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Design, synthesis, molecular dockingstudy andtoxicological evaluation potential of novel spiro and fused heterocyclic derivatives against agricultural insect pests

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Abstract

Reactions of 4'-(2-oxo-3-(thiophen-2-ylmethylene) furan-5-yl) acetanilide with amines, carbon nucleophiles and isatin, under various conditions provided a diversification of spiro-, fused- and heteocyclic deivatives. The constructions of the novelcomposites were distinguished by spectral data and elemental analysis. larvicidal activities of the synthesized compounds were examined against *Plutella xylostella* and *Helicoverpa armigera* larvae in vitro. The molecular docking simulationresults towards acetylcholinesterase of *Drosophila Melanogaster* demonstrated the role of the novel compounds as prominent larvicides.

Keywords: furanone; pyrrolone; spiroxyindoline; dihydropyridazine; Plutella xylostella; Helicoverpa armigera.

1. Introduction

Designer chemical insecticides have a major role in agricultural pest management,sustained application of thesepesticides has led to development of the insect pest resistance and environmental problems [1], which reduces the yields of control. Therefore, there is a quick need to develop safe, selective, and efficacious pesticides with structural efficacy and mode of operation [2]. The diamondback moth, Plutella xylostella L. (Lepidoptera: Plutellidae) and American bollworm, Helicoverpa armigera (Hübner) (Lepidoptera: Noctuidae are among the crucial pests of around the world [3,4]. They are among the most challenging pests to control, and they developed resistance to a wide range of synthetic insecticides. Therefore, it is of greatest importance to evolve novelinsecticidal molecules against these pests [5].

The furanone moiety is the structural feature of many biologically active analogues including anticancer activity [6-10], anti-inflammatory activity[11-14], pain-relieving activity [15-18], anti-fungal activity[19, 20], anti-asthmatic activity [21,22], antirheumatic activity[23,24], and neurodegenerative diseases like Alzheimer[25-28], antioxidant[29-31], and pesticidal activity [32, 33]. simultaneously time, many 2(5H)-furanone composites are important organic intermediates [34-41]. This work aims at closing that gap in awareness insecticidal agents on untargeted organisms are discussed in relation to the specific action mechanism of the drug compounds, in an attempt to illuminate why certain green insecticidal heterocyclic compounds are more pestilential for insects than another non-safe hydrocarbon for human.

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2. Experimental

All reported melting points were determined using digital AC/DC electric melting point apparatus, Stuart™ model SMP3 (Micro-analytical center, Ain Shams University, Cairo, Egypt) without additional correction. Elemental analyses were carried out by Vario Macro cube organic elemental. IR spectra (KBr) were registered using Nicolet Impact 400D FT-IR Spectrometer, Thermo Scientific, using OMNIC software and the recorded frequencies of absorption were with reference to cm^{-1}. ^{1}H-NMR spectra were reported via Bruker spectrophotometer, Rheinstetten, Germany at 400 MHz using TMS as internal standard and with residual signals of the deuterated solvent δ = 7.26 ppm ($CHCl_3$ residue) in $CDCl_3$ and δ 2.51 ppm for DMSO-d_6. ^{13}C-NMR spectra were recorded using the same spectrometer at 100 MHz and cited to solvent signals δ= 77 ppm for CDC_{l3} and δ 39.50 ppm for DMSO-d_6. The mass spectra were documented using Shimadzu GCMS-QP-1000 EX mass spectrometer; Kyoto, Japan using the electron ionization technique at 70 e.v. The consistency of all manufactured compounds was investigated by TLC. Commonmethodwas followed for synthesis furanone **(1)** [42].

N-(4-(6-oxo-5-(thiophen-2-ylmethyl)-1,6-dihydro-pyridazin-3-yl) phenyl) acetamide (2)

A mixture of furanone (**1**) (0.01 mol) and hydrazine hydrate (0.01 mol) was stirred in (30 mL) ethanol for 10h., pour into ice and drops of acetic acid. The solid was separated, filtered off, dried and recrystallized from ethanol. Yield 78% mp 154-156ºC. IR(KBr), υ, cm^{-1}: 3325, 3225(NH), 1675, 1667(CO), 1630(C=N). ^{1}HNMR (DMSO -d6), δ ppm, (J, Hz): 2.12 (s, 3H, CH_3), 3.27 (s, 2H, thiophene-CH2-pyridzinone; 68%), 6.51 (s, 1H, CH pyridazinone), 6.82 (s, 1H, thiophen-CH=; 32%), 6.93-8.12 (m, 7H, Ar-H), 10.14 (s, 1H, NHCO, D_2O exchangeable), 14.26 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO), δ ppm 57.9, 73.6, 77.2, 125.8(2), 126.8, 127.7, 128.5(2), 129.3(2), 129.7, 133.1, 134.0, 145.2, 155.2 and 161.7.Anal. Calc. for $C_{17}H_{15}N_3O_2S$, %: C 62.75, H 4.65, N 12.91, S 9.85; found, %: C 62.60, H 4.46, N 12.70, S 9.72.

N-(4-(3-(thiophen-2-yl)-2,3,6,7-tetrahydro-1H-pyrazolo[3,4-c] pyridazin-5-yl) phenyl) acetamide(3)

(1.5 mL , 0.03 mol) of Hydrazine hydrate and (0.01 mol) of furanone derivative (**1**) were added as a mixture then refluxed in ethanol (30 mL) for 3h., after that itis concentrated,filtered off, dried the solid that was formed was crystallized from butanol. Yield 72%, mp 224-226ºC. IR(KBr), υ, cm^{-1}: 3220(NH), 1686 (CO), 1628(C=N). 1HNMR (DMSO-d_6), δ ppm, (J, Hz): 2.10 (s, 3H, CH_3), 4.78 (d, 1H, CHpyrazole), 5.64 (m, 2H, 2NHpyrazole), 5.96(s, 1H, CHpyridazine), 6.93–8.00 (m, 7H, ArH), 10.52 (bs, 1H, NHCO exchangeable by D_2O), 11.22 (bs, 2H, 2NHpyridazine exchangeable by D_2O).^{13}C-NMR (DMSO), δ ppm 58.6, 75.5, 78.8, 125.8, 127.0(2), 127.8, 129.1(2), 129.7, 129.9(2), 132.7, 134.3, 144.9, 157.2 and 161.9. Anal. Cal for $C_{17}H_{17}N_5OS$, %: C 60.16, H 5.05, N 20.63, S 5.45; found, %: C 60.00, H 4.85, N 20.47, S 5.20.

N-(4-(1-(4-chlorophenyl)-5-oxo-4-(thiophen-2-ylmethylene)-4,5-dihydro-1H-pyrrol-2-yl)phenyl) acetamide (4)

A mixture of the furanone (**1**) (0.01 mol) and 4-chloroaniline (0.01 mol) were refluxed in boiling ethanol (30 mL) for 3 h. The reaction composition was pumped out on hot, left to cool. The solid was separated out, filtered off, dried and recrystallized from ethanol. Yield 78%. mp 192-194ºC. IR(KBr), υ, cm^{-1}: 3211 (NH), 1690, 1665(CO), 1630(C=N). ^{1}HNMR (DMSO -d6), δ ppm, (J, Hz): 2.08 (s, 3H, CH_3), 6.21 (s, 1H, CH pyrrolone), 6.92 (s, 1H, thiophen-CH=), 6.97-8.11 (m, 11H, Ar-H), 10.23 (s, 1H, NHCO, D_2O exchangeable). ^{13}C-NMR (DMSO), δ ppm 21.3, 56.4, 75.4, 79.5, 126.8, 127.3, 127.8(2), 129.1, 129.6(2), 129.8, 132.1, 132.5, 134.2, 149.3, 157.2 and 162.1. Anal. Calc. for $C_{23}H_{17}N_2O_2SCl$, %: C 65.63, H 4.07, N 6.66, S 7.62, Cl 8.42; found, %: C 65.40, H 3.86, N 6.30, S 7.41, Cl 8.19.

N-(4-(7-(4-chlorophenyl)-4-(thiophen-2-yl)-2-thioxo-2,3,4,7-tetrahydro-1H-pyrrolo[2,3-d] pyrimidin-6-yl) phenyl) acetamide (5)

A mixture of pyrrol-2-one (**4)** (0.01 mol) and thiourea (0.01 mol) in (40 mL) boiling ethanol was refluxed for 3 h. The solid obtained after cooling, filter off and crystalized from dioxane. Yield 43%. mp 160-162ºC. IR (KBr), υ, cm^{-1}: 3332, 3211, 3183 (NH), 1631 (C=N), 1354 (C=S). ^{1}HNMR (DMSO -d_6), δ ppm, (J, Hz): 2.11 (s, 3H, CH_3), 4.27 (s, 2H, CH pyrimidinthione), 6.51 (s, 1H, CH pyrrole), 6.91-8.06 (m, 11H, Ar-H), 9.72 (s, 1H, 3-NH pyrimidinthione, D_2O exchangeable), 10.52 (s, 1H, NHCO, D_2O exchangeable), 13.26 (s, 1H, 1-NH pyrimidinthione, D_2O exchangeable). Anal.Calc. for $C_{24}H_{19}ClN_4OS_2$, %: C 60.18, H 4.00, N 11.70, S 13.39, Cl 7.40; found, %: C 60.00, H 3.78, N 11.50, S 13.13, Cl 7.21.

2-(5-(4-acetamidophenyl)-2-oxo-3-(thiophen-2-ylmethylene)-2,3-dihydro-1H-pyrrol-1-yl) benzoicacid (6)

Anthranilic acid (0.01 mol) and (0.01 mol) of furanone (**1)** was mixed and heated under reflux in ethanol (30 mL) for 3 h. The reaction mixture was filtered off on hot, then left to cool. The solid was separated out, filtered off, dried and recrystallized from ethanol. Yield 75%, mp 212-214ºC. IR(KBr),

υ, cm^{-1}: 3397,3224 (NH), 1718, 1669 (CO), 1634 (C=N), 1587 (COO^-). ^{1}HNMR (DMSO-d_6), δ ppm, (J, Hz): δ 2.23(s, 3H, CH_3), 6.71 (s, 1H, CH pyrrolone), 7.01 (s, 1H, thiophene-CH=), 7.05-8.08 (m, 11H, Ar-H), 10.12 (bs, 1H, NHCO exchangeable by D_2O). ^{13}C-NMR (DMSO), δ ppm 54.3, 64.5, 69.9, 126.8, 127.0(2), 128.0, 129.0(2), 129.5, 129.9(2), 132.2, 133.8, 145.5, 156.1, and 168.9 .Anal.Calc. for $C_{24}H_{18}N_2O_4S$, %: C 66.96, H 4.21, N 6.51, S 7.45; found, %: C 66.78, H 4.02, N 6.32, S 7.23.

Ethyl-2-(5-(4-acetamidophenyl)-2-oxo-3-(thiophen-2-ylmethylene)-2,3-dihydro-1H-pyrrol-1-yl) acetate (7)

Compound (**1**) (0.01 mol), ethylglycinate (0.015 mol) and sodium ethoxide (0.8 mol) were mixed in ethanol (30 mL) then heated under reflux for 3 h. The solvent was evaporated, and the residue obtained was pour into 15 mL aq. HCl, filtered off and crystallized from pet. ether (80-100), yield 77% as white crystals, mp 134-136ºC. IR(KBr), υ, cm^{-1}: 3211 (NH), 1732, 1685, 1666(CO). ^{1}HNMR (DMSO-d_6), δ ppm, (J, Hz): δ;1.18 (t, 3H, $CH_2\underline{CH_3}$), 2.27 (s, 3H, CH_3), 4.14 (q, 2H, $\underline{CH_2}CH_3$, J=7.4 Hz), 4,35 (s, 2H, CH_2CO), 6.58 (s, 1H, CH pyrrolone), 7.08 (s, 1H, thiophene-CH=), 7.05-8.08 (m, 7H, Ar-H), 10.26 (bs, 1H, NHCO exchangeable by D_2O). Anal. Calc for $C_{21}H_{20}N_2O_4S$, %: C 63.62, H5.08, N 7.07, S 8.09; found, %: C 63.40, H 4.95, N 6.92, S 7.91.

N-(4-(7-oxo-5-(thiophen-2-yl)-1,7-dihydropyrano-[2,3-c][1,2]oxazin-3-yl)phenyl)acetamide (8)

Compound (**1**) (0.01 mol) and ethylcyanoacetate (0.015 mol), were mixed in hydroxyl amine (0.01 mol) in boiling pyridine then heated under reflux for 6 h. The reaction mixture was poured in ice/HCl and the residue obtained was filtered off, dried and crystallized from proper solvent. Crystallized from ethanol, yield 74% as white crystals, mp 110-112 ºC. IR(KBr), υ, cm^{-1}: 3224, 3170 (NH), 1741, 1658(CO). ^{1}HNMR (DMSO-d_6), δ ppm, (J, Hz): 2.41 (s, 3H, $ArCH_3$), 5.12 (bs, 1H, NH oxazine exchangeable by D_2O), 6.83–8.28 (m, 9H, Ar-H)10.12 (bs, 1H, NHCO exchangeable by D_2O). ^{13}C-NMR (DMSO), δ ppm 33.6, 53.8, 75.5, 78.8, 125.8, 127.0, 127.8, 128.9,129.1, 129.7, 129.9, 132.7, 134.3, 134.9, 137.3, 147.2 and 157.9, 163.5, 190.3. Anal. Calc for $C_{19}H_{14}N_2O_4S$, %: C 62.29, H 3.85, N 7.65, S 8.75; found, %: C 62.00, H 3.60, N 7.36, S 8.56.

N-(4-(6-oxo-4-(thiophen-2-yl)-6,7-dihydro-1H-pyrrolo [2,3-b] pyridin-2-yl) phenyl) acetamide (9)

Compound (**1**) (0.01 mol) and ethyl cyanoacetate (0.015 mol), was mixed in ammonium acetate (0.01 mol) in boiling acetic acid then heated under reflux for 6 h. The solvent was evaporated, and the residue obtained was filtered off, dried and crystallized from ethanol, yield 68%, white crystal, mp 232-234ºC. IR(KBr), υ, cm^{-1}: 3311, 3285, 3193 (NH), 1676,1658(CO), ^{1}HNMR (DMSO-d_6), δ ppm, (J, Hz): δ 2.03(s, 3H, CH_3), 6.31 (s, 1H, CH pyrrole), 6.85 (s, 1H, CH pyridone), 6.95-7.98 (m, 7H, Ar-H), 10.12 (bs, 1H, NHCO exchangeable by D_2O) 11.32 (s, 1H, NHpyrrole exchangeablebyD$_2$O),11.83 (bs, 1H, NH pyridine exchangeable by D_2O). ^{13}C-NMR (DMSO), δ ppm 53.8, 78.5, 79.7, 123.8, 127.0, 127.6, 129.1, 129.7, 131.1, 132.7, 134.3, 134.9, 145.2, 157.9, 161.1, 164.3 and 167.2. Anal. Calc. for $C_{19}H_{15}N_3O_2S$, %: C 65.31, H 4.33, N 12.03, S 9.18; found, %: C 65.15, H 4.12, N 11.84, S 9.00.

N-(4-(7-oxo-5-(thiophen-2-yl)-1,2,7,8-tetrahydro-pyrido[2,3-c] pyridazin-3-yl) phenyl) acetamide (10)

Compound (**1**) (0.01 mol), malononitrile and ethylcyanoacetate (0.015 mol) were mixed withhydrazine hydrate (0.01 mol) in boiling pyridine then heated under reflux for 6 h. The reaction mixture was poured in ice/HCl and the residue obtained was filtered off, dried and crystallized from proper solvent. Crystallized from ethanol, yield 74% as white crystals Crystallized from benzene, yield 44% as white crystals, mp 214-216ºC. IR(KBr), υ, cm^{-1}: 3231 (NH), 1738, 1668(CO). ^{1}HNMR (DMSO-d_6), δ ppm, (J, Hz): 2.21 (s, 3H, $ArCH_3$), 6.12 (s, 1H, CHpyrone), 6.93–8.28 (m, 8H, Ar-H)10.26 (bs, 1H, NHCO exchangeable by D_2O).^{13}C-NMR; (DMSO), δ ppm 54.3, 64.5, 69.9, 126.8, 127.0, 128.0, 129.0, 129.5, 129.9, 132.2, 133.8, 135.5, 146.1, 158.9, 163.2, 168.2 and 172.9. Anal.Calc for $C_{19}H_{13}N_3O_3S$, %: C 62.80, H 3.61, N 11.56, S 8.82; found, %: C 62.58, H 3.45, N 11.32, S 8.57.

N-(4-(3-acetyl-2-oxo-4-(thiophen-2-yl)-2,7-dihydro-pyrano[2,3-b] pyrrol-6-yl) phenyl) acetamide (11)

the furanone (**1**) (0.01mol), ethylacetooacetate (0.015 mol) and ammonium acetate (0.01 mol) in one stepreaction in boiling acetic acid was refluxed for 3 h. The excess solvent was vaporized, and the solid gained was filtered off, dried, and crystallized from ethanol, yield 68%, white crystalmp 124-126ºC. IR(KBr), υ, cm^{-1}: 3447, 3256(NH),1692,1652 (CO). ^{1}HNMR (DMSO-d_6), δ ppm, (J, Hz): 2.13 (s, 3H, CH_3), 2.43 (s, 3H, CH_3CO), 6.21 (s, 1H, CHpyrrole), 7.46-8.23 (m, 7H, Ar-H), 10.16 (bs, 1H, NHCO exchangeable by D_2O).Anal. Calc. for $C_{21}H_{16}N_2O_4S$, %: C 64.27, H 4.11, N 7.14, S 8.17; found, %: C 64.08, H 3.95, N 6.91, S 8.00.

Synthesis of compounds 12 and 13

A mixture of compound (**1**) (0.01 mol) ethylcyanoacetate, and ethylacetoacetate (0.015 mol), in the presence of hydrazine hydrate and/or methylglycinate (0.01 mol) in boiling ethanol was refluxed for 6 h. The excess solvent was vaporized, and the solid obtained was filtered off, dried and crystallized from ethanol, yield 68%, white crystal.

N-(4-(4-((3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)(thiophen-2-yl)methyl)-5-oxo-4,5-dihydrofuran-2-yl)phenyl)acetamide (12)

Yield 40%, mp 202-204 ºC. IR(KBr), υ, cm^{-1}: 3325, 3211 (NH), 1778, 1697, 1675 (CO). ^{1}HNMR (DMSO-d_6), δ ppm, (J, Hz): 2.12 (s, 3H, CH_3), 2.34-2.35 (m, 1H, C_4H-pyrazole), 3.11-3.13 (m, 1H, C_3H-furanone), 3.37-3.39 (m, 1H, CH-thiophene), 4.21 (s, 1H, C_5H-pyrazole),5.15 (s, 1H, 4-CHfuranone), 6.97-7.92 (m, 7H, Ar-H), 10.23 (bs, 1H, acidic NHCO group). ^{13}C NMR (125 MHz, DMSO-d_6) δ 177.42, 163.41, 136.44, 132.08, 131.70, 130.95, 130.32, 129.02, 128.55, 72.27, 67.40 (2CH), 57.13, 55.35, 52.66, 44.40, 42.96, 39.33; Anal. Calc. for $C_{21}H_{19}N_3O_4S$, %: C 61.60, H 4.68, N 10.26, S 7.83; found, %: C 61.34, H 4.44, N 10.00, S 7.61.

Ethyl-2-(6-(4-acetamidophenyl)-3-acetyl-2-oxo-4-(thiophen-2-yl)pyrano[2,3-b]pyrrol-7-(2H)-yl)acetate (13)

Yield 26%, mp 138-140 ºC. IR(KBr), υ, cm^{-1}: 3211 (NH), 1743, 1686, 1671 (CO). ^{1}HNMR (DMSO-d_6), δ ppm, (J, Hz): δ; 1.32 (t, 3H, $CH_2\underline{CH_3}$), 2.23(s, 3H, CH_3), 2.48 (s, 3H, CH_3CO), 4.03 (q,2H, $\underline{CH_2}CH_3$, J = 7.4 Hz), 4,52 (s, 2H, CH_2CO), 6.18 (s, 1H, CH pyrrole), 7.05-8.08 (m, 7H, Ar-H), 10.26 (bs, 1H, NHCO exchangeable by D_2O). Anal. Calc. for $C_{25}H_{22}N_2O_6S$ %: C 62.75, H 4.63, N 5.85, S 6.70; found, %: C 62.59, H 4.41, N 5.62, S 6.46.

Synthesis of compounds 14, 15 and 16

A mixture of furanone (**1)** (0.01 mol) and isatin (0.01 mol),in the presence of (0.01 mol) of each of thioglycolic, sarcosine, or benzyl amine was refluxed in ethanol (40 mL) for 3 h, after cooling, the solid gained was crystallized from ethanol to afford the products **14, 15** and **16** respectively.

N-(4-(2,2''-dioxo-4'-(thiophen-2-yl)-4',5'-dihydro-2H-dispiro[furan-3,3'-thiophene-2',3''-indolin]-5-yl)phenyl) acetamide (14)

Yield 52%, white crystals, mp 234-236ºC. IR(KBr), υ, cm^{-1}: 3311, 3245 (NH), 1775, 1670, 1660, (CO). ^{1}HNMR (DMSO-d_6), δ ppm, (J, Hz): 2.15 (s, 3H, CH_3Ar), 2.56(dd, 2H, methylene proton (diastereotopic protons, J =14.2, 6.5),2.65 (s, 3H, N-CH_3), 3.22 (dd, 1H, thiophene-CH(stereogenic proton, J = 14.2, 6.5), 5.25 (s, 1H, CH furanone), 7.19-8.25 (m, 11H, Ar-H).10.26 (bs, 1H, NHCO exchangeable by D_2O), 10.68 (bs, 1H, NHisatin exchangeable by D_2O). ^{13}C NMR (125 MHz, DMSO-d_6) δ 175.59 (CON), 170.23 (O-C=), 161.36 (C= fur), 141.26(C-N), 136.44 (C-CO), 132.08 (C-CH), 131.70 (C-C Spiro), 130.95 (CH 3-Ar), 130.32 (CH 4-Ar), 129.02 (CH, 5-Ar), 128.55(CH, 6-Ar, 72.27 (C-spiro), 68.20 (CH), 57.13 (CH_2), 55.35 (CH_2), 52.66 (CHCO), 44.40 (CH_2), 42.96 (CH_2), 39.33(CH_2);Anal. Calc. for $C_{27}H_{23}N_3O_4S$, %: C 66.79, H 4.77, N 8.65, S 6.60; found, %: C 66.50, H 4.43, N 8.29, S 6.37.

N-(4-(1'-methyl-2,2''-dioxo-4'-(thiophen-2-yl)-2H-dispiro[furan-3,3'-pyrrolidine-2',3''-indolin]-5-yl)phenyl) acetamide (15)

Yield 86%, white crystals crystallized from benzene. mp 184-186ºC. IR(KBr), υ, cm^{-1}: 3170(NH), 1673 (CO) 1630(C=N), ^{1}HNMR (DMSO-d_6), δ ppm, (J, Hz): 2.14 (s, 3H, CH_3Ar), 2.62(dd, 2H, methylene proton (diastereotopic protons)), 3.37(dd, 1H, thiophene-CH(stereogenic proton)), 5.42 (s, 1H, CH furanone), 7.19-8.25 (m, 11H, Ar-H).10.14 (bs, 1H, NHCO exchangeable by D_2O), 10.58 (bs, 1H, NH isatin exchangeable by D_2O). Anal. Calc. for $C_{27}H_{23}N_3O_4S$, %: C 63.92, H 4.13, N 5.73, S 13.12; found, %: C 63.72, H 3.93, N 5.45, S 12.90.

N-(4-(2,2''-dioxo-5'-phenyl-4'-(thiophen-2-yl)-2H-dispiro[furan-3,3'-pyrrolidine-2',3''-indolin]-5-yl)phenyl) acetamide (16)

Yield 66%, mp 224-226ºC. IR(KBr), υ, cm^{-1}: 1604(C=N), 1666(CO) and 3170(NH). ^{1}HNMR (DMSO-d_6), δ ppm, (J, Hz): 2.22 (s, 3H, CH_3Ar), 2.57 (dd, 2H, methylene proton (diastereotopic protons, J = 13.7, 5.7 Hz), 2.11 (s, 1H, NH pyrrolidine), 3.22 (dd, 1H, thiophene-CH(stereogenic proton, J = 13.7, 5.7 Hz), 5.32 (s, 1H, CH furanone), 7.19-8.25 (m, 16H, Ar-H).10.21 (bs, 1H, NHCO exchangeable by D_2O), 10.65 (bs, 1H, NH isatin exchangeable by D_2O). ^{13}C-NMR (125 MHz, DMSO-d_6) δ 177.42-173.65 (2CON), 162.26 (C=N), 141.65 (CH=), 136.44 (C-C=N), 133.43 (C, Ph), 132.08 (C-Cl), 131.70 (C-C Spiro), 130.95 (CH 3-Ar), 130.32 (CH 4-Ar), 129.02 (CH, 5-ArCl), 128.55(CH, 6-Ar, 128.20 (CH, Ph), 127.13 (2CH, Ph), 113.55 (CH, Ph), 111.33 (CH, Ph), 72.27 (C-spiro), 68.20 (CH), 56.54 (CHCO), 54.66 (CH), 54.35 (CH_2), 51.21 (OCH_2), 44.40 ($2CH_2$), 42.96 (CH_2), 39.33 (CH_2); Anal. Calc. for $C_{32}H_{25}N_3O_4S$, %: C 70.18, H 4.60, N 7.67, S 5.85; found, %: C 69.96, H 4.39, N 7.31, S 5.57.

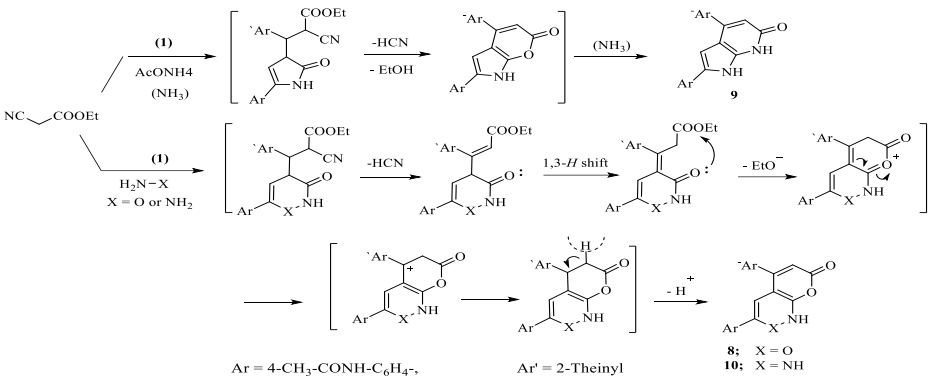
3. Results and discussion

3.1. Chemistry

According to the reaction conditions, reactions of the4'-(2-oxo-3-(thiophen-2-ylmethylene)furan-5-yl)acetanilide **(1)** [42] with hydrazine hydrate afforded different products.

Thus, on stirring with an equivalent amount of hydrazine hydrate pathway **I**, furanone **1** gave the pyridazinone **2**;whereas, on reflux with an excess of the amine; it afforded the pyrazolopyridazine **3**, pathway **I** andpathway **II**, respectively (**Scheme 1)**.

As outlined inpathway **I**, hydrazine hydrate affected cleaving of the furo ring, forming the pyridazinone **2**, with elimination of one molecule of water.



Scheme 1: Reaction of the furanone **1** with hydrazine hydrate

However, in pathway **II** it turns out that pyridazinone intermediate**2** was formed, which by its reaction with another molecule ofhydrazine offered the pyrazolopyridazine**3**. The IR spectrum of the pyridazinone **2** reveals absorption bands at 3325, 3225(NH), 1675, 1667(CO), 1630(C=N) indicate that the presence of lactam-lactim dynamic equilibrium. Furthermore, the ^{1}H-NMR spectrum revealed that **2** existed in two isomeric forms; exocyclic **2** (form **a**) and endocyclic **2** (form **b)**, which were characterized by the thienyl-$\underline{CH_2}$- and thienyl-$\underline{CH}$= moieties, respectively (**Figure 1**).

The ^{1}HNMR ($DMSO_{d6}$), of the pyridazine **2** reveals δ ppm, (J, Hz): 2.12 (s, 3H, $\underline{CH_3}$), 3.27 (s, 2H, thienyl-CH_2- (68%), 6.51 (s, 1H, CH pyridazinone), 6.82 (s, 1H, thiophen-CH= (32%)), 6.93-8.12 (m, 7H, Ar-H), 10.14 (s, 1H, NH, D_2O exchangeable), 14.26 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO), δ ppm exocyclic C6-C7 at 134.5, 135.7 in % 30.8 and endocyclic C1-C6 at 144.7, 142.3 and become C7(CH_2) 34.5 ppm in 69.19% that proved the isomer **2b** is in major form.

Theintegration ratios indicated that the CH_2-, in **2b** represented 68% of the isomeric mixture, in comparison with the ratios of the -$\underline{CH}$= and the imine $\underline{NH}$, in **2a** (see Experimental). It is believe that **2b** formed the largest proportion of the mixture due to the relative stability gained from its ability to exist in an aromatic form, compared to **2a**.

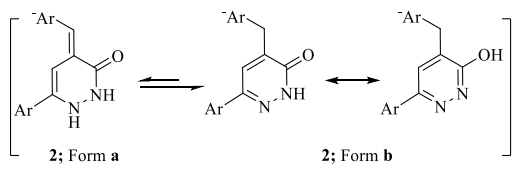
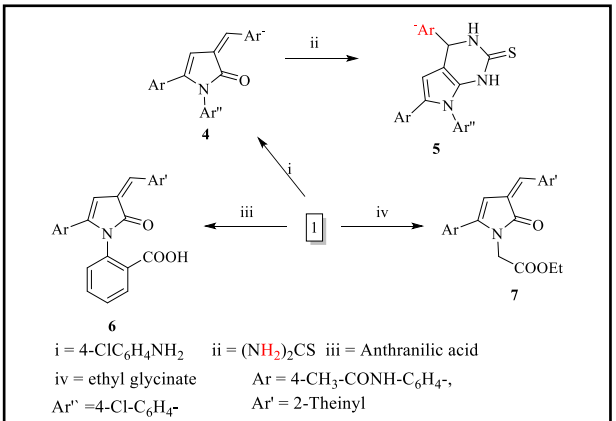


Figure 1: Form **a** and **b** of compound **2**

Furthermore, a one pot reaction of the furanone (**1**) and ethyl cyanoacetate with each of hydroxyl amine,

On the other hand, reaction of the furanone **1** with 4-chloroaniline afforded the corresponding N-aryl pyrrolone derivative **4**that could be treated with thiourea to give the pyrrolo[2,3-d] pyrimidin-2-thione derivative **5 (Scheme 2)**.

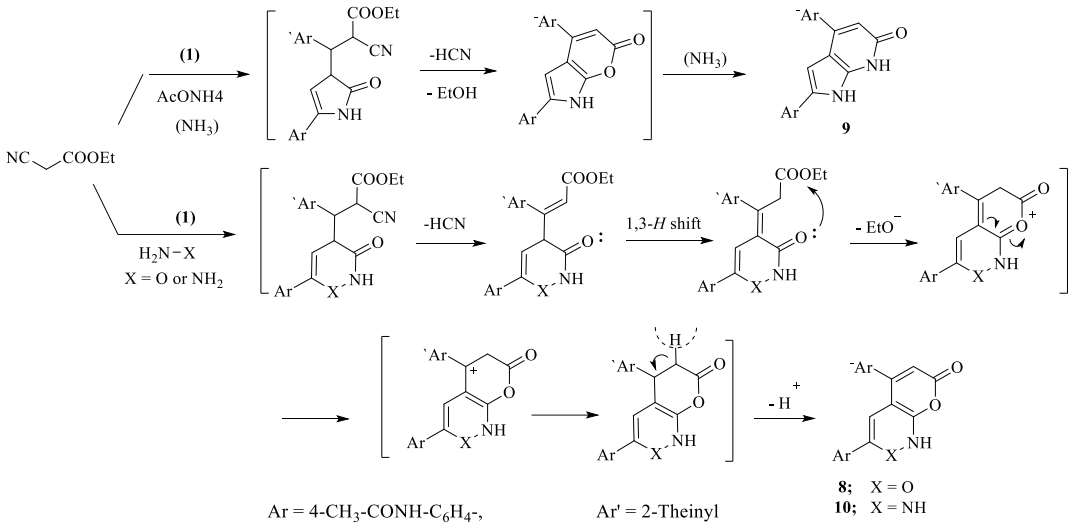
Similarly, the furanone (**1**) reacted with anthranilic acid and ethyl glycinate afforded pyrrol-2-(1H)one derivatives **(6)** and (**7**) respectively. The ^{1}H-NMR data exhibited only one singlet signal attributed for the olefinic ═CH at δ= 7.08, 6.71, 6.92 and 6.82 ppm, for compounds (**4**), **(6)** and (**7**), respectively. Accordingly, we can't able to determine the configuration of these pure *E* or *Z* isomers.



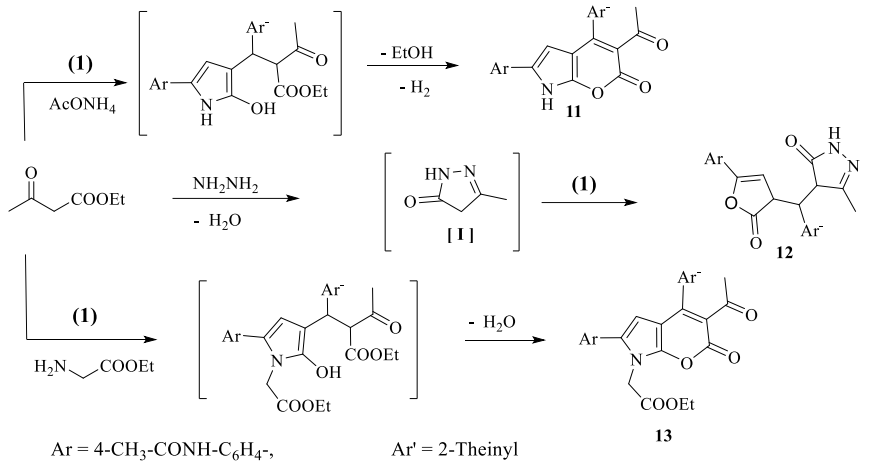
Scheme 2; Behaviour of **1** towards amines

ammonium acetate and hydrazine hydrate yielded pyronoisoxazine (**8**), pyrrolo-pyridone (**9**) and pyranopyridazinone (**10**) respectively **(Scheme 3)**. In addition to their conversion the furanone **(1)** into the respective pyrrole ring, these amines affected the elimination of the cyano group from all products as reported before [43].

In case of ammonium acetate, it is believed that the pyranopyrrole was formed as an intermediate; however, the excess of the evolved ammonia gas converted the pyranone into pyridinone ring.



Scheme 3: Behaviour of furanone **1** towards electrophilic CH_2



Scheme 4: Behaviour of the furanone **1** towards ethyl cyanoacetate and amines

Moreover, the furanone **(1)** was allowed to react with ethylacetoacetate in the presence of different amines; NH_3 (from ammonium acetate), hydrazine hydrate and ethylglycinate.

In case of NH_3, and ethylglycinate, the ethyl acetoacetate added at the olefinic link, whilst the amine attacked the furo ring, providing the respective pyrroles **(11)** and (**13),** respectively. However, in the other case, hydrazine hydrate reacted, first, with ethylacetoacetate, providing the pyrazol-3-one [**I**], which in turn, added the furanone, giving the adduct product **(12)**(**Scheme 4**).

Also, furanone (**1**) was allowed to react with isatin, in the presence of thioglycolic acid, sarcosine and benzyl amine.

These reagents attacked the ketonic C═O of isatin, providing the intermediates **[IIa],[IIb]** andtheSchiff base **[IIc]**, with the elimination of one molecule of water. Thus, decarboxylation [44] of **[IIa]** and **[IIb]**, yielded the respective zwitterion intermediates **[IIa'']** and **[IIb'']**; whereas the azomethine zwitterion **[IIc'']** isexpected to derive from theintermediate Schiff base [44].

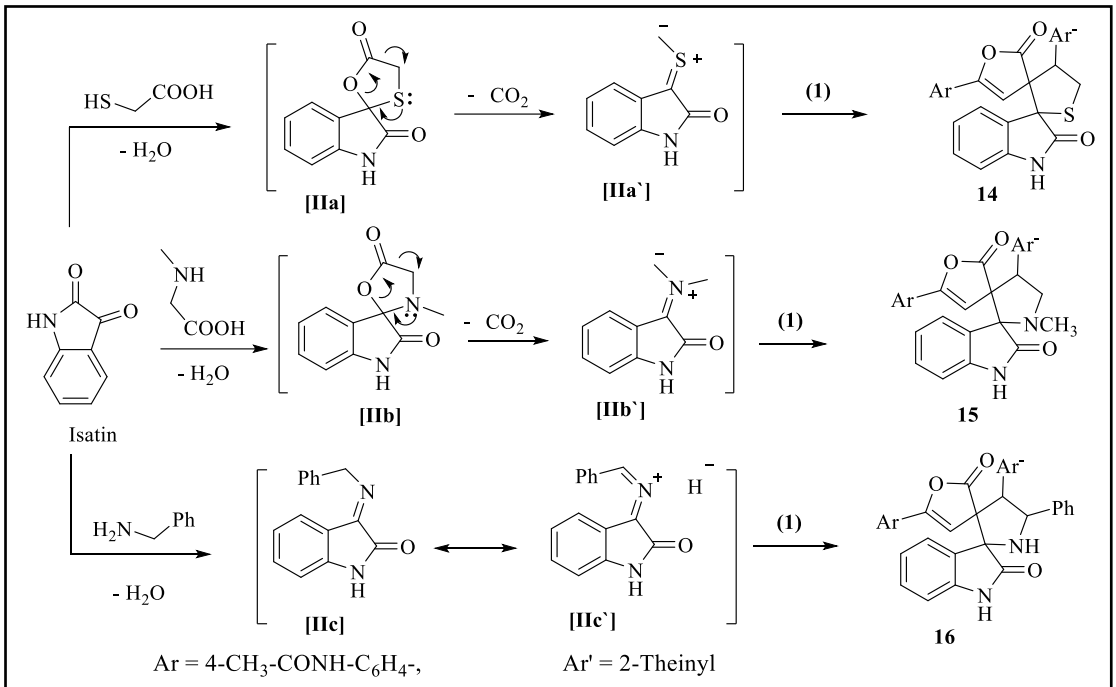
Thus, **[IIa'']**, **[IIb'']**and **[IIc'']** endured [3+2] cycloaddition with the olefinic linkage, in furanone **1,** giving the spiro furanone derivatives (**14)**, **(15)**, and (**16**), respectively (**Scheme 5**).

3.2. Biological activity

3.2.1. Insecticidal activity

The toxicological results listed indicated that some of the synthesized compounds displayed good insecticidal activities against the two tested pests (**Table1**). The results revealed that compounds (**4), (6), (10), (12), (13)** and (**14)** showed a robust insecticidal activity against *P. xylostella* larvae with 84.9 %, 85.8%, 100 %, 83.8, 87.2% and 91% activities at 500 µg mL $^{-1}$, respectively, compared with 90.8% for chlorpyrifos (CPS).

Increasing the electrophilic carbonyl sites in the compound **13** e.g. acetyl, lactone and ester groups enhanced the efficacy of proteinase inhibitors (PIs). Spiro compound **14** has unique non-planar structures and great potential for binding to biomolecules (HGP) because of their inherent rigid chiral structure. Molecular docking computational study is considered as a robust tool for the detection of the potential larvicidal activity of many previously reported structures [52].



Scheme 5: Reaction of the furanone **1** with isatin under different conditions

Moreover, they exhibited 50.3 %, 77.2%, 66.7%, 27.8, 35.9% and 57.6% activities at 25 µg mL $^{-1}$, respectively, compared to 47.4% for CPS. While, for testing against H. armigera larvae, compounds **(10), (12), (13)** and (**14)** displayed an excellent larvicidal action with 92 %, 91.9 %, 94.8% and 89.5% activities, respectively, compared with 84.2% for (CPS) at 500 µg mL $^{-1}$.. Moreover, the activities of the same compounds using 25 µg mL $^{-1}$ concentrations were 46.2%, 39.6%, 41.7% and 31.5% respectively, are more preferred than chlorpyrifos. Therefore, and at all times, compounds (**10)** and **(14)** can be selected as excellent larvicidal activities against both *H. armigera* and *P. xylostella* larvae with reference to CPS. Moreover, Fig 1 outlines the optimization of the 3-Arylidene-1,5-aryl-pyrrolone **4** and **6** that clarify they have a larvicidal activity.

Two electrophilic sites (Arylidine and amide groups) in the pyrrolone derivatives **4** and **6** inhibited the H. armigera gut proteinases (HGP) activity efficiently that present in the H. armigera larvae [45-51].

In this context, the molecular docking simulations was employed to explore the potential activity of the synthesized furanone derivatives using thecrystalline structure of native acetylcholinesterase (AchE) from *Drosophila Melanogaster* (PDB ID: 1QO9), and the results evinced their high affinity towards the receptor binding sites and this agree with experimental results of the tested insect's larvae.The docking simulations were performed for the most bioactive compounds of **4, 6, 10, 11, 12, 13** and **14** in order to give Insilco reasoning for the mentioned bioassay studies, whereas their results were compared to chlorpyrifos that acted as a positive control.

The outcomes of the docking simulations are listed in **Table 2**. They comprise the docking parameters of Gibbs free binding energy (ΔG_b), the predicted inhibition constant (Ki), which is a universal parameter denotes the potency of the used enzyme inhibitor [53]. In addition, ligand Root Mean Square deviation (L-RMSD), the *H*-bond count and other π-interactions are given. The manifested data showed

the binding affinity values of the compounds under study, ranging between – 8.75 to – 7.75, which are lower than that scored for Chlorpyrifos (CPS) – 4.32. According to these results, we expect that these compounds have a high ability to be bound competitively into the binding sites of the AchE substrate. Most ligands have showed strong H-bonding ability towards the active binding sites, where they interacted with residues such as ARG70, ASN84, ASN564, TRP321 as well as CH-O contact with GLU197.

Figure 2 portrays the 2D (left-hand side) and the 3D (right-hand side) docking interactions of compounds **6, 10, 11** and **12**.The 2D visualizations pose with the binding site of ACHE, depicting the listed bonds in (**Table 2**). The L-RMSD value is considered as a parameter for validating the performed docking simulations, the alignment of the

Table 1: Test of the new compounds againstPlutella xylostella and Helicoverpa armigera as larvicidal agents

Compd. No	The concentrations (µg/ mL^{-1}) of the compounds (%) against the tested pests									
	Plutella xylostella					***Helicoverpa armigera***				
	500	**200**	**100**	**50**	**25**	**500**	**200**	**100**	**50**	**25**
1	57.1	18.5	13.7	6.7	2.3	36.2	11.9	6.1	1.7	-
2	39.9	32.8	29.9	22.5	14.8	34.6	29.1	16.1	9..1	-
3	29.9	23.9	20.11	12.2	7.9	35.9	12.2	8.3	2.9	-
4	84.1	70.4	80.6	87.1	82.3	74.2	60.8	55.3	31.8	20.3
5	56.1	41.2	35.9	19.9	12.1	34.9	12.9	-	-	-
6	94.6	88.0	85.2	89.5	87.2	86.7	74.9	65.4	37.5	15.6
7	25.3	17.6	9.1	-	-	37.9	15.8	-	-	-
8	30.2	13.2	5.2	-	-	13.2	-	-	-	-
9	60.3	51.5	42.1	30.3	21.7	52.4	38	27.6	22.1	15.9
10	100	80.0	86.4	73.7	67.1	90	75.0	63.2	50.4	27.8
11	64.7	54.3	45.3	36.3	24.9	79.6	68.1	46.2	33.3	27.6
12	72.9	56.2	33.8	23.8	16.9	92.2	78.1	45.2	24.5	17.9
13	70	87.2	63.7	53.7	24.1	95.2	86.1	67.2	51.0	22.8
14	90.4	76.2	75.1	73.8	69.6	88.7	66.6	52.0	29.8	11.9
15	45	30	24.3	19.6	5.3	44.9	22.8	12.9	10.7	3
16	35.6	23.9	20.1	9.9	8.6	20.9	12.9	8.3	3	-
CPS	**90.8**	**85.8**	**79.5**	**67.7**	**47.4**	**84.2**	**67.9**	**56.9**	**33.1**	**20.1**

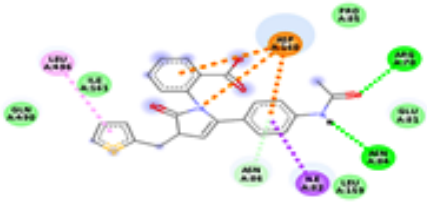
Table 2: docking parameters for selectedactive structures with AchE of *Drosophila Melanogaster*

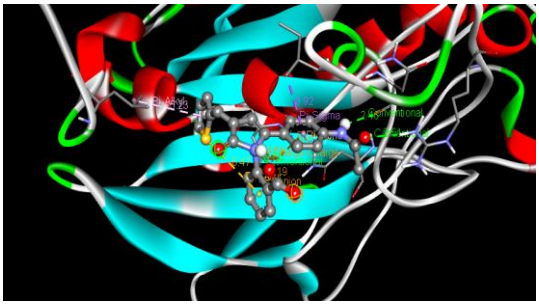
Compd.	ΔGb (Kcal/mol)	Ki (µM)	L-RMSD (Å)	Sum of H-bond	H-Bond length (Å)	π-interaction
4	-8.59	0.505	2.178	-	-	5
6	-7.76	2.05	1.867	2	2.46, 2.51	4
10	-8.75	0.387	1.112	1	2.13	4
11	-8.01	1.35	1.143	-	-	2
12	-7.96	1.46	2.409	1	1.96	2
13	-7.75	2.06	2.169	-	-	5
14	-7.79	1.96	0.996	2*	3.69, 3.52	2
CPS	-4.32	679.90	1.963	1	2.23	5

* Carbon-Hydrogen bond (CH-O contact)

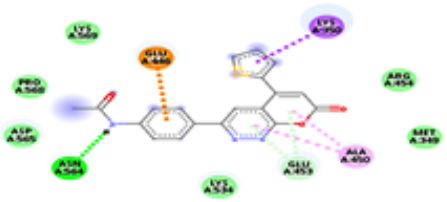
native compound structures with the docked one, as a representation for the performed L-RMSD analysis. The listed data in Table 2 shows that all the calculated L-RMSD values was lower than 3 Å, signifying the reproducibility of the docking parameters [54].

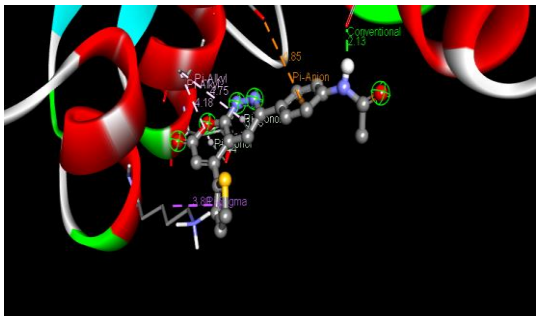
The docking pose of compound **6** with various types of interactions is outlined(**Figure3**).



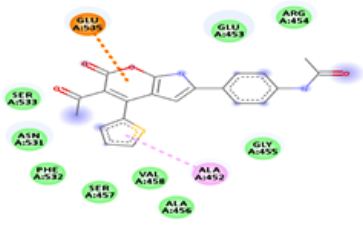


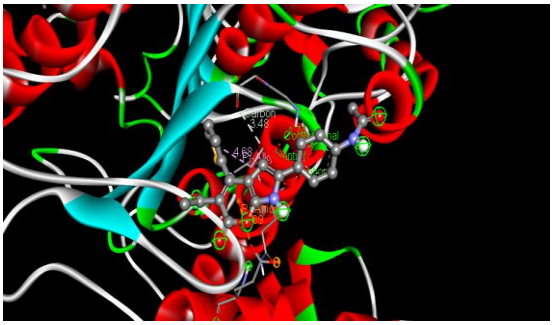
Compound **6** binding energy: -7.76
2D interactions: 3D interactions:



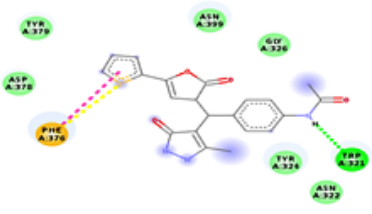


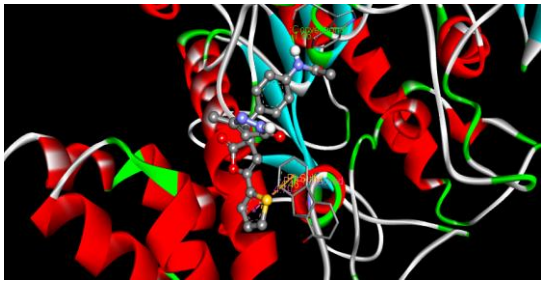
Compound **10** binding energy: -8.75
2D interactions: 3D interactions





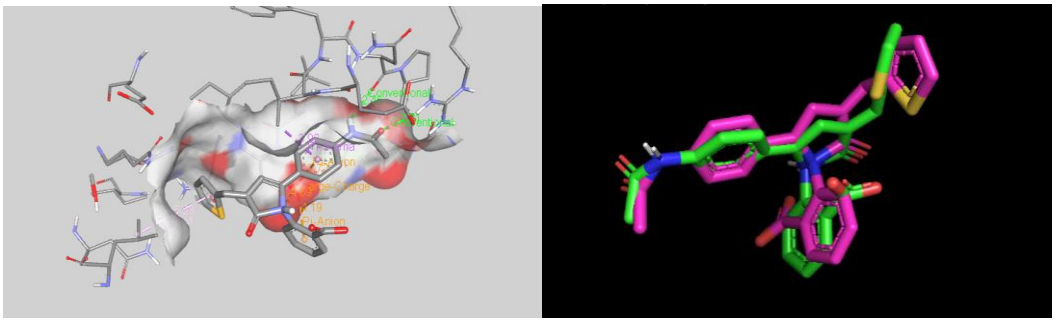
Compound **11** binding energy: -8.01
2D interactions: 3D interactions





Compound **12** binding energy: -7.96
2D interactions: 3D interactions

three-dimensional configuration using Chem3D V19.0 (PerkinElmer Informatics).



3A **3B**

Figure 3: 3A outlines the 2D visualization for the docking pose of compound **6** with various types of interactions and **3B** outlines its docking pose, where the hydrogen bonds are marked with light green colour:the superimposed structures of the native compound **6** ligand (light green colour) with the docked one (pink colour) for LRMSD analysis.

3.2.2. Biological assay

The *Plutella xylostella* and *Helicoverpa armigera* were reared at Plant Protection Research Institute, Agriculture Research Centre, Dokki, Giza, Egypt. under laboratory conditions set at 25 ±2°C, 65±5% R.H and l6: 8 h Light: Dark [45] according [46] with some modifications. The insecticidal activities of compounds **1-16** were tested against insects larvae according to the standard test [47,48] with a slight modification. The tested analogues were dissolved in DMF and serially diluted with water containing Triton X-80 (0.1 mg/L) to obtain the required concentrations. Cabbage leaves were dipped in the chemical concentrations, for ten seconds and allowed to dry on filter papers.

These leaves were fitted in Petri dishes and to avoid desiccation, wet filter paper was placed underneath. Twenty larvae of third instar were transferred to leaves in Petri dishes per treatment and three replicates per each.

For control, larvae were placed on leaves treated solvent diluted with distilled water. Assessments of mortality were calculated 72 h by the number and size of the live insects relative to those in the control. Evaluations were based on a percentage scale of (0 = no activity and 100 = complete death) [49]. The mortality rates were subjected to probite analysis [50] Chlorpyrifos was used as positive control while water containing Triton X-80 (0.1 mg/L) was used as negative control [51].

The two-dimensional (2D) structures of the proven biologically active compounds (structures: **4, 6, 10, 11, 12, 13** and **14)** in addition to Chlorpyrifos (CPS) as a positive control was first drawn using ChemDraw V19.0 software then converted into the

The previously titles compounds were subsequently marked as ligands and the PDB formatted files were imported to Auto Dock Tools V1.5.6 software for the following step. The X-ray crystallographic 3D structure of the target protein was available on (http://www.rcsb.org) (PDB ID: 1QO9) [52 53], that corresponds the highly resolved (2.70Å). acetylcholinesterase (AchE) crystal of *Drosophila Melanogaster*, which represents an essential enzyme for the regulation of the neurotransmissions through the central nervous system. This protein mainly serves as a key target for designated potential larvicides for a more selective pest control [54]. The protein was earlier subjected to structure optimization whereas water molecules were removed and essential polar hydrogens and kollman charges were assigned to the protein, while Gasteiger- Hukel charges were assigned to the ligands. The interacting ligands were made in a torsion-free state, while the protein retained a rigid configuration.

In order to screen all possible active binding sites of *Dm*AchE, blind docking approach was implemented to scan the entire protein surface to detect the most probable binding sites and the modes of ligand-protein interaction [52]. The docking process was carried out using the hybrid global/local search algorism known as; Lamarckian Genetic Algorithm (LGA) embedded in Auto Dock V4.2.6 software (The Scripps Research Institute) with its graphical user interface (GUI) of Auto Dock Tools V1.5.6 for 100 interations. The binding energy scoring in Auto Dock comprises the summation of the Final Inter-Atomic Energy (FIA), Final Total Internal Energy (FTI), Torsional Free Energy (TF) and Unbound System's Energy (US), where the

former one is composed of the energies of interactions such as H-bond (EHB), van der Waal forces (EVDW), electrostatic interactions (EELEC), desolvation (EDESOLV) and ref-energies (EREF) [55].

4. Conclusion

The aim of this work is synthesis of some interesting heterocyclic compounds to study the influence of the molecular structure on the reactivity of the starting towards the nitrogen nucleophiles. Moreover, the study included the bioactivity assay of the synthesized compounds as larvicidal agent. In addition, this biological investigation was reinforced by molecular docking simulations, which provided reasoning for the obtained experimental results.

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