**UNIVERSIDADE FEDERAL DE SERGIPE**
**CENTRO DE CIÊNCIAS BIOLÓGICAS E DA SAÚDE**
**DEPARTAMENTO DE FARMÁCIA**

**MONOGRAFIA II (FISOL0105)**

# SÍNTESE, ATIVIDADE E ESTUDOS DE QSAR DE DERIVADOS DE TRIPTAMINA SOBRE LARVAS DE TERCEIRO ESTÁGIO DE *Aedes aegypti* Linn.

**Thaysnara Batista Brito**

**São Cristóvão**

**2015**

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# SÍNTESE, ATIVIDADE E ESTUDOS DE QSAR DE DERIVADOS DE TRIPTAMINA SOBRE LARVAS DE TERCEIRO ESTÁGIO DE Aedes *aegypti* Linn.

Monografia apresentada pela aluna à disciplina de
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## RESUMO

A dengue é uma doença de cunho urbano, aguda, sistêmica e de etiologia viral. Atinge 50 milhões de indivíduos/ ano, considerada um grande problema de saúde pública. Seu controle se dá, principalmente, pelo uso de inseticidas químicos tendo como alvo o sistema nervoso do inseto. Porém vem causando resistência em suas populações. Larvicidas, tais como o organofosforado temefós, reguladores do crescimento de insetos e toxinas de bactérias (ex. Bti) têm sido utilizados em locais de procriação. No entanto, o crescimento desordenado das zonas urbanas dá condições ideais, como criadouros escondidos, para o crescimento do mosquito. Uma forma alternativa é a utilização de inseticidas fundamentais à segurança do meio ambiente, inclusive do ser humano. Sendo assim, o objetivo do presente estudo foi avaliar a atividade larvicida dos derivados sintéticos da triptamina frente às larvas de *Ae. aegypti,* visando uma possível inibição da via da quinurenina. Foi realizado um estudo QSAR baseado em nove derivados da triptamina sintetizados e testados de modo a obter a concentração letal que mata 50% da população de larvas de *Ae. aegypti*. Com relação à atividade larvicida, a 2,2,2-tricloro-*N*-[2-(1H-indol-3-il) etil] acetamida, demonstrou um excelente efeito tóxico frente às larvas de *Ae. aegypti* com um valor de $CL_{50}$ de 48,69 ppm. O composto *N*-[2-(1H-indol-3-il) etil] acetamida, exibiu a menor potência larvicida com um valor de $CL_{50}$ de 884,83 ppm. Observou-se também uma contribuição negativa do efeito estérico quando comparado ao parâmetro hidrofóbico, pois além das análises das equações, o coeficiente angular hidrofóbico foi positivo e maior do que o parâmetro estérico.



**Palavras chave:** Síntese, QSAR, *Aedes aegypti*.

# SUMÁRIO

## INTRODUÇÃO

O processo dinâmico e progressivo de seleção adaptativa para a sobrevivência das espécies, que ocorre cotidianamente na natureza, envolve importantes fenômenos que interferem no estado de saúde das populações humanas. Isto pode ser bem evidenciado na força da reemergência das infecções causadas pelos vírus da dengue, pois as agressões dos quatro sorotipos destes agentes às populações humanas vêm crescendo em magnitude e extensão geográfica desde meados do século XX em função da velocidade de circulação e replicação viral, facilitada pela extraordinária capacidade de adaptação das populações de mosquitos que lhes servem como transmissores e pela incapacidade do homem, neste momento, de se proteger contra estas infecções (TEXEIRA *et al*, 2009).

A dengue é uma doença infecciosa, de origem viral, transmitida para o homem por meio da picada de fêmeas de mosquitos contaminadas pertencentes ao gênero *Aedes*. O principal vetor é o inseto *Aedes aegypti* (L.) (Diptera: Culicidae), também vetor da febre amarela urbana (COELHO; DE PAULA; ESPÍNDOLA, 2009). Os mosquitos *Ae. albopictus* e *Ae. polynesiensis* também podem atuar como vetores secundários em algumas localidades (SINGHI; KISSOON; BANSAL, 2007). Quatro sorotipos diferentes foram descritos, DENV-1, DENV-2, DENV-3 e DENV-4, todos os membros do gênero *Flavivirus*, pertencente à família Flaviviridae (GUZMÁN & KOURI, 2001).

A distribuição e frequência das infecções pelos vírus da dengue estão intrinsecamente relacionadas com a plasticidade e poder de adaptação do *Ae. aegypti* ao ambiente habitado pelo homem, principalmente, nos espaços com grandes adensamentos populacionais, pois a transmissão e circulação destes vírus são condicionadas pela densidade e dispersão deste mosquito. Cada sorotipo específico dos vírus da dengue, quando introduzido em grandes cidades com elevada densidade vetorial é disseminado rapidamente provocando epidemias explosivas (SOUZA, 1999; TEXEIRA *et al*., 2009; WHO, 1997).

Na tentativa de manter a incidência da enfermidade sob controle, são destinadas, continuamente, quantias significativas de recursos para programas de controle ao vetor, porém surtos de epidemias são freqüentes. Esse fato

decorre de fatores relacionados à biologia e ao comportamento do vetor, somados a problemas típicos dos grandes centros urbanos (MARZOCHI, 1994).

A dengue apresenta-se, clinicamente, sob quatro formas diferentes: Infecção assintomática, dengue clássica (DC), febre hemorrágica da dengue (FHD) e por fim, dengue atípica. A dengue clássica apresenta-se como uma enfermidade febril com dois ou mais dos seguintes sintomas: cefaléia, dor retro-orbital, mialgia artralgia, exantema (maculopapular) e petéquias com prova do laço positiva. Já a forma hemorrágica acontece geralmente após reinfecções com dengue, mas em alguns casos acontece após infecções primárias. Esses pacientes têm carga viral consideravelmente mais alta e taxa mais lenta de redução da carga viral e complexos imunes contendo vírus do que pacientes com dengue clássico. A forma hemorrágica da dengue, nos casos mais graves, resulta em síndrome de choque da dengue (SCD), podendo levar o paciente a coma e morte. A FHD e a SCD são as manifestações mais graves das infecções por dengue (WHO, 1997, 1999).

A dengue clássica e a dengue hemorrágica estão amplamente distribuídas em mais de 100 países. Aproximadamente 2,5 bilhões de pessoas habitam áreas endêmicas, com uma estimativa de 50 milhões de infecções por ano (FUNASA, 2009). No Brasil, a dengue é hoje objeto da maior campanha de saúde pública, pois se encontra presente em todos os 27 estados da Federação. Entre 04 de Janeiro a 13 de Junho de 2015, foram registrados 1.125.955 casos da dengue contra 223.227 em 2014. No estado de Sergipe, neste mesmo período, houve um aumento de 47,7% dos casos (PIMENTA, 2005; Ministério da Saúde, Boletim epidemiológico, nº 18. 2015; Portal da saude. Ministério da saude, 2015 (*acessado em 19/07/2015*)).

A incidência crescente e amplo alcance geográfico da dengue fazem com que o desenvolvimento de uma vacina eficaz contra essa doença seja considerado uma prioridade de saúde internacional (REITER, 2010).

Com esse intuito, os laboratórios acadêmicos e as empresas farmacêuticas têm desenvolvido diversas vacinas candidatas contra a dengue, utilizando diferentes tecnologias, como, por exemplo, vacinas contendo vírus vivos atenuados; vetores virais recombinantes que expressam os antígenos do

envelope (E) do vírus da dengue; proteínas recombinantes; e vacinas de DNA (RAVIPRAKASH, 2009; WHITEHEAD, 2007).

Entretanto, até o presente, nenhuma vacina contra a dengue foi registrada. A vacina candidata desenvolvida pela Sanofi Pasteur é uma vacina tetravalente que contém vírus recombinantes atenuados e que tem como base a cepa da vacina 17D contra a febre amarela (YF17D). Esta vacina candidata contra a dengue é imunogênica e segura em humanos e vem sendo avaliada em estudos de eficácia de larga escala (GUY *et al*., 2011).

Como ainda não existe uma vacina validada, a prevenção consiste em dois fatores básicos: controle vetorial e implementação de bons sistemas de vigilância. O controle vetorial é muito importante, consistindo, principalmente, na eliminação de criadouros naturais e artificiais dos mosquitos, além da aplicação de inseticidas, tanto para as larvas quanto para os adultos (LIGON, 2005).

Nesse sentido, vários inseticidas sintéticos têm sido utilizados ao longo dos anos no combate ao vetor, no entanto, a crescente resistência dos mosquitos a estes inseticidas tem motivado um grande interesse em utilizar novas fontes com poder larvicida (BRAGA *et al*., 2004).

Uma das classes de inseticidas mais utilizadas é a dos organofosforados. Os organofosforados inibem irreversivelmente a enzima acetilcolinesterase, que é importante na transmissão colinérgica no sistema nervoso central do mosquito e na regulação dos níveis de acetilcolina, um neurotransmissor (BOURGUET *et al*., 1997). A inibição ocorre devido a uma ligação estável estabelecida entre um grupo hidroxila do sítio ativo da enzima com o átomo de fósforo desses compostos. A fosforilação da serina presente no sítio ativo leva a um acúmulo de acetilcolina, causando uma hiperestimulação colinérgica nos insetos com consequente hiperexcitabilidade, tremores, paralisia e morte (OZMEN *et al*., 1999).

O uso disseminado dessas substâncias químicas inseticidas levou à ocorrência de resistência de populações de *Ae. aegypti* em todos estados brasileiros (LIMA *et al*., 2003; MACORIS, 2003; BRAGA *et al*., 2004), assim como em outros países, por exemplo, Panamá e Cuba (BISSET *et al*., 2003; RODRIGUEZ *et al*., 2004).

Além disso, a utilização indiscriminada de inseticidas sintéticos tem contaminado o meio ambiente e os organismos vivos (TAUIL, 2008; SANTIAGO *et al*., 2005), como é o caso dos piretróides, que já foi verificada neurotoxicidade em mamíferos após exposições agudas ou subcrônicas, fazendo-se necessário, portanto, o desenvolvimento de produtos com menos impacto ambiental e melhores benefícios a saúde humana.

A triptamina é encontrada em quantidades de traços nos cérebros de mamíferos e tal presença é atribuída a um papel como um neurotransmissor (JONES, 1982). Na via de metabolismo do triptofano, a qual é considerada uma importante via de desintoxicação em mosquitos, especialmente durante as fases larvais, os principais compostos são a quinurenina e 3-hidroxi-quinurenina (3-HK). No entanto, 3-HK é oxidada facilmente sob condições fisiológicas, o que resulta na produção de espécies reativas de oxigênio (HAN *et al*., 2007). Para superar este problema, os mosquitos desenvolveram um eficiente mecanismo para evitar o acumulo de 3-HK, convertendo este composto reativo em um ácido quimicamente estável, ácido xanturênico. Interessantemente, o 3-HK é um precursor para a produção de pigmentos dos olhos durante as fases de pupa e adulto, consequentemente, os mosquitos têm a necessidade de preservar e transportar 3-HK para pigmentação dos olhos nesse estágio (LI *et al*., 1999).

Muitos trabalhos confirmam a necessidade de proteínas para a produção de ovos nos mosquitos. Estudos indicam a necessidade de pelo menos dez aminoácidos essenciais na dieta para que ocorra a produção normal de ovos: arginina, isoleucina, leucina, lisina, fenilalanina, treonina, triptofano, valina, histidina e metionina (LEIPNITZ, 2006).

Com base em uma possível inibição da via de metabolismo do triptofano, o qual tem como análogo a triptamina, motivo pelo qual o presente trabalho teve o interesse de sintetizar derivados da triptamina e determinar a atividade larvicida frente às larvas de *Ae. Aegypti*, visando identificar as características estruturais que contribuem para o efeito larvicida destes análogos. A relevância deste trabalho é maior devido ao fato de que, até a presente data, nenhum composto foi sintetizado com o objetivo de inibir a via do metabolismo do triptofano.

Adicionalmente, alguns dos compostos sintetizados possuem atividades biológicas importantes, amplamente descritas na literatura, pode-se citar: antimalárica, bactericida, leishmanicida, antiinflamatória e larvicida (ANDRADE, 2005; PEREIRA *et al*., 2007).

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# Synthesis, Activity, and QSAR Studies of Tryptamine Derivatives on Third-instar Larvae of *Aedes Aegypti* Linn

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**Abstract:** Special attention has been given to the mosquito *Aedes aegypti* Linn. (Diptera: Culicidae) owing to numerous dengue epidemic outbreaks worldwide. Failure to control vector spreading is accounted for unorganized urban growth and resistance to larvicides and insecticides. Therefore, researchers are currently searching for new and more efficient larvicides and insecticides to aid dengue control measures. Triptamine is known to affect insect behavior, development, and physiology. Expression of this compound in plants has reduced the growth rate of herbivore insects. In view of these facts, it was of our interest to synthesize triptamine amide derivatives as potential larvicides against *Ae. aegypti*, establishing a Structure-Activity Relationship. Eleven amide derivatives of triptamine were synthesized, characterized, and evaluated for their larvicidal activity against third-instar *Ae. aegypti* larvae. *N*-(2-(1*H*-indol-3-yl)ethyl)-2,2,2-trichloroacetamide exhibited the highest overall larvicidal potency, while *N*-(2-(1*H*-Indol-3-yl)ethyl) acetamide displayed the lowest larvicidal potency. A regression equation correlating the larvicidal activity with Log P was obtained. We have found a clear relationship between the larvicidal activity of non-chlorinated compounds and Log P. Analysis of the relationship between Log P and larvicidal activity against *Ae. aegypti* may be useful in the evaluation of potential larvicidal compounds.

**Keywords:** QSAR, tryptamine derivatives, *Aedes aegypti*, larvicidal activity, dengue, neglected diseases.

## INTRODUCTION

Numerous diseases are transmitted by insects. Warm and humid tropical regions provide suitable climate conditions to disseminate disease vectors and spread insect transmitted diseases. Although vector control actions are being accomplished by government agencies, some diseases, such as malaria, Chagas disease, and filariasis, case burdens are still high [1]. Dengue fever is an example of vector control measures failure. Larvicides, such as the organophosphate temephos, insect growth regulators (*i.e.* pyriproxyfen, novaluron, and methoprene), and bacterial toxins (*i.e.* Bti) have been used in breeding sites [2]. However, disordered urban growth provides hidden breeding sites which are suitable for mosquito growth.

Currently, larvicidal agents act by three specific mechanisms, organophosphates, such as temephos act in the central nervous system, irreversibly inhibiting acetylcholinesterase, therefore causing cholinergic hyperstimulation, followed by hyperexcitability, convulsion, paralysis, and death [3]. Conversely, insect growth regulators act by either interfering with hormonal regulation [4] or inhibiting chitin synthesis [5]. Additionally, pro-toxins from bacteria (*e.g. Bacillus thuringiensis*, Bti) are activated by larvae digestive proteases, promoting peristaltic reduction, declined feeding and death [6]. However, resistance, resulted by indiscriminate use of larvicides and insecticides has spread the dengue fever vector, *Aedes aegypti* Linn. Linn. (Diptera: Culicidae), over 100 countries worldwide. An estimated 50-100 million dengue infections occur worldwide every year [7]. As a response to this global threat, researchers are currently searching for new and more effective larvicides and insecticides to aid dengue control measures. The search for novel larvicides and insecticides acting by different mechanisms than the previously mentioned ones may give support to control programs in reducing resistance rates, consequently reducing mosquito infestation and disease spread.

Examples of compounds acting in different targets are found in the literature. For example, aryl triazines, possibly acting at voltage-gated calcium channels, with activity against *Ae. aegypti* larvae have been proposed by the development of insecticide lead compounds using an *ab initio* pharmacophore mimic approach [8]. Plant products and their derivatives have been screened with the goal to find novel larvicides and insecticides [9-11]. Various classes of organotin compounds displaying high insecticidal and larvicidal activities have been synthesized and tested against *Ae. aegypti* [12-14].

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Tryptophan metabolism in *Ae. aegypti* is an important pathway for the synthesis of ommochromes (eye pigments in some insects) and detoxification of reactive oxygen species [15]. Additionally, it synthesizes neurotransmitters, such as tryptamine. Tryptamine is a phenyl alkyl amine, which may affect insect behavior, development, and physiology [16]. In insects, this indole alkaloid is biosynthesized by the decarboxylation of tryptophan *via* a tryptophan decarboxylase and function as precursor to many biologically endogenic compounds with a wide range of physiological roles. Additionally, tryptamine derivatives are present in many plants with high alkaloid content and are known to influence insect feeding and reproduction. Elevated levels of tryptamine expressed in transgenic poplar and tobacco plants are capable of reducing the growth rate of the herbivore insects forest tent caterpillar moth (*Malacosoma disstria* Hbn.) and tobacco hornworm (*Manduca sexta* L.) by reducing the feeding behaviors, which result in reduced growth rate of insects fed by this plant, due to lower conversion of digested food to body tissues, suggesting some form of chronic toxicity [17]. When tryptophan decarboxylase is expressed in plants, tryptamine is produced as a result of the decarboxylation of tryptophan discouraging insect reproduction upon these plants [18]. Moreover, this compound and possibly its derivatives may act as inhibitors of larval and pupal development [19].

Besides insect-related activities, tryptamine derivatives are known to have a variety of biological effects which include antifungal [20], $\alpha_2$-blocker for the treatment of erectile dysfunction [21], against human breast-cancer cell line MCF-7, against insect hemocytes from the greater wax moth *Galleria melonella* [22], and in addition act as melatonin receptor ligands [23].

In previous unpublished screenings, tryptamine exhibited moderate larvicidal activity against *Ae. aegypti*. In view of these facts, this study aims to obtain tryptamine amide derivatives and evaluate their median lethal concentration ($LC_{50}$) against *Ae. aegypti* larvae.

## MATERIALS AND METHODS

### Synthesis

#### *General*

Melting points were determined on a Logen Scientific melting point apparatus and are uncorrected. NMR spectra were recorded on an Avance Bruker DRX-400 spectrometer operating at 400 MHz for $^1$H NMR and at 100 MHz for $^{13}$C NMR, using $CDCl_3$ as solvent, and the chemical shifts are reported in ppm ($\delta$) relative to TMS. Coupling constants ($J$) are reported in hertz (Hz). The abbreviations used are *s* (singlet), *brs* (broad singlet), *d* (doublet), *t* (triplet), *dpt* (doublet of pseudo-triplet), *pq* (pseudo-quartet), *m* (multiplet), and *sep* (septet). FT-IR spectra were recorded on a Perkin Elmer Spectrum BX FT-IR system in KBr disks. Mass spectra were recorded on a Bruker micrOTOF II - ESI-TOF mass spectrometer. Column chromatography was carried out at atmospheric pressure using Silica Gel 60 (Sigma Aldrich) using mixtures of dichloromethane/methanol as eluent. Solvents used in the reactions were anhydrous.

#### *General Procedure for the Synthesis of Tryptamides [21]*

To a stirred suspension of tryptamine **1** (1.0 g, 3.83 mmol) in $CH_2Cl_2$ (15 mL), a solution of acetic anhydride or acid chloride (4 mmol) and triethylamine (1.7 mL, 12.46 mmol) in $CH_2Cl_2$ (3.5 mL) was added dropwise. After 2 h stirring at room temperature, the reaction mixture was treated with saturated aqueous $NaHCO_3$ solution. The organic layer was separated and the aqueous layer extracted with $CH_2Cl_2$. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Purification by column chromatography using $CH_2Cl_2$:$CH_3OH$ (98:2) afforded amides **2** to **12**.

***N-[2-(1H-indol-3-yl)ethyl] Acetamide (2)***

Light brownish powder, (74%). mp 123-125°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.68 (*brs*, 1H, Ar-NH, $D_2O$ exch.), 7.56 (*d*, 1H, $J$ = 7.9 Hz, Ar-H), 7.33 (*d*, 1H, $J$ = 8.1 Hz, Ar-H), 7.17 (*dpt*, 1H, $J$ = 7.1, 1.0 Hz, Ar-H), 7.09 (*dpt*, 1H, $J$ = 7.0, 1.0 Hz, Ar-H), 6.95 (*d*, 1H, $J$ = 1.5 Hz, C=CH), 5.79 (*brs*, 1H, NH-CO, $D_2O$ exch.), 3.54 (*pq*, 2H, $J$ = 6.7 Hz, $CH_2$-N), 2.93 (*t*, 2H, $J$ = 6.8 Hz, Ar-$CH_2$), 1.87 (*s*, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.4, 136.4, 127.2, 122.2, 122.0, 119.2, 118.5, 112.5, 111.4, 39.9, 25.2, 23.3. IR (KBr, $cm^{-1}$) 3260 (N-H), 1636 (C=O). MS (ESI) *m/z* 203 $[M+H]^+$, 225 $[M+Na]^+$.

***N-[2-(1H-indol-3-yl)ethyl] Propanamide (3)***

Light brownish crystals, (96%). mp 84-87°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.60 (*brs*, 1H, Ar-NH, $D_2O$ Exch.), 7.58 (*d*, 1H, $J$ = 8.1 Hz, Ar-H), 7.35 (*d*, 1H, $J$ = 8.1 Hz, Ar-H), 7.18 (*dpt*, 1H, $J$ = 7.1, 1.0 Hz, Ar-H), 7.09 (*dpt*, 1H, $J$ = 8.0, 1.0 Hz, Ar-H), 6.97 (*d*, 1H, $J$ = 2.2 Hz, C=CH), 5.67 (*brs*, 1H, NH-CO, $D_2O$ Exch.), 3.57 (*pq*, 2H, $J$ = 6.7 Hz, $CH_2$-N), 2.94 (*t*, 2H, $J$ = 6.8 Hz, Ar-$CH_2$), 2.11 (*q*, 2H, $J$ = 7.6 Hz, CO-$CH_2$), 1.09 (*t*, 3H, $J$ = 7.6 Hz, $CH_3$). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.0, 136.4, 127.3, 122.1, 122.0, 119.3, 118.6, 112.7, 111.3, 39.8, 29.7, 25.3, 9.9. IR (KBr, $cm^{-1}$) 3398 (NH), 1636 (C=O). MS (ESI) *m/z* 217 $[M+H]^+$, 239 $[M+Na]^+$.

***N-[2-(1H-indol-3-yl)ethyl] Butanamide (4)***

Light brownish crystals, (64%). mp 67-70°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.56 (*brs*, 1H, Ar-NH, $D_2O$ Exch.), 7.58 (*d*, 1H, $J$ = 7.8 Hz, Ar-H), 7.35 (*d*, 1H, $J$ = 8.1 Hz, Ar-H), 7.18 (*dpt*, 1H, $J$ = 7.1, 0.8 Hz, Ar-H), 7.10 (*dpt*, 1H, $J$ = 7.7, 0.5 Hz, Ar-H), 6.97 (*d*, 1H, $J$ = 1.8 Hz, C=CH), 5.65 (*brs*, 1H, NH-CO, $D_2O$ Exch.), 3.58 (*pq*, 2H, $J$ = 6.6 Hz, $CH_2$-N), 2.95 (*t*, 2H, $J$ = 6.8 Hz, Ar-$CH_2$), 2.06 (*t*, 2H, $J$ = 7.4 Hz, CO-$CH_2$), 1.65-1.56 (*m*, 2H, $CH_2$-$CH_3$), 0.89 (*t*, 3H, $J$ = 7.3 Hz, $CH_3$). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.1, 136.4, 127.3, 122.1, 122.0, 119.3, 118.6, 112.7, 111.3, 39.7, 38.7, 25.3, 19.1, 13.7. IR (KBr, $cm^{-1}$) 3270 (N-H), 1630 (C=O). MS (ESI) *m/z* 231 $[M+H]^+$, 253 $[M+Na]^+$.

***N-[2-(1H-indol-3-yl)ethyl]-2-methyl-propanamide (5)***

Light brownish crystals, (78%). mp 64-68°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.53 (*brs*, 1H, Ar-NH, $D_2O$ Exch.), 7.59 (*d*, 1H, $J$ = 7.8 Hz, Ar-H), 7.36 ( *d*, 1H, $J$ = 8.1 Hz, Ar-H), 7.19 (*dpt*, 1H, $J$ = 7.0, 1.0 Hz, Ar-H), 7.10 (*dpt*, 1H, $J$ = 7.1, 1.0 Hz, Ar-H), 6.98 (*d*, 1H, $J$ = 2.3 Hz, C=CH), 5.63 (*brs*, 1H, NH-CO, $D_2O$ Exch.), 3.58 (*pq*, 2H, $J$ = 6.7 Hz,

$CH_2$-N), 2.95 (*t*, 2H, *J* = 6.1 Hz, Ar-$CH_2$), 2.48 (*sep*, 1H, *J* = 6.9 Hz, CO-CH), 1.09 (*d*, 6H, *J* = 6.9 Hz, $(CH_3)_2$). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 177.1, 136.4, 127.3, 122.1, 122.0, 119.3, 118.6, 112.7, 111.3, 39.6, 35.6, 25.3, 19.6. IR (KBr, $cm^{-1}$) 3282 (N-H), 1616 (C=O). MS (ESI) *m/z* 231 $[M+H]^+$, 253 $[M+Na]^+$.

***N-[2-(1H-indol-3-yl)ethyl] Pentanamide (6)***

Light brownish crystals, (68%). mp 73-75°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.55 (*brs*, 1H, Ar-NH, $D_2O$ Exch.), 7.58 (*d*, 1H, *J* = 7.8 Hz, Ar-H), 7.35 (*d*, 1H, *J* = 8.1 Hz, Ar-H), 7.18 (*dpt*, 1H, *J* = 8.0, 1.1 Hz, Ar-H), 7.10 (*dpt*, 1H, *J* = 8.0, 0.9 Hz, Ar-H), 6.97 (*d*, 1H, *J* = 2.3 Hz, C=CH), 5.64 (*brs*, 1H, NH-CO, $D_2O$ Exch.), 3.58 (*pq*, 2H, *J* = 6.7 Hz, $CH_2$-N), 2.95 (*t*, 2H, *J* = 6.8 Hz, Ar-$CH_2$), 2.09 (*t*, 2H, *J* = 7.5 Hz, CO-$CH_2$), 1.59-1.52 (*m*, 2H, $CH_2$-$CH_2$-$CH_3$), 1.33-1.24 (*m*, 2H, $CH_2$-$CH_2$-$CH_3$), 0.87 (*t*, 3H, *J* = 7.4 Hz, $CH_3$). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.3, 136.4, 127.3, 122.1, 122.0, 119.3, 118.6, 112.7, 111.3, 39.7, 36.5, 27.8, 25.3, 22.3, 13.8. IR (KBr, $cm^{-1}$) 3256 (N-H), 1634 (C=O). MS (ESI) *m/z* 245 $[M+H]^+$, 267 $[M+Na]^+$.

***N-[2-(1H-indol-3-yl)ethyl]-3-methyl-butanamide (7)***

White crystals, (63%). mp 103-106°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.50 (*brs*, 1H, Ar-NH, $D_2O$ Exch.), 7.59 (*d*, 1H, *J* = 7.8 Hz, Ar-H), 7.36 (*d*, 1H, *J* = 8.1 Hz, Ar-H), 7.19 (*dpt*, 1H, *J* = 8.0, 1.0 Hz, Ar-H), 7.10 (*dpt*, 1H, *J* = 7.9, 0.9 Hz, Ar-H), 6.98 (*d*, 1H, *J* = 2.2 Hz, C=CH), 5.61 (*brs*, 1H, NH-CO, $D_2O$ Exch.), 3.59 (*pq*, 2H, *J* = 6.7 Hz, $CH_2$-N), 2.95 (*t*, 2H, *J* = 6.7 Hz, Ar-$CH_2$), 2.13-2.01 (*m*, 1H, CH-$(CH_3)_2$), 1.95 (*d*, 2H, *J* = 7.2 Hz, CO-$CH_2$), 0.90 (*d*, 6H, *J* = 6.6 Hz, $(CH_3)_2$). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.6, 136.4, 127.3, 122.1, 122.0, 119.3, 118.6, 112.7, 111.3, 46.2, 39.6, 26.1, 25.4, 22.4. IR (KBr, $cm^{-1}$) 3258 (N-H), 1618 (C=O). MS (ESI) *m/z* 245 $[M+H]^+$, 267 $[M+Na]^+$.

***N-[2-(1H-indol-3-yl)ethyl] Hexanamide (8)***

Light brownish crystals, (62%). mp 83-86°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.55 (*brs*, 1H, Ar-NH, $D_2O$ Exch.), 7.58 (*d*, 1H, *J* = 7.8 Hz, Ar-H), 7.35 (*d*, 1H, *J* = 8.1 Hz, Ar-H), 7.18 (*dpt*, 1H, *J* = 8.1, 1.0 Hz, Ar-H), 7.10 (*dpt*, 1H, *J* = 7.9, 0.9 Hz, Ar-H), 6.98 (*d*, 1H, *J* = 2.1 Hz, C=CH), 5.65 (*brs*, 1H, NH-CO, $D_2O$ Exch.), 3.58 (*pq*, 2H, *J* = 6.6 Hz, $CH_2$-N), 2.95 (*t*, 2H, *J* = 6.7 Hz, Ar-$CH_2$), 2.08 (*t*, 2H, *J* = 7.5 Hz, CO-$CH_2$), 1.61-1.53 (*m*, 2H, CO-$CH_2$-$CH_2$), 1.32-1.19 (*m*, 4H, $CH_2$-$CH_2$-$CH_3$), 0.86 (*t*, 3H, *J* = 7.1 Hz, $CH_3$). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.3, 136.4, 127.3, 122.1, 122.0, 119.3, 118.6, 112.7, 111.3, 39.7, 36.8, 31.4, 25.4, 25.3, 22.4, 13.9. IR (KBr, $cm^{-1}$) 3248 (N-H), 1632 (C=O). MS (ESI) *m/z* 259 $[M+H]^+$, 281 $[M+Na]^+$.

***2-chloro-N-[2-(1H-indol-3-yl)ethyl] Acetamide (9)***

Light brownish crystals, (70%). mp 67-70°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.28 (*brs*, 1H, Ar-NH, $D_2O$ Exch.), 7.60 (*d*, 1H, *J* = 7.8 Hz, Ar-H), 7.36 (*d*, 1H, *J* = 8.1 Hz, Ar-H), 7.21 (*dpt*, 1H, *J* = 7.1, 1.0 Hz, Ar-H), 7.13 (*dpt*, 1H, *J* = 7.9, 0.9 Hz, Ar-H), 7.01 (*d*, 1H, *J* = 2.2 Hz, C=CH), 6.69 (*brs*, 1H, NH-CO, $D_2O$ Exch.), 3.99 (*s*, 2H, $CH_2Cl$), 3.62 (*pq*, 2H, *J* = 6.7 Hz, $CH_2$-N), 3.00 (*t*, 2H, *J* = 6.8 Hz, Ar-$CH_2$). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.9, 136.4, 127.1, 122.2, 122.1, 119.5, 118.6, 112.3, 111.3, 42.7, 40.0, 25.0. IR (KBr, $cm^{-1}$) 3306 (N-H), 1638 (C=O). MS (ESI) *m/z* 238 $[M+H]^+$, 240 $[M+H+2]^+$, 259 $[M+Na]^+$, 261 $[M+Na+2]^+$.

***N-[2-(1H-indol-3-yl)ethyl]-2,2-dimethyl-propanamide (10)***

Light brownish crystals, (80%). mp 134-136°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.58 (*brs*, 1H, Ar-NH, $D_2O$ Exch.), 7.61 (*d*, 1H, *J* = 7.9 Hz, Ar-H), 7.36 (*d*, 1H, *J* = 8.1 Hz, Ar-H), 7.19 (*dpt*, *J* = 7.1, 1.1 Hz, Ar-H), 7.11 (*dpt*, *J* = 7.9, 1.0 Hz, Ar-H), 6.98 (*d*, 1H, *J* = 2.2 Hz, C=CH), 5.79 (*brs*, 1H, NH-CO, $D_2O$ Exch.), 3.57 (*pq*, 2H, *J* = 6.7 Hz, $CH_2$-N), 2.96 (*t*, 2H, *J* = 6.8 Hz, Ar-$CH_2$), 1.12 (*s*, 9H $C(CH_3)_3$). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 178.5, 136.4, 127.3, 122.1, 122.0, 119.3, 118.6, 112.8, 111.3, 39.8, 38.6, 27.5, 25.2. IR (KBr, $cm^{-1}$) 3286 (N-H), 1638 (C=O). MS (ESI) *m/z* 245 $[M+H]^+$, 267 $[M+Na]^+$.

***N-[2-(1H-indol-3-yl)ethyl] Heptanamide (11)***

Brownish crystals, (74%). mp 86-89°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.49 (*brs*, 1H, Ar-NH, $D_2O$ Exch.), 7.58 (*d*, 1H, *J* = 7.9 Hz, Ar-H), 7.36 (*d*, 1H, *J* = 8.1 Hz, Ar-H), 7.19 (*dpt*, 1H, *J* = 7.1, 0.9 Hz, Ar-H), 7.10 (*dpt*, 1H, *J* = 7.1, 0.8 Hz, Ar-H), 6.98 (*d*, 1H, *J* = 2.1 Hz, C=CH), 5.64 (*brs*, 1H, NH-CO, $D_2O$ Exch.), 3.58 (*pq*, 2H, *J* = 6.7 Hz, $CH_2$-N), 2.95 (*t*, 2H, *J* = 6.8 Hz, Ar-$CH_2$), 2.09 (*t*, 2H, *J* = 7.5 Hz, CO-$CH_2$), 1.64-1.53 (*m*, 2H, CO-$CH_2$-$CH_2$), 1.30-1.21 (*m*, 6H, $CH_2$-$CH_2$-$CH_2$-$CH_3$), 0.86 (*q*, 3H, *J* = 7.0 Hz, $CH_3$). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.4, 136.4, 127.3, 122.1, 122.0, 119.3, 118.6, 112.8, 111.3, 39.7, 36.8, 31.5, 28.9, 25.7, 25.3, 22.5, 14.0. IR (KBr, $cm^{-1}$) 3256 (N-H), 1630 (C=O). MS (ESI) *m/z* 273 $[M+H]^+$, 295 $[M+Na]^+$.

***2,2,2-trichloro-N-[2-(1H-indol-3-yl)ethyl] Acetamide (12)***

Light brownish crystals, (48%). mp 95-98°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.20 (*brs*, 1H, Ar-NH, $D_2O$ Exch.), 7.62 (*d*, 1H, *J* = 7.9 Hz, Ar-H), 7.38 (*d*, 1H, *J* = 8.1 Hz, Ar-H), 7.22 (*dpt*, 1H, *J* = 8.0, 1.0 Hz, Ar-H), 7.14 (*dpt*, 1H, *J* = 8.0, 1.0 Hz, Ar-H), 7.05 (*d*, 1H, *J* = 2.3 Hz, C=CH), 6.82 (*brs*, 1H, NH-CO, $D_2O$ Exch.), 3.68 (*pq*, 2H, *J* = 6.6 Hz, $CH_2$-N), 3.07 (*t*, 2H, *J* = 6.7 Hz, Ar-$CH_2$). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.9, 136.4, 126.9, 122.4, 122.3, 119.6, 118.5, 111.8, 111.4, 92.6, 41.6, 24.6. IR (KBr, $cm^{-1}$) 3318 (N-H), 1670 (C=O). MS (ESI) *m/z* 304 $[M+H]^+$, 305 $[M+H+2]^+$, 308 $[M+H+4]^+$, 310 $[M+H+6]^+$, 327 $[M+Na]^+$, 329 $[M+Na+2]^+$, 331 $[M+Na+4]^+$, 333 $[M+Na+6]^+$.

**Larvicidal Activity**

Larvicidal assays were performed according to an adapted World Health Organization procedure [24, 25]. In summary, 20,000 ppm stock solutions were prepared using each compound, Tween-80 (10% v/v), DMSO (30% v/v), and dechlorinated water (60% v/v). The stock solution was used to make 20 mL water solutions ranging from 10 to 1000 ppm (three replicates). A mortality count was conducted 24 h after the treatment. Controls were prepared with Tween-80, DMSO, and water at the highest concentration used in each experiment. Concentration ranges were determined by a previous curve concentration-response with 20 third-instar larvae. The organophosphate temephos, a standard insecticide for larvae control, was used as positive control.

### Statistics

Probit analysis [26] was conducted on mortality data collected after 24 h exposure to different concentrations of testing solutions to establish the median lethal concentration ($LC_{50}$) and 95% confidence intervals (CI) values for the respective compounds. $LC_{50}$ is reported in ppm and was converted to molar for use in the regression analysis described in the QSAR section. In all cases where deaths had occurred in the control experiment, the data was corrected using Abbott's [27] formula (%Deaths = [1-(test/control)] × 100). Compound's activity is considered significantly different when the 95% CI fails to overlap.

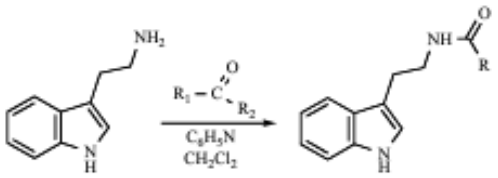
### QSAR

Hydrophobic and topological descriptors were generated utilizing the GAMESS [28] program for Chemoffice™. The selection of log P for the correlation studies was made based on permutation and correlation matrices among the descriptors to avoid collinearity issues. Regression analysis was performed to obtain QSAR equation, square of the correlation coefficient ($r^2$), and the standard deviation ($s$) by utilizing Minitab™ statistical software package. The quality ratio $Q$ was obtained by the formula: $Q = r / s$. The Fischer ratio, $F$ was calculated using the following formula: $F = fr^2 / [(1-r^2)m]$, where $f$ is the number of degrees of freedom, $f = n-(m+1)$, $n$ is the number compounds, and $m$ is the number of descriptors. The cross-validated $r^2$ ($q^2$) was obtained by using the leave-one-out (LOO) procedure according to Cramer *et al.* [29].

## RESULTS AND DISCUSSION

### Synthesis

The syntheses of tryptamine acyl amides derivatives were accomplished by treatment of the corresponding amine with acetic anhydride or acyl chloride in the presence of triethylamine and dichloromethane as summarized in (Scheme **1**). Yields for the acylation reactions ranged from 48% for the trichloroacetyl derivative (**12**) to 96% for the propionyl derivative (**3**). All compounds are known and their spectroscopic data are reported in the literature [21, 22, 30-34].




| | |
|---|---|
| $R_1 = CH_3$ (**2**) | $R_2 = OCOCH_3$ |
| $R_1 = CH_2CH_3$ (**3**) | $R_2 = Cl$ |
| $R_1 = (CH_2)_2CH_3$ (**4**) | $R_2 = Cl$ |
| $R_1 = CH(CH_3)_2$ (**5**) | $R_2 = Cl$ |
| $R_1 = (CH_2)_3CH_3$ (**6**) | $R_2 = Cl$ |
| $R_1 = CH_2CH(CH_3)_2$ (**7**) | $R_2 = Cl$ |
| $R_1 = (CH_2)_4CH_3$ (**8**) | $R_2 = Cl$ |
| $R_1 = CH_2Cl$ (**9**) | $R_2 = Cl$ |
| $R_1 = C(CH_3)_3$ (**10**) | $R_2 = Cl$ |
| $R_1 = (CH_2)_5CH_3$ (**11**) | $R_2 = Cl$ |
| $R_1 = C(Cl)_3$ (**12**) | $R_2 = Cl$ |

**Scheme 1.** Synthesis of triptamine derivatives.

The synthesized compounds were characterized by $^1H$ and $^{13}C$ NMR, IR, Mass Spectrometry and melting point. The broad singlet signals observed in the $^1H$ NMR spectra around δ 8.3 ppm represent the NH pyrrole protons, while the broad singlet signals around δ 5.6 ppm (δ 6.7 ppm for chlorinated compounds) represent the NH proton at the amide. This clearly signifies that the acyl group was attached to the alicyclic nitrogen by replacing one of the two $NH_2$ protons as previously reported [21, 22, 30-34]. Similarly, two doublet signals in the region δ 7.62 - 7.33 ppm, correspond to the presence of two aromatic protons of the benzene ring at $C_4$ and $C_7$. Additionally, two doublets of pseudo-triplet peaks in the region δ 7.22 - 7.09 ppm correspond to the remaining benzene ring protons at $C_5$ and $C_6$. The presence of the pyrrole ring in the obtained compounds was further confirmed by doublets around δ 7.00 ppm showing long range coupling of about 2.2 Hz. The ethyl group of tripamine was confirmed by the presence of two proton signals around δ 3.60 and 3.00 ppm as pseudo-quartets and triplets, respectively. Acyl proton signals were observed ranging from δ 3.99 to δ 0.86 ppm.

The singlet signal for $COCH_3$ of compound **2** was observed at δ 1.87 ppm. Astolfi *et al.* [30] reported the $COCH_3$ as a singlet signal of *N*-acetyltryptamine at δ 1.91 ppm. In compound **3**, a quadruplet at δ 2.11 ppm and a triplet at δ 1.09 ppm having integrals of two and three protons, respectively, revealed the presence of a propionyl group. Similar data were reported by Yamada *et al.* [21], describing a quartet at δ 2.14 ppm and a triplet at δ 1.11 ppm. The acyl group of compound **4** was confirmed by the presence of two signals, each having integrals of two protons and one peak having integral of three protons at δ 2.06 ppm (triplet), δ 1.65 - 1.56 ppm (multiplet), and δ 0.89 ppm (triplet), respectively.

The appearance of four signals of the linear amide chain methylene and methyl groups of compounds **6** and **8** at about δ 2.08 ppm (triplets having integrals of two protons), δ 1.61 - 1.52 ppm (multiplets having integrals of two protons), δ 1.33 - 1.19 ppm (multiplets having integrals of two and four protons, respectively), and δ 0.86 ppm (triplets having integrals of three protons) further confirms that the pentanoyl and hexanoyl groups are attached at the alicyclic amine of triptamine. Methylene and methyl protons of long acyl chain compounds, such as in **8** and **11** appeared in the range of δ 2.09 to 0.86 ppm as triplets, quadruplets, or multiplets often superposed exhibiting integrals of two, three, four, or six protons.

The structures of compounds **5** and **7** were confirmed by the presence of the $(CH_3)_2$ equivalent proton signals at approximately δ 1.00 ppm as doublets having integrals of six protons. Additionally, compound **5** exhibited one septet signal having integral of one proton at δ 2.48 ppm and compound **7** exhibited one multiplet at δ 2.13-2.01 ppm, as well as, one doublet at δ 1.95 ppm, each having integrals of one and two protons, respectively.

The singlet at δ 3.99 ppm signal corresponding to the $COCH_2Cl$ confirmed the effective synthesis of compound **9**. Similarly, a typical singlet signal at δ 1.12 ppm with integral of nine protons corroborates the successful synthesis of compound **10**.

**Table 1. Lethal concentration for 50% mortality ($LC_{50}$) and 95% confidence intervals (CI) values (expressed in ppm and Log $1/CL_{50}$ molar) and calculated Log P of tryptamine and its derivatives.**

| Compound | $LC_{50}$ (CI) ppm | Log $1/LC_{50}$ (CI) Molar | Log P* |
|---|---|---|---|
| **1** | 495.6 (477.5 to 513.8) | 2.51 (2.49 to 2.52) | 1.42 |
| **2** | 884.8 (791.2 to 984.3) | 2.35 (2.31 to 2.40) | 1.31 |
| **3** | 443.2 (413.7 to 473.4) | 2.68 (2.66 to 2.71) | 2.01 |
| **4** | 271.4 (257.4 to 286.2) | 2.93 (2.90 to 2.95) | 2.45 |
| **5** | 233.6 (217.0 to 250.3) | 2.99 (2.96 to 3.02) | 2.55 |
| **6** | 222.0 (207.6 to 237.1) | 3.04 (3.01 to 3.07) | 2.89 |
| **7** | 188.8 (171.7 to 207.7) | 3.11 (3.07 to 3.15) | 2.74 |
| **8** | 181.2 (163.1 to 200.9) | 3.15 (3.11 to 3.20) | 3.34 |
| **9** | 134.9 (128.7 to 141.2) | 3.24 (3.22 to 3.26) | 1.84 |
| **10** | 123.3 (117.2 to 129.8) | 3.30 (3.27 to 3.32) | 3.10 |
| **11** | 65.9 (54.2 to 77.8) | 3.61 (3.55 to 3.72) | 3.78 |
| **12** | 48.6 (45.9 to 51.3) | 3.79 (3.79 to 3.82) | 3.06 |

*Calculated using GAMESS.

Although compound **12** does not exhibit proton signals for the acyl group, its structure was confirmed by the presence of a $^{13}C$ NMR carbonyl signal at δ 161.9 ppm and a $CCl_3$ signal at δ 92.6 ppm in addition to typical carbonyl IR absorption at 1670 $cm^{-1}$.

$^{13}C$ NMR spectra of obtained compounds exhibit typical amide carbonyl signals around 178.5 - 161.9 ppm in addition to eight aromatic signals from δ 136.4 to 111.3 ppm and high field peaks ranging from δ 42.7 to 9.9 ppm corresponding to CH, $CH_2$, and $CH_3$ of the lateral amide chain.

The IR spectra of synthesized compounds revealed the presence of vibrational frequencies corresponding to a carbonyl functional group around 1630 - 1616 $cm^{-1}$ suggesting the presence of an acyl group.

Analysis of the mass spectra in the molecular ion region reveals the $[M+H]^+$ and $[M+Na]^+$ peaks for all compounds. Additionally, the chlorinated compound **9** displays the molecular ion peaks $[M+H+2]^+$ and $[M+Na+2]^+$. In addition to the previous peaks, compound **12** shows the molecular ion peaks $[M+H+4]^+$, $[M+H+6]^+$, $[M+Na+4]^+$, $[M+Na+6]^+$, which arise because of the various combinations of chlorine isotopes that are possible.

Spectroscopic data of the synthesized compounds are in accordance with data reported elsewhere [21, 22, 30-34]. In addition, long range coupling constants are visualized in the 400 MHz $^1H$ NMR.

### Larvicidal Activity

Synthesized compounds were evaluated for their biological activity as larvicidal agents against *Ae. aegypti* and the results are summarized in (Table **1**). Replacement of amine acidic proton resulting in amide derivatives was performed with the goal to examine the effects of amide groups in modulating tryptamine larvicidal activity. *N*-(2-(1*H*-indol-3-yl)ethyl)-2,2,2-trichloroacetamide (**12**) exhibited the highest overall larvicidal potency, with $LC_{50}$ of 48.6 ppm, while *N*-(2-(1*H*-Indol-3-yl)ethyl)acetamide (**2**) displayed the lowest larvicidal potency, $LC_{50}$ = 884.8 ppm. Chlorinated derivatives exhibited higher potency than non-chlorinated compounds, resulting in up to ten-fold increase in potency; such results are probably related to a different mode of action of chlorinated compounds. Apart from chlorinated compounds, increasing the number of methylene carbons in the amide hydrocarbon chain results in increased larvicidal potency, therefore hydrophobicity seems to be responsible for the observed enhancement in larvicidal activities. Previous studies suggested that hydrophobicity is important for *Ae. aegypti* larvae toxicity. For example, Cantrell *et al.* [10] found a relationship between *Ae. aegypti* larvicidal activity and the number of C-atoms in alantolactone, isoalantolactone, and their linear amine Michael addition reaction products. In view of these facts, a theoretical analysis was further conducted.

### QSAR STUDIES

An empirical analysis of the larvicidal activities described above led us to generate a regression plot of observed Log $1/CL_{50}$ *vs.* predicted Log $1/CL_{50}$ (Fig. **1**). (Fig. **1**) shows a clear relationship between larvicidal activity of non-chlorinated compounds and Log P. Therefore, the generated Eq. (1) is statistically not significant ($r^2$ = 0.657, s = 0.256, and $q^2$ = 0.521), probably due to the presence of the outlier compounds **9** (R = $OCOCH_2Cl$) and **12** (R = $OCOCCl_3$).

$$Log\ 1/LC_{50} = 1.94 + 0.44\ Log\ P$$

$$n = 12,\ r^2 = 0.657,\ s = 0.256,\ q^2 = 0.521,$$

$$Q = 3.166,\ F = 19.15 \qquad (1)$$

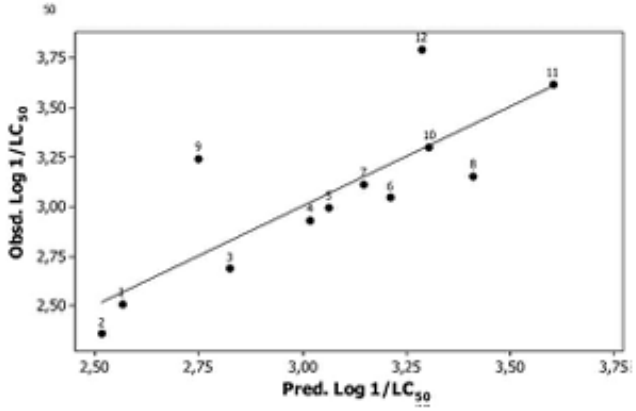



**Fig. (1).** Plot of observed larvicidal activity of tryptamine derivatives to *Aedes aegypti* versus activity predicted by Eq. (1).

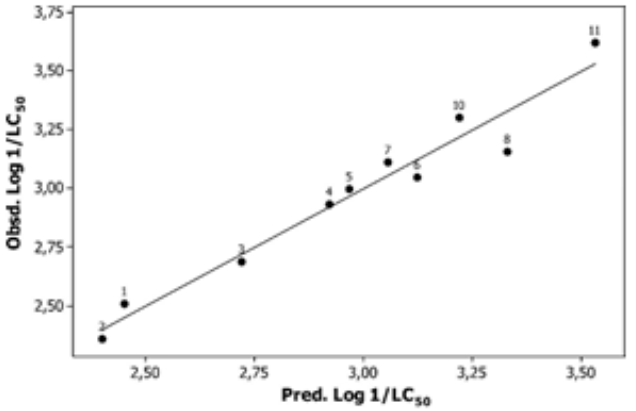



**Fig. (2).** Plot of observed larvicidal activity of tryptamine derivatives to *Aedes aegypti* versus activity predicted by Eq. (2).

where, $n$ is the number of molecules, $r^2$ is the square of the correlation coefficient between observed and calculated values and represents the goodness of fit, $s$ is the standard deviation, $q^2$ is the cross-validated $r^2$ (measures the quality of the QSAR model, improved QSAR models are obtained when $q^2 > 0.5$ and $r^2 > 0.8$), $Q = r/s$, and $F$ (Fischer ratio) is the ratio between explained and unexplained variance for a given number of degrees of freedom, high values of $Q$ and $F$ means high predictive QSAR power [14]. Although the value of $q^2 > 0.5$, the resulting equation has low squared correlation coefficient value, high standard deviation and small values of $Q$ and $F$, which indicate a low predictive power of the model.

The previous equation substantiates our findings for a different mechanism of action for the chlorinated derivatives. Therefore, two outlier compounds (**9** and **12**) were excluded from the derivation of Eq. (2). Removal of compounds **9** and **12** is attributable to their high deviation between the observed and predicted $LC_{50}$ of the compound, according to Eq. (1). The resulting equation, which is statistically significant ($r^2 = 0.951$, $s = 0.087$), describes appropriately the training set Eq. (2).

$$Log\ LC_{50} = 1.80 + 4.58\ Log\ P$$
$$n = 10,\ r^2 = 0.951,\ s = 0.087,\ q^2 = 0.915,$$
$$Q = 11.112,\ F = 155.37 \quad (2)$$

Furthermore, our analysis of $q^2$ demonstrates that the model may be used to predict larvicidal activity. High values of $Q$ and $F$ in Eq. (2), comparing with Eq. (1), show the high predictive power of the model. The goodness of fit of Eq. (2) is demonstrated in (Fig. **2**) by a plot of observed versus predicted activity.

Although our results demonstrate that a linear increase in the amide side-chain results in increased larvicidal activity, a comparison among linear side-chain compounds and compounds **9** ($LC_{50}$ = 134.9 ppm), **10** ($LC_{50}$ = 123.3 ppm), and **12** ($LC_{50}$ = 48.6 ppm) also indicate that bulky side-chain, such as compounds **10** and **12** or electron-rich groups in the amide side chain, such as the chlorinated compounds **9** and **12** increase the larvicidal activity. However, due to the limited number of bulky and electron-rich compounds, further studies are necessary to confirm these results.

## CONCLUSION

Our results indicate that an increase in the linear amide chain leads to increased larvicidal activity against *Ae. Aegypti*. The QSAR study supports a direct relationship between Log P and larvicidal activity, which corroborates with the previous finding. Additionally, electron-rich groups in the amide side chain may further increase the larvicidal potency. Analysis of the relationship between Log P and larvicidal activity against *Ae. aegypti* may serve as a useful influence to be considered in the evaluation of potential larvicidal compounds. However, due to the restricted number of compounds used in generating the QSAR analysis, care should be taken in its use.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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