.00    | 85.42        |
| 1c        | 41 ± 0.00             | 65 ± 1.31     | 100 ± 1.34   | –            | 20.92        |
| 1d        | 5 ± 1.76              | 22 ± 1.12     | 43 ± 1.87    | 60 ± 1.61    | 74.17        |
| 1e        | 4 ± 1.14              | 15 ± 1.48     | 38 ± 1.46    | 54 ± 0.88    | 86.27        |
| 1f        | –                     | –             | 0 ± 0.00     | 20 ± 0.47    | >100         |
| 1g        | 22 ± 1.87             | 46 ± 1.21     | 62 ± 0.56    | 88 ± 0.30    | 37.95        |
| 1h        | 0 ± 0.00              | 10 ± 1.87     | 20 ± 0.67    | 40 ± 1.89    | >100         |
| 1i        | –                     | –             | 21 ± 0.00    | 38 ± 0.09    | >100         |
| 1j        | 22 ± 0.95             | 36 ± 1.65     | 57 ± 1.41    | 100 ± 1.14   | 37.59        |
| 1k        | –                     | –             | 0 ± 0.00     | 40 ± 1.23    | >100         |
| Permethrin| 23 ± 1.76             | 55 ± 1.23     | 82 ± 1.94    | 100 ± 0.00   | 25.49        |

*Values are the means of three replicates ± SD.
3. Result and discussion

3.1. Chemistry

The compound 1a-1k was synthesized from anthraquinone reached with aldehyde and primary amine in the ethanol medium by condensation method. The mixture was reflexed by 24 hr at 60 °C. The final products were obtained yield between 80 and 89 %. The method of preparation was outlined in scheme 1. Structures 1a-1k were definite via FT-IR, 1H and 13C NMR, mass spectral studies, the importance of the IR spectral peak at C–N–C, =O, OH corresponding to the average peak at 1641–1697, 174–1769, and 1451–1469 cm⁻¹ respectively. 1H NMR spectral obtained important proton peaks range between δ 4.49–5.26, and 5.32–5.42 ppm conforming to the protons HC–N, and OH respectively. The 13C NMR carbon peaks were obtained the range of value between δ 54.9–72.6, 187.0–187.9, and 151.6–153.6 conforming to the C–N–C, C=O, and C–OH carbons respectively. All compounds were conformed the mass values according to the molecular ion peak obtain in mass spectral values.

3.2. Larvicidal activity

Larvicidal activity was screened for all synthesized anthraquinones (1a-1k) derivatives against second instar C. quinquefasciatus larvae. Compound 1c exerted more larvicidal activity (LD₅₀ 20.92 μg/mL) than other compounds and standard permethrin LD₅₀ 25.49 μg/mL. Compounds 1a, 1f, 1h, 1i, and 1k were less active against C. quinquefasciatus with LD₅₀ values of above >100 μg/mL. All values are represented in Table 1.
3.3. Docked results with AutoDock Vina

The Autodock Vina program was used to study for compound (1c) and permethrin docking with 3OGN protein. The compound 1c shows significant binding affinity (−9.8 kcal/mol) than permethrin (−9.7 kcal/mol). Stability of protein and ligand was confirmed through the bond distance calculation, which is less than 3.5 Å from H-donor and the H-acceptor of bond distance (Taha et al., 2015). The compound 1c was not conceded for any hydrogen bond in 3OGN. The residues Ala18, Leu19, Leu22, Ala62, Lys63, Val64, Lys75 and Pro81 were complex with hydrophobic connections. The molecular interaction of compound 1c and 3OGN were shown in Fig. 2. The control permethrin was also not conceded any hydrogen bond in 3OGN. The hydrophobic interactions were involved due to the formation of Leu15, Leu19, Phe59, Leu73, Leu76, His77, Leu80, Ala88, Met89, Gly92, His111, Trp114, Phe123, and Leu124. Fig. 3 shows that the molecular interaction of permethrin with 3OGN. Therefore, the compound 1c having remarkable inhibition capability than permethrin in mosquito odorant-binding protein. The results are presented in Table 2.

4. Conclusion

Novel anthraquinones (1a-1k) moiety were synthesized and screened for larvicidal activity. The Compound 1c was highly active (LD50 20.92 μg/mL) against second instar C. quinquefasciatus mosquito larvae than permethrin with LD50: 25.49 μg/mL. Molecular docking findings supported the potent larvicidal activity of compound 1c (−9.8 Kcal/mol) compared with Permethrin with binding energy values of (−9.7 Kcal/mol). Therefore, these compounds might serve as a new class of products with larvicidal activity and prospective foundation for emerging ecologically important bioactive compound.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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