Summary of the original work

The original work of this thesis includes three parts beside the general introduction about synthesis, reactions and biological activities of 1,3,4-thiadiazoles. Each part deals with synthesizing a set of new functionalized, condensed and non-condensed thiadiazole with other heterocycles aiming to enhance the biological activity of the thiadiazole nucleus. Stearic acid was utilized as starting material for these syntheses. The biological activity of the new synthesized compounds was evaluated against some gram positive, gram negative bacteria and some fungi. Also, the surface active properties after propoxylation of some synthesized compounds were determined as nonionic surfactants.

Part 1

Synthesis and reactions of 2-amino-5- heptadecyl-1,3,4-thiadiazole;
Facile procedure for one pot synthesis of novel functionalized thiadiazoles, thiadiazolo[3,2-a]pyrimidines, imidazo[2,1-b]thiadiazole and triazole carrying a long chain moiety:

In this part 2-amino-5-heptadecyl-1,3,4-thiadiazole **(1)** was prepared from the reaction of stearic acid and thiosemicarbazide in refluxing phosphorus oxychloride. In one-pot and convenient route, 1,3- dielectrophilic carbon compounds (ethyl cyanoacetate, ethyl acetoacetate, diethyl malonate, acetylacetone) and/or 1,2- dielectrophilic carbon compounds as oxalyl chloride were reacted in different solvents with 2-amino-5-heptadecyl-1,3,4-thiadiazole and produced different products depending on the nature of 1,3- and 1,2- dielectrophilic carbon compounds employed and also on the reaction conditions.

When the aminothiadiazole **(1)** was reacted with ethyl cyanoacetate in boiling ethanol, 2-cyano-*N*-(5-heptadecyl[1,3,4]thiadiazol-2-yl)acetamide **(2)**

was obtained while When this reaction was carried out in boiling glacial acetic acid and in the presence of catalytic amount of sodium acetate, a bicyclic product of 5-amino-2-heptadecyl[1,3,4]thiadiazolo[3,2-a]pyrimidin-7-one **(3)** was obtained.

When acetylacetone was refluxed in glacial acetic acid and sodium acetate as a catalyst, a sole product was obtained in a good yield, which assigned to be 4-(5-heptadecyl-[1,3,4]thiadiazol-2-ylimino)pentan-2-one **(4)** .The same product was obtained when the reaction was carried out in ethanol. But when aminothiadiazole **1** was reacted with diethyl malonate, and/or ethyl acetoacetate in refluxing ethanol and/or glacial acetic acid in sodium acetate, the bicyclic products of thiadiazolo[3,2-*a*]pyrimidine derivatives **(5,6)** were produced.

1,2-Dicarbonyl compounds such as oxalylchloride was reacted with aminothiadiazole to yield imidazo[2,1-*a*]thiadiazole derivatives **(7)**.

The reaction of compound **1** with triethylorthoformate, 2-naphthaldehyde, succinic anhydride and hydroxylamine hydrochloride were achieved and produced compounds; thiadiazolyl formamidate **(8)**, Schiff's base **(9)**, thiadiazolyl pyrrolidine **(10)** and triazole derivative **(11)**.

Part 2

Behaviour of 5-heptadecyl-1,3,4-thiadiazole-2-diazonium chloride toward active methylene compounds:

Formation of (azo ⟷ hyrdrazono tautomer and cyclization of the product:

Diazotization of 2-amino-5-heptadecyl-1,3,4-thiadiazole **(1)** with sodium nitrite in concentrated hydrochloric acid containing glacial acetic acid produce the non-isolated compound 5-heptadecyl-1,3,4-thiadiazole-2-diazonium chloride **(12)** which was used *in situ* during the reaction with

active methylene compounds (ethyl acetoacetate, ethyl cyanoacetate, diethyl malonate and acetylacetone). In all the synthesized compounds **(13-16),** azo⟷ hydrazono tautomerism was detected spectroscopically by IR and from fragmentation patterns of mass spectra. Also, it was detected chemically by reaction with nitrogen nucleophiles as hydrazine hydrate, hydroxylamine hydrochloride and thiourea which were reacted via azo tautomer and affording 5-heptadecyl-2-(5-hydroxy-3-methyl-1*H*-pyrazol-4-ylazo)-1,3,4-thiadiazole **(18)**, 5-heptadecyl-2-(5-hydroxy-3-methyl-isoxazol-4-ylazo)-1,3,4-thiadiazole **(19)**, 5-(5-heptadecyl-[1,3,4]thiadiazol-2-ylazo)-2-mercapto-6-methyl- pyrimidin-4-ol **(20)**.

While carbon electrophliles as phenylisocyanate was reacted via hydrazono tautomer to give 6-acetyl-2-(5-heptadecyl[1,3,4]thiadiazol-2-yl)-4-phenyl-2*H*-[1,2,4]triazine-3,5-dione **(21)**.

5-Heptadecyl-1,3,4-thiadiazole-2-diazonium chloride **(12)** was also reacted with β-naphthol through coupling reaction and gave the corresponding azo dye intermediate which converted to compound **(17)**.

UV-visible spectrum of the synthesized compounds was screened at concentration ($1x10^{-5}$ M) and the maximum wave length (λ_{max}) was determined (ε, λ).

Part 3 :

Synthesis of some condensed and non-condensed thiadiazoles based on 2-chloro-5-heptadecyl[1,3,4]thiadiazole:

2-Chloro-5-heptadecyl[l,3,4]thiadiazole **(22)** was obtained by leaving the diazonium salt **(12)** for two hours at room temperature. Chlorothiadiazole was proved to be an easy access to synthesize some condensed and non-condensed thiadiazole systems because nitrogen and/or oxygen nucleophiles

easily displace halogen atom from the thiadiazole nucleus.

Reaction of 2-chloro-5-heptadecyl-[l,3,4]thiadiazole **(22)** with nitrogen nucleophiles as acetylhydrazine, *o*-phenylenediamine, anthranilic acid and/or sodium azide produced the bridgehead nitrogen compounds 6-heptadecyl-3-methyl-[l,2,4]triazolo[3,4-b][l,3,4]thiadiazole **(23)**, 2-heptadecyl benzo[4,5]imidazo[2,l-b][l,3,4]thiadiazole **(24)**, 2-heptadecyl-5*H*-[l,3,4] thiadiazolo[2,3-b]quinazolin-5-one **(25)**, 6-heptadecyl[l,3,4]thiadiazolo[3,2-d]tetrazole **(26)** respectively, While the reaction with piperidine gave l-(5-heptadecyl-[l,3,4]thiadiazol-2-yl)piperidine **(27)**.

2-Hydrazino-5-heptadecyl-[l,3,4]thiadiazole **(28)** [prepared from 2-chlorothiadiazole derivative **(22)** by hydrazinolysis] was reacted with β-benzoylpropionic acid, β-aroylacrylic acid and/or phthalic anhydride and yielded 2-(5-heptadecyl[l,3,4]thiadiazol-2-yl)-6-phenyl-4,5-dihydro-2*H*-pyridazin-3-one **(29),** 6-(4-chloro-3-methylphenyl)-2-(5-heptadecyl[1,3,4]-thiadiazol-2-yl)-2*H*-pyridazin-3-one **(30),** and 2-(5-heptadecyl[l,3,4]-thiadiazol-2-yl)-2,3-dihydrophthalazine-l,4-dione **(31)** respectively.

The possible reaction mechanisms of most prepared compounds were illustrated. Also, the fragmentation patterns of mass spectra for some compounds were discussed.

Structures of all synthesized compounds were established by:

1- Elemental analysis. 2- IR spectra.

3- ^{1}H-NMR spectra. 4- Mass spectra.

The antimicrobial activities of the synthesized compounds were screened against some selected bacteria and fungi. Tetracycline was taken as standard antibacterial agent and Amphotericin B as standard antifungal agents. Some of the prepared compounds exhibited moderate to excellent activity against bacteria. Some tested compounds showed good antifungal

activity while others revealed no antifungal activities.

Also, the nonionic surfactants were prepared in this thesis by addition of propylene oxide (3, 5, 7 moles) to any active hydrogen in the molecule, the surface active properties like surface tension, interfacial tension, cloud point, wetting time, emulsion stability and foam height of these compounds were measured and shows a pronounced surface activities, good emulsifying properties (which indicate that these compounds can be used in drugs, cosmetics and pesticides). The biodegradability was evaluated and it was found that all the tested compounds shows good biodegradability properties which manifested the importance of their application avoiding pollution problems, and make them safe for human as well as environments.