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Synthesis and Antimicrobial Studies of New [Tetrakis (1, 2, 4-Triazole / 1, 3, 4-Oxadiazole / 1, 3, 4-Thiadiazole] [Bis-(Benzene-1, 3, 5-Triyl)] Dioxymethylene Compounds

Ahmed Neamah Ayyash
Department of Applied Chemistry, College of Applied Science, University of Fallujah, Anbar, Iraq

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Abstract

Synthesis of new heterocyclic compounds containing four five-membered rings together was the main goal of this work. The new derivatives of [tetrakis (1,2,4-triazole /1,3,4-thiadiazole /1,3,4-oxadiazole][bis-(benzene-1,3,5-triyl)] dioxymethylene A7-A18 were synthesized by the reaction of [bis-(dimethyl 5-yl-isophthalate)] dioxymethylene compound A1 which was previously prepared from the reaction of 1,2-dibromomethan and dimethyl 5-hydroxyisophthalate, then treated with hydrazine hydrate to yield the corresponding acid hydrazide A2. In the next step, compound A2 was refluxed with 4-substituted isothiocyanate to give substituted thiosemicarbazides A3-A6. The treatment of the latter compounds in basic medium of 2M of NaOH afforded 1,2,4-Triazole derivatives A7-A10. Whereas the reaction of the same compounds with concentrated sulfuric acid gave 1,3,4-thiadiazoles A11-A14. Furthermore, the new derivatives of 1,3,4-oxadiazole A15-A18 were obtained by the reaction of thiosemicarbazides and tosyl chloride in presence of pyridine. (C. H. N.) elemental analysis, FT-IR, and ^{1}HNMR techniques were used to characterize the chemical structure of some of the new synthesized compounds which also exhibited an important biological activity.

Keywords: Triazole, Dimethyl 5-hydroxyisophthalate, Isothiocyanate, Dioxymethylene.

تحضير ودراسة بايولوجية لمشتقات جديدة من [رباعي (4، 2 ،1- ترايازول / 4، 3 ،1- اوكسادايازول / 4،3،1- ثايادايازول)] (ثنائي البنزين المعوض)] دايوكسي مثيلين

احمد نعمة عياش

قسم الكيمياء التطبيقية، كلية العلوم التطبيقية، جامعة الفلوجة، الانبار، العراق

الخلاصة

تحضير مجموعة من المركبات الحلقية غير المتجانسة والتي تحتوي اربع حلقات خماسية هو الهدف الرئيسي من هذا العمل. حيث تم تحضير مشتقات جديدة من رباعي (4،2،1- ترايازول / 4،3،1- اوكسادايازول / 4،3،1- ثايادايازول) دايوكسي مثيلين A7-A18 عن طريق تفاعل مركب ثنائي (داي مثيل ايزوفثالات) دايوكسي مثيلين A1 والمحضر مسبقا من تفاعل داي برومو ميثان داي مثيل هيدروكسي ايزوفثالات ، ليعامل بعد ذلك مع الهيدرازين لينتج الاسيد هيدرازايد المقابل **A2**. وفي خطوة لاحقة يصعد

Email: ahmedn.ayyash@uofallujah.edu.iq

مركب A2 مع الايزوثايوسيانات المعوضة ليعطي مشتقات الثايوسيمكاربازايد المعوضة **A3–A6**. ثم يعامل الناتج الاخير مع محلول قاعدي من هيدروكسيد الصوديوم ليعطي مشتقات 4،2،1- ترايازول A7–A10. بينما تفاعل نفس المركبات مع حامض الكبريتيك المركز اعطى مشتقات 4،3،1- ثاياديازول A11–A14. اضافة الى `ذلك، مشتقات جديدة من مركبات 4،3،1- اوكساديازول A15–A18 تم الحصول عليها من تفاعل معوضات الثايوسيميكاربازايد مع التوسيل كلورايد بوجود البريدين. شخصت المركبات الناتجة (البعض منها) بوساطة اطياف الاشعة تحت الحمراء واطياف الرنين النووي المغناطيسي البروتوني وتقنية تحليل العناصر (C. H. N.). تمت دراسة فعاليتها البايولوجية وبنتائج جيدة نسبيا.

Introduction

Oxadiazols, thiadiazoles and triazoles are important classes of five-membered heterocycles with three hetero atoms; oxygen, sulfur and nitrogen. In the literature, a large number of 1,2,4-triazoles have been prepared as biologically active compounds, such as anti-inflammatory, antimicrobial, and antifungal agents [1-3]. Similarly, some of the 1,3,4-thiadiazole derivatives are defined as antifungal, antibacterial, anti-inflammatory, analgesic, anticancer and anticonvulsant drugs [4-9]. Also, a variety of substituted 1,3,4-oxadiazoles have been reported as anticancer, antimicrobial and antiviral materials [10-17]. Due to their wide and extensive range of biological properties, as well as the structural feature as a synthetic intermediate for many pharmaceutical agents, there is a remarkable attraction by all the interested chemists to synthesis and development of new derivatives of five-membered heterocyclic compounds. Hence, synthesis of bis-1,3,4-thiadiazol-2-yl-]-5,5-dimethylcyclohexane and bis-1,2,4-triazol-3-yl-]-5,5-dimethylcyclohexane have been based on the ring closer to acylthiosemicarbazones [18]. While, a new method for the synthesis of 2-amino-1,3,4-oxadiazoles from acylsemicarbazides has been applied using tosyl chloride and pyridine [19]. Moreover, some new derivatives of 5-phenyl-1,3,4-oxadiazole were yielded by reaction of an acid hydrazine and different benzoic acid derivatives in the presence of phosphorous oxychloride [20]. Furthermore, by ring closure mechanism, bis-1,3,4-oxadiazole compounds were prepared from an acid hydrazide which was resulted from the reaction of an aromatic ester and hydrazine hydrate [21]. Recently, 4-amino-5-(3,5-dimethoxyphenyl)-4*H*-[1,2,4]triazole-3-thiol compound was prepared from the reaction 3,5-dimethoxy benzoic acid and thiocarbohydrazide in presence of sodium bicarbonate [22]. More recently and for the current year, a new series of [5-(3,5-dinitrophenyl)-1,3,4-thiadiazole] derivatives were prepared by different methods and evaluated for their antimicrobial and antitumor inhibition activity [23]. Otherwise, the other latterly new derivatives of 1,3,4-oxadiazole bearing sulfonamide were synthesized via [5-(5-cyclohexyl-1,3,4-oxadiazol-2-yl)-2-methyl-benzenesulfonyl chloride] and screened for their biological activities [24].

Consequently, we decided to synthesize some new derivatives of [tetrakis (1,2,4-triazole /1,3,4-tiadiazole /1,3,4-oxadiazole][bis(benzene-1,3,5-triyl)] dioxymethylene, as a part of our interest in the development of new heterocycles with three hetero-atom compounds which are expected to confer good biological activities.

Materials and Methods

Starting materials, reagents, and solvents were obtained from different commercial sources. Thin layer chromatography (TLC) was performed on aluminum plates coated with silica gel 60 F_{254} (20 cm x 20 cm), with a layer thickness of 0.2 mm. for reaction monitoring. Uncorrected melting points of newly synthesized derivatives were determined in open capillary on SMP30 melting point apparatus. Carlo Erba 1108 (C. H. N.) Elemental Analyzer was used for determinations of (C. H. N.) elements. IR spectra were recorded using KBr disc on 8400s FTIR-Shimadzu spectrophotometer. The ^{1}HNMR (300 MHz) was recorded on Bruker DPX 300 spectrometer in DMSO-d6 using TMS as internal standard reference and chemical shift data were expressed in (δ) ppm. Chemical structures were illustrated with CS Chem Draw Ultra (6.0).

General synthetic procedure for the [bis(dimethyl 5-yl-isophthalate)] dioxymethylene, A1: To a mixture of dimethyl 5-hydroxyisophthalate (4.2 g, 0.02mol) of and dibromomethane (1.74 mL, 0.01 mol) in 15 ml of DMF, anhydrous sodium carbonate (2.65 g, 0.025 mol) was added with stirring. The mixture was refluxed for 4h., allowed to cool, poured onto cold water, then cooled at 5°C overnight. The precipitated solid was filtered and washed with water, then recrystallized from ethanol [25].

General procedure for the synthesis of [bis(1,3-phenyldihydrazide-5-yl)] dioxymethylene, A2: A mixture of 4.32 g, 0.01 mol of compound **A1**, excess of 80% hydrazine hydrate (3.0 ml, 0.06 mol), and sodium acetate (3.30 g, 0.04 mole) was dissolved in 30 ml of absolute ethanol and placed in a round bottom flask. Then the reaction mixture was heated under reflux for 2h. in water bath, and poured onto crushed ice. The solid obtained was filtered, and recrystallized from ethanol.

General procedure for the synthesis of [tetrakis(4-substitutedphenylthiosemicarbazide)]-[bis(benzene-1,3-dicarboxy-5-yl)] dioxymethylene A3-A6: The acid hydrazide compound **A2** (2.16 g, 0.005 mol) and appropriate 4-substituted isothiocyanate (0.02 mol) in absolute ethanol (15 ml) were placed in a round bottom flask and refluxed for 3 h. The contents were cooled in ice bath. The precipitated product was filtered, washed with water, and recrystallized from ethanol.

General procedure for the synthesis of [tetrakis(N-(4-substitutedphenyl)-5-mercapto-1,2,4-triazole-3-carboxyl][bis(benzene-1,3,5-triyl)] dioxymethylene, **A7-A10**: In a round bottom flask, a mixture of 0.005 mol of suitable substituted thiosemicarbazide **A3-A6** and 2M solution of sodium hydroxide (20 ml) was heated under boiling in water bath for 4h. The solid product was separated, washed with water, and recrystallized from ethyl acetate [18].

General procedure for the synthesis of [tetrakis(5-(4-substitutedphenyl)-1,3,4-thiadiazole-2-carboxyl)][bis-(benzene-1,3,5-triyl)] dioxymethylene, A11-A14: A mixture of 0.005 mol of different substituted thiosemicarbazide, **A3-A6,** and 10 ml of concentrated H_2SO_4 was stirred at 0°C for 3 h., left at room temperature for 4h., then poured onto crushed ice. The precipitated solid was filtered off, washed with water, and recrystallized from ethyl acetate.

General procedure for the synthesis of [tetrakis(5-(4-substitutedanilinyl)-1,3,4-oxadiazole-2-yl][bis-(benzene-1,3,5-triyl)] dioxymethylene, A15-A18: A mixture of 0.005 mol of suitable substituted thiosemicarbazide **A3-A6**, tosyl chloride (3.81 g, 0.02 mol), and pyridine (0.8 ml, 0.01 mol) was dissolved in 15 ml of tetrahydrofuran (THF) and placed in a round bottom flask. The mixture was heated under reflux for 4-5 hrs. The solid obtained was filtered, washed with water, and recrystallized from ethyl acetate. The nomenclature and physiochemical data of all synthesized compounds are listed in Table-1.

Results and Discussion

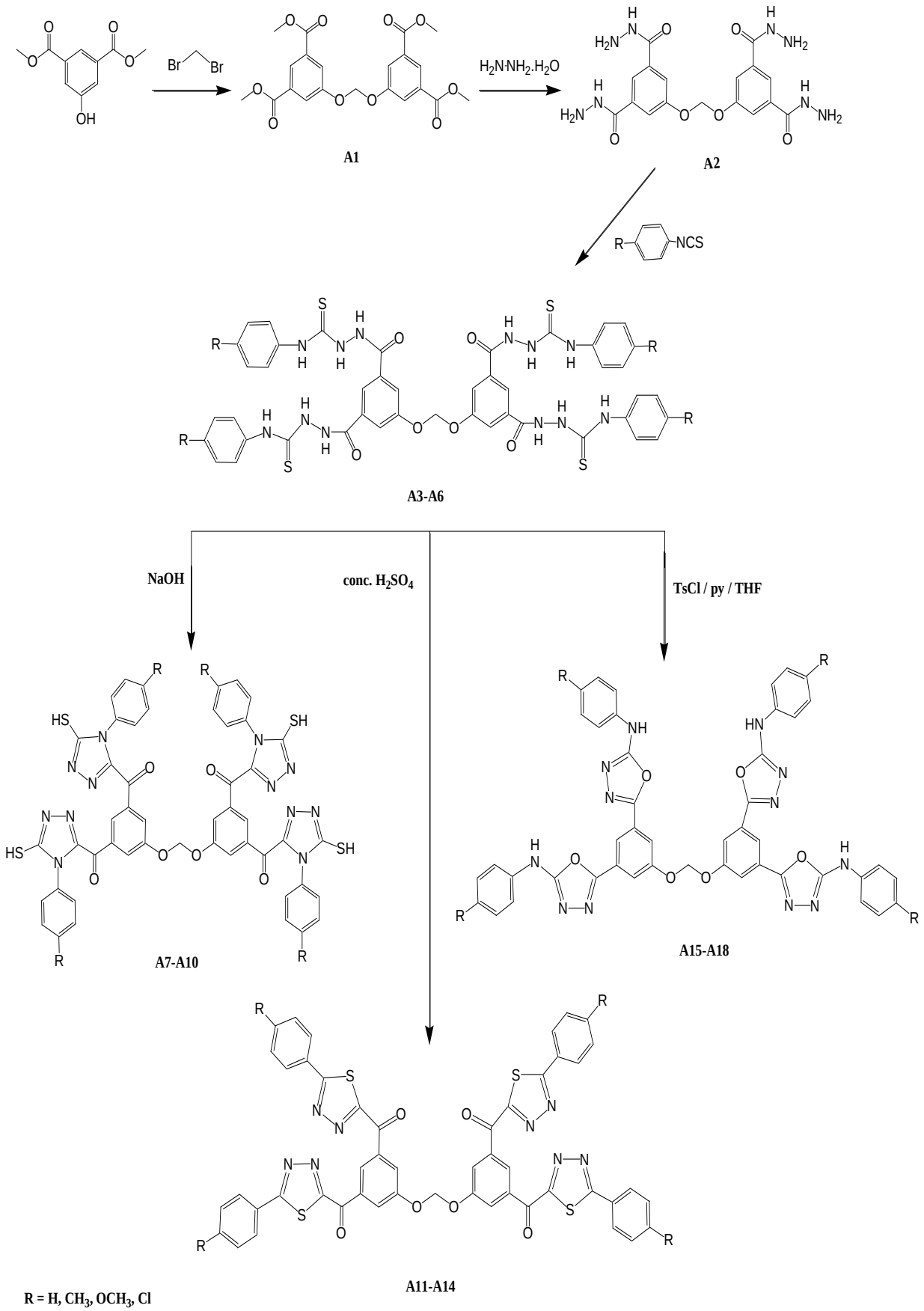
The main synthetic route of the titled compounds includes several steps as described in scheme 1. Firstly, [bis(dimethyl 5-yl-isophthalate)] dioxymethylene **A1** was prepared by the nucleophilic substitution reaction between dimethyl 5-hydroxy isophthalate and 1,2-dibromomethan in presence of anhydrous sodium carbonate as a catalyst base. Then, the compound **A1** was treated with an excess of hydrazine hydrate and sodium acetate in refluxing ethanol to yield the corresponding acid hydrazide compound **A2.** The next step of the outlined scheme involved the preparation of [tetrakis(4-substitutedphenylthiosemicarbazide)][bis(benzene-1,3-dicarboxy-5-yl)] dioxymethylene **A3-A6** by the refluxing of **A2** with various 4-substitutedphenyl isothiocyanates jn absolute ethanol. Further, compounds **A3-A6** were reacted with a dilute solution of 2M of sodium hydroxide under mild.

Table 1-Nomenclature and physiochemical properties of the newly synthesized compounds

No.	R	Mol. Formula	mol. wt. (g/mol)	yield (%)	mp (^{0}C)	Nomenclature
A1		$C_{21}H_{20}O_{10}$	432.38	78	132-134	[bis(dimethyl 5-yl-isophthalate)] dioxymethylene
A2		$C_{17}H_{20}N_8O_6$	432.15	69	155-159	[bis(1,3-phenyldihydrazide-5-yl)] dioxymethylene
A3	H	$C_{45}H_{40}N_{12}O_6S_4$	973.14	58	178-179	[tetrakis(phenylthiosemicarbazide)][bis(benzene-1,3-dicarboxy-5-yl)] dioxymethylene
A4	CH_3	$C_{49}H_{48}N_{12}O_6S_4$	1029.25	61	188	[tetrakis(4-methylphenylthiosemicarbazide)]-[bis(benzene-1,3-dicarboxy-5-yl)] dioxymethylene
A5	OCH_3	$C_{49}H_{48}N_{12}O_{10}S_4$	1093.24	66	212-215	[tetrakis(4-methoxyphenylthiosemicarbazide)]-[bis(benzene-1,3-dicarboxy-5-yl)] dioxymethylene

A6	Cl	$C_{45}H_{36}C_{l4}N_{12}O_6S_4$	1110.92	48	204-205	[tetrakis(4-chlorophenylthiosemicarbazide)]-[bis(benzene-1,3-dicarboxy-5-yl)] dioxymethylene
A7	H	$C_{49}H_{32}N_{12}O_6S_4$	1013.12	47	224	[tetrakis(N-phenyl-5-mercapto-1,2,4-triazole-3-carboxyl][bis(benzene-1,3,5-triyl)]dioxymethylene
A8	CH_3	$C_{53}H_{40}N_{12}O_6S_4$	1069.23	59	232-234	[tetrakis(N-(4-methylphenyl)-5-mercapto-1,2,4-triazole-3-carboxyl][bis(benzene-1,3,5-triyl)] dioxymethylene
A9	OCH_3	$C_{53}H_{40}N_{12}O_{10}S_4$	1133.22	54	241-244	[tetrakis(N-(4-methoxyphenyl)-5-mercapto-1,2,4-triazole-3-carboxyl][bis(benzene-1,3,5-triyl)] dioxymethylene
A10	Cl	$C_{49}H_{28}C_{l4}N_{12}O_6S_4$	1150.90	44	234	[tetrakis(N-(4-chlorophenyl)-5-mercapto-1,2,4-triazole-3-carboxyl][bis(benzene-1,3,5-triyl)] dioxymethylene
A11	H	$C_{49}H_{28}N_8O_6S_4$	953.06	51	218-221	[tetrakis(5-phenyl-1,3,4-thiadiazole-2-carboxyl)][bis-(benzene-1,3,5-triyl)] dioxymethylene
A12	CH_3	$C_{53}H_{36}N_8O_6S_4$	1009.17	54	229-231	[tetrakis(5-(4-methylphenyl)-1,3,4-thiadiazole-2-carboxyl)][bis-(benzene-1,3,5-triyl)] dioxymethylene
A13	OCH_3	$C_{53}H_{36}N_8O_{10}S_4$	1073.16	54	256-258	[tetrakis(5-(4-methoxyphenyl)-1,3,4-thiadiazole-2-carboxyl)][bis-(benzene-1,3,5-triyl)] dioxymethylene
A14	Cl	$C_{49}H_{24}C_{l4}N_8O_6S_4$	1090.84	40	244-247	[tetrakis(5-(4-chlorophenyl)-1,3,4-thiadiazole-2-carboxyl)][bis-(benzene-1,3,5-triyl)] dioxymethylene
A15	H	$C_{45}H_{32}N_{12}O_6$	836.81	71	197-199	[tetrakis(5-anilinyl)-1,3,4-oxadiazole-2-yl][bis-(benzene-1,3,5-triyl)] dioxymethylene
A16	CH_3	$C_{49}H_{40}N_{12}O_6$	892.92	78	201-203	[tetrakis(5-(4-methylanilinyl)-1,3,4-oxadiazole-2-yl][bis-(benzene-1,3,5-triyl)] dioxymethylene
A17	OCH_3	$C_{49}H_{40}N_{12}O_{10}$	956.92	77	219-220	[tetrakis(5-(4-methoxyanilinyl)-1,3,4-oxadiazole-2-yl][bis-(benzene-1,3,5-triyl)] dioxymethylene
A18	Cl	$C_{45}H_{28}C_{l4}N_{12}O_6$	974.59	62	211-212	[tetrakis(5-(4-chloroanilinyl)-1,3,4-oxadiazole-2-yl][bis-(benzene-1,3,5-triyl)] dioxymethylene

conditions to produce 1,2,4-triazole derivatives A7-A10. Likewise, the treatment of the same compounds A3-A6 with concentrated sulfuric acid afforded 1,3,4-thiadiazoles A11-A14. Whereas 1,3,4-oxadiazol derivatives A15-A18 were obtained from the reaction of A3-A6 with tosyl chloride and pyridine in refluxing THF.



Scheme 1-Synthetic route for the designed compounds

Table 2-The characteristic spectral data of the newly synthesized compounds (most of them)

Compd.	**Spectral data**
(**A1**); IR (cm^{-1}): 2955-2922 (CH), 1674 (C=O), 1253 (C-O). 1H NMR, (DMSO-d6, δ, ppm): 7.09-8.55 (m, 6H, ArH), 6.65 (s, 2H, CH2), 3.41 (s, 12H, OCH3).	
(**A2**); IR (cm-1): 3371-3198 (NH2), 2960-2882 (CH), 1668 (C=O), 1248(C-O). ^{1}H NMR, (DMSO-d6, δ, ppm): 8.31 (s, 4H, CONH), 7.15-8.29 (m, 6H, ArH), 6.69 (s, 2H, CH2), 2.50 (s, 8H, NH2).	
(**A3**); IR (cm^{-1}): 3227 (NH), 2956-2876 (CH), 1687 (C=O), 1651 (C=N), 1238 (C=S). ^{1}H NMR, (DMSO-d_6, δ, ppm): 8.28 (s, 4H, CONH), 7.14 - 8.11 (m, 26H, ArH), 6.64 (s, 2H, OCH_2), 3.88 (s, 4H, ArNH), 2.50 (s, 4H, NH). Anal. found (calcd.) % : C, 55.57 (55.54); H, 4.14 (4.14); N, 17.30 (17.27).	
(**A4**); IR (cm^{-1}): 3188 (NH), 2858-2960 (CH), 1689 (C=O), 1664 (C=N). 1HNMR, (DMSO-d_6, δ, ppm): 8.78 (s, 4H, CONH), 7.48 - 8.78 (m, 21H, ArH), 5.49 (s, 2H, OCH_2), 3.82 (s, 4H, ArNH). Anal. found (calcd.) % :. C, 48.68 (48.65); H, 3.27 (3.27); N, 15.16 (15.13).	
(**A7**); IR (cm^{-1}): 2955-2874 (CH), 1691 (C=O), 1651 (C=N),1450 (C-S).1H NMR ((DMSO-d_6, δ, ppm)): 7.98 (m, 26H, ArH), 6.55 (s, 2H,CH2), 3.35(s,4H, ArSH). Anal. found (calcd.): C, 58.03 (58.09); H, 3.18 (3.18);N,16.55 (16.59) %.(**A8**); IR (cm^{-1}): 2955-2874 (CH), 1691(C=O), 1651(C=N),1450(C-S).^{1}H NMR (DMSO-d_6, δ, ppm)): 7.92-6.84(m, 22H, ArH), 6.44 (s, 2H, CH2), 4.57 (s, 4H, ArSH). Anal. found (calcd.): C, 50.57 (59.54); H, 3.77 (3.77); N, 15.75 (15.72) %.	
(**A9**); IR (cm^{-1}): 2872-2975 (CH), 1692 (C=O), 1530 (C=N),1415 (C-S). 1HNMR (DMSO-d_6,δ,ppm): 7.14-8.29 (m, 18H, ArH), 6.24 (s, 2H, CH2), 3.87 (s, 4H, ArSH), 3.33 (s, 12H, OCH_3). Anal. found (calcd.): C, 56.11 (56.17); H, 3.50 (3.56); N, 14.77 (14.83) %.	
(**A12**); IR (cm^{-1}): 2880-2989(CH),1705(C=O),1618(C=N),1465(C-S-C).^{1}HNMR (DMSO-d_6, δ, ppm): 8.25-8.28 (m, 22H, ArH), 6.58 (s, 2H, CH2), 2.51 (s, 12H, CH3). Anal. found (calcd.): C, 63.03 (63.08); H, 3.60 (3.60); N, 11.08 (11.10) %.	
(**A13**); IR (cm^{-1}): 3010-2989 (CH), 1695 (C=O), 1615 (C=N), 1449 (C-S-C). 1H NMR (DMSO-d_6, δ, ppm): 7.28-7.92 (m, 22H, ArH), 6.24 (s, 2H, CH2), 3.15 (s, 12H, OCH3). Anal. found (calcd.): C, 59.36 (59.32); H, 3.38 (3.38); N, 10.45 (10.44) %.	
(**A17**); IR (cm^{-1}): 3345 (NH), 2854-2944 (CH), 1634 (C=N), 1365-1425 (C-O-C); 1H NMR (DMSO-d_6, δ, ppm): 6.98-7.62 (m, 22H, ArH), 6.45 (s, 2H, CH2), 4.00 (s,4H, ArNH), 3.47 (s, 12H, OCH3). Anal. found (calcd.): C, 61.47 (61.50); H, 4.21 (4.21); N, 15.52 (17.56) %.	
(**A18**); IR (cm^{-1}): 3182 (NH), 2976-2858 (CH), 1680 (C=N), 1392-1338 (C-O-C); 1H NMR (DMSO-d_6, δ, ppm): 8.38-7.34 (m, 22H, ArH), 5.60 (s, 2H, O-CH2-O), 4.18 (s,4H, NH). Anal. found (calcd.): C, 55.48 (55.46); H, 2.90 (2.90); N, 17.28 (17.25) %.	

The chemical structures of the desired compounds were deduced from their spectroscopic analysis data which are given in table 2. However, the IR spectrum of the tri-ester compound A1 showed the disappearance of (OH) phenolic absorption band, whereas the absorption band of the (C-O) group appeared at 1253 cm^{-1}. Further, the stretching absorption band of the ester carbonyl group (C=O) at 1674 cm^{-1} was recorded (Figure-1). On the other hand, the ^{1}HNMR spectrum of A1 exhibited multiplet signals at 7.25-7.69 ppm corresponding to the aromatic protons. Singlet signals were recorded at 6.27 ppm and a singlet at 3.24 ppm was attributed to the methylene (O-CH_2-O) and methoxy (-OCH_3) protons, respectively (Figure-2). For compound A2, the spectral data gave an agreement with the designed structure [26, 27]. Hence, the IR spectrum showed absorption bands at 3382-3452 cm^{-1} corresponding to (NH_2) group stretching vibrations (Figure-3). While the ^{1}HNMR spectrum of the same compound exhibited some peaks at 7.44-8.69 ppm, 6.24 ppm, and 2.24 ppm due to the aromatic, methylene (O-CH_2-O) [27], and amino (NH_2) protons, respectively (Figure-4). The IR spectrum of A3 showed some bands in the region 3227-3183 cm^{-1} belonging to the stretching vibrations of (NH) group. In addition, another stretching vibrational band of the carbonyl group (C=O) at 1687 cm^{-1} was noted, while other stretching absorption bands were recorded at 1651cm^{-1} and 1238 cm^{-1} due to the imino (C=N) and thiocarbonyl (C=S) groups, respectively [28] (Figure-5). As for the titled compounds A7-A18, the spectroscopic analysis revealed the disappearance of the stretching absorption bands of the secondary amide carbonyl (HN-CO) and thiocarbonyl (C=S), while the chemical shifts caused by the (OCNH-) protons of thiosemicarbazides A3-A6 were not observed, which is a considerable directory for the expected structures. In contrast, the FTIR spectra of A7-A18

recorded some new bands in the region 1620-1651 cm^{-1} due to (C=N) of the five-membered ring as shown, for instance, in Figures-(7 and 9), for instance. On the other hand, the spectroscopic analysis of ^{1}H NMR spectra gave a consequence of the designed structures. For example, the ^{1}H NMR spectrum of compounds A9 and A18, as depicted in figures 8 and 10, exhibited the singlet signals in the region 3.67-4.55 ppm which are corresponding to the (Ar.SH) and (Ar.NH) protons, beside the others signals which are listed in Table-2.

Antimicrobial Activity

Some of the synthesized compounds were tested for their antimicrobial activities against two types of bacteria (*Bacillus subtilis* and *Escherichia coli*), and two fungi microorganisms, *Candida albicans* and *Aspergillus niger*) using the disc diffusion method [29]. The zone inhibition area was measured in millimeters (mm), while the concentration of all tested compounds which were dissolved in N,N-dimethylformamide (DMF) was 1ppm. The plates were kept at 37 ^{0}C and examined after 24h. Streptomycin and fluconazole were used as standard antibiotics and antifungal references, respectively. The results showed that all the tested compounds exhibited weak antibacterial activities. In contrast, some of the examined compounds such as A6, A14 and A18 revealed a good activity as antifungal agents (Table-3).

Table 3-Antibacterial and antifungal activities of some synthesized compound

Compd.	Zone inhibition (mm)			
	Bacterial strains		Fungal strains	
	Bacillus subtilis	*E. coli*	*Aspergillus flavus*	*Candida albicans*
A6	02	0	18	10
A7	0	03	12	13
A11	07	0	09	12
A14	12	0	13	18
A17	10	04	11	14
A18	12	02	16	18
Streptomycin	28	21		
Fluconazole			30	34
DMF	0	0	0	0

Conclusion

In summary, a new series of tetrakis (1,2,4-triazole/ 1,3,4-thiadiazole/1,3,4-oxadiazol) derivatives were synthesized in a simple, easy, and cost-effective method. Structures of some of the new compounds were established from their spectroscopic and C.H.N. elemental analysis with satisfactory results. Some of these compounds were screened for their antimicrobial activities. For antibacterial activities, the results were insignificant whereas good antifungal activities were achieved.

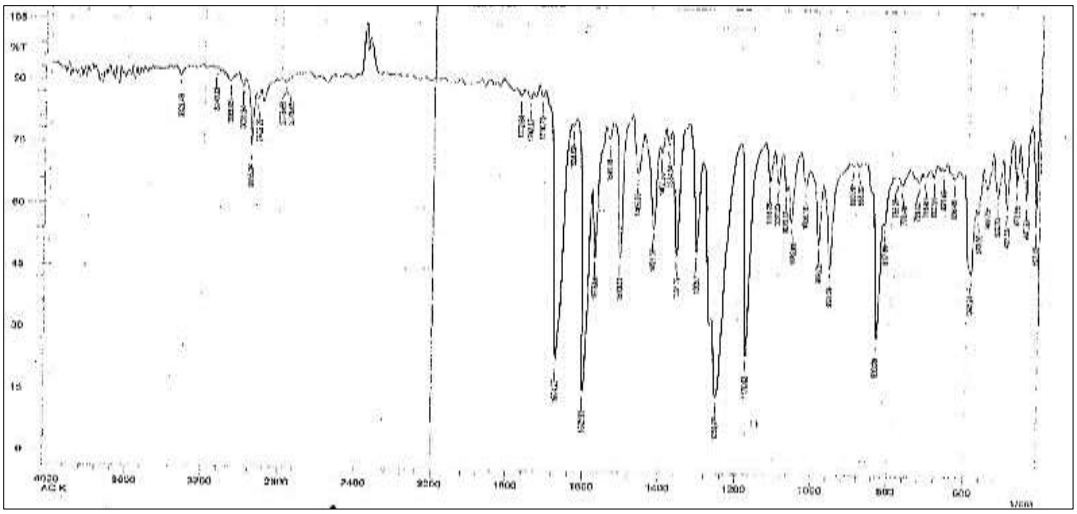


Figure 1-FTIR Spectrum of compound (**A1**)

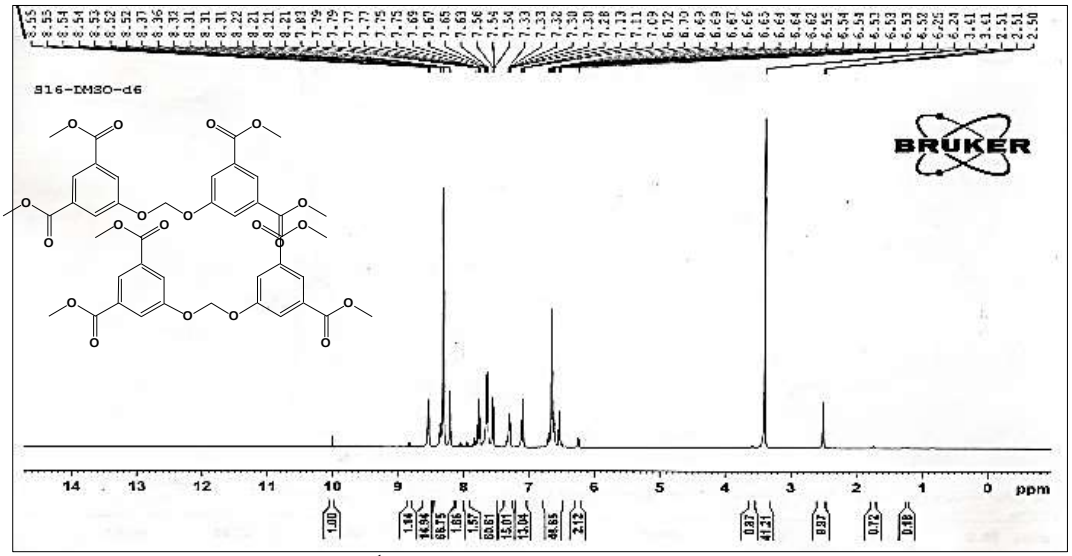


Figure 2-[1]HNMR Spectrum of compound (**A1**)

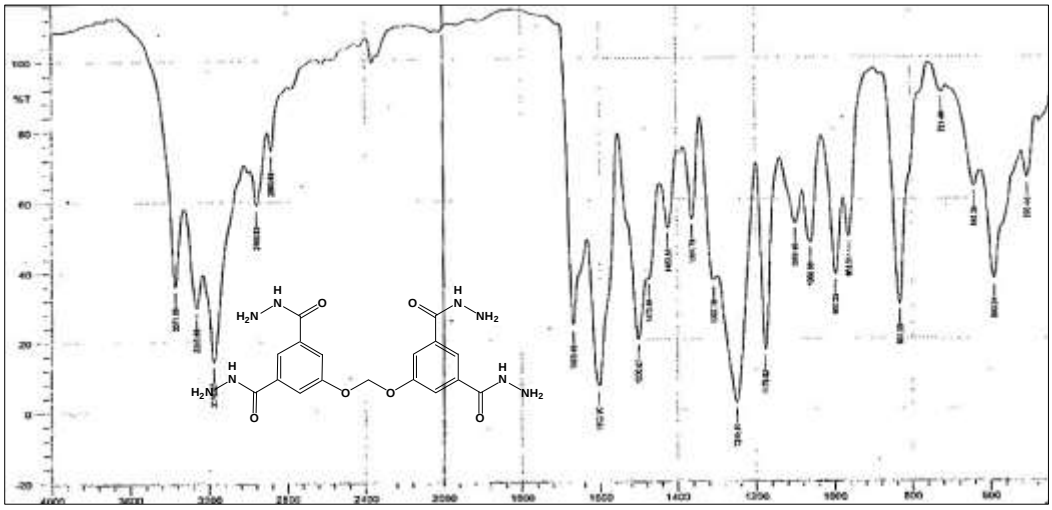


Figure 3-FTIR Spectrum of compound (**A2**)

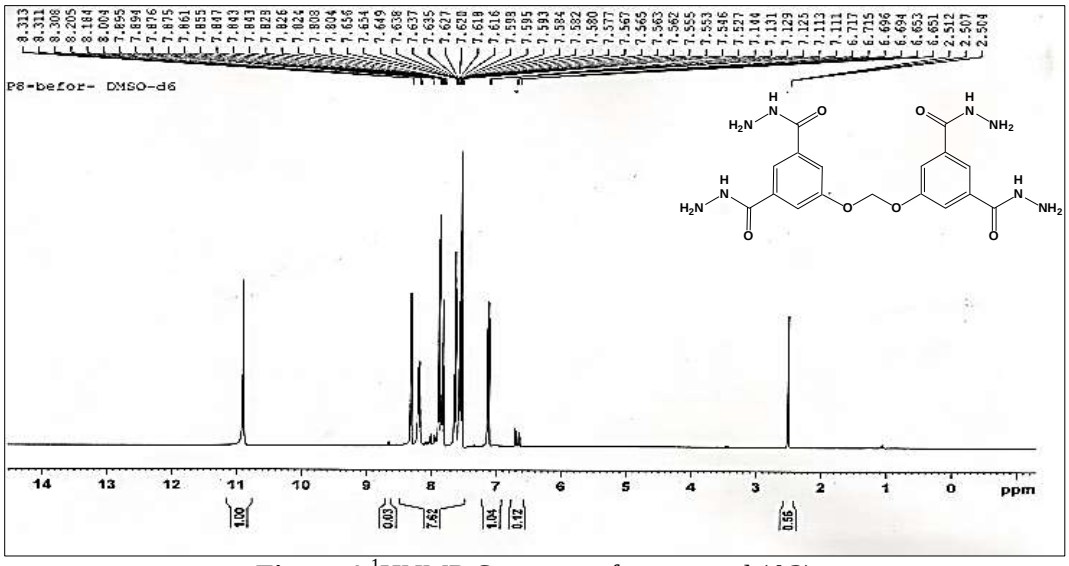


Figure 4-[1]HNMR Spectrum of compound (**A2**)

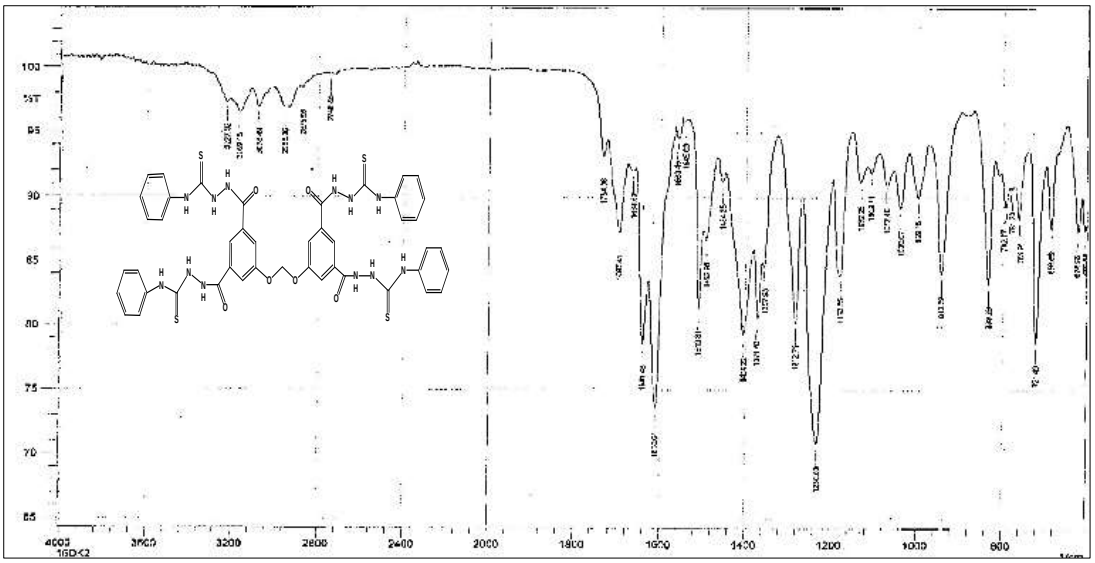


Figure 5-FTIR Spectrum of compound (**A3**)

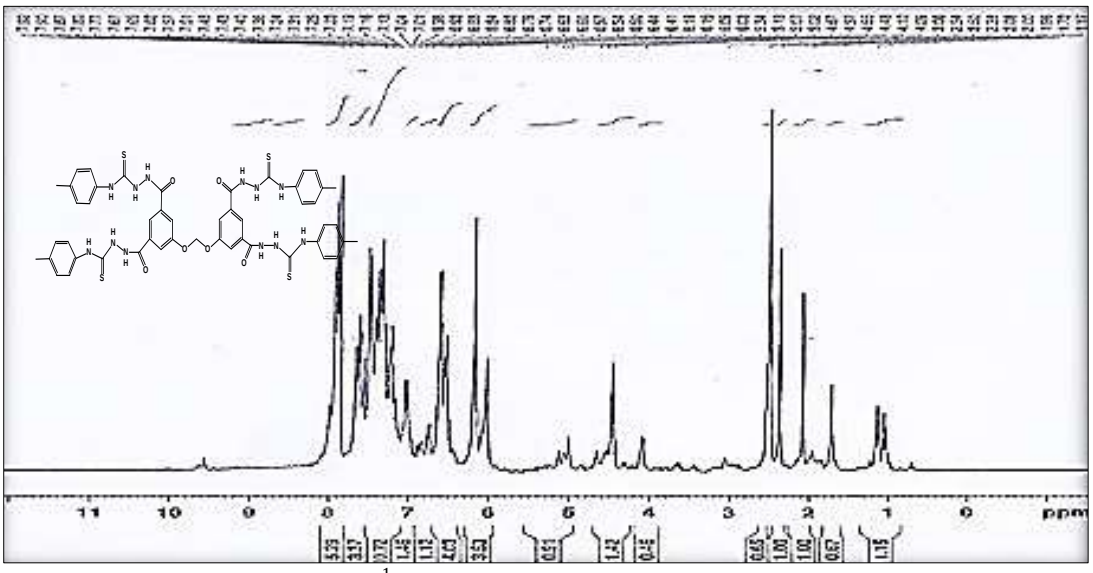


Figure 6-^{1}HNMR Spectrum of compound (**A4**)

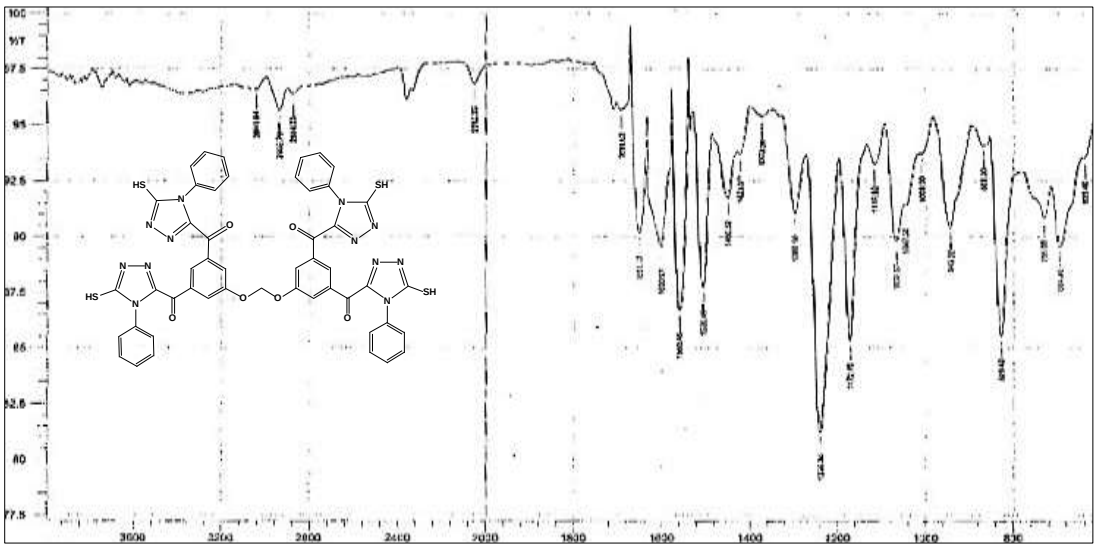


Figure 7-FTIR Spectrum of compound (**A7**)

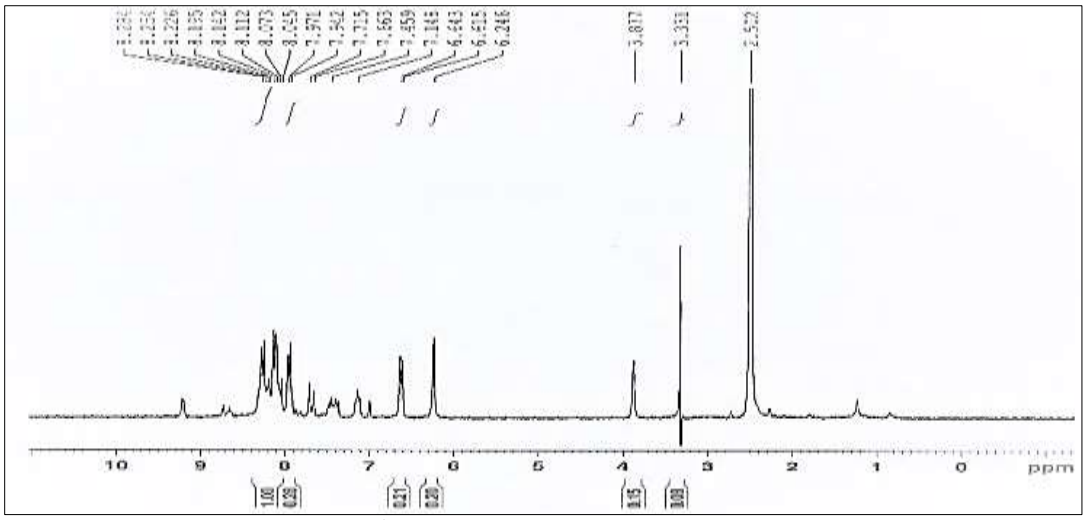


Figure 8-[1]HNMR Spectrum of compound (**A9**)

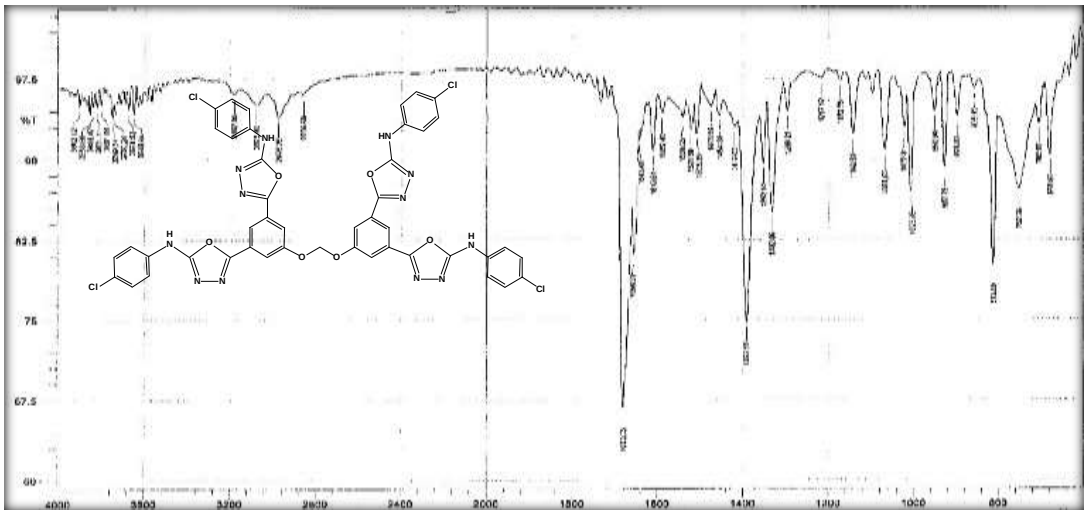


Figure 9-FTIR Spectrum of compound (**A18**)

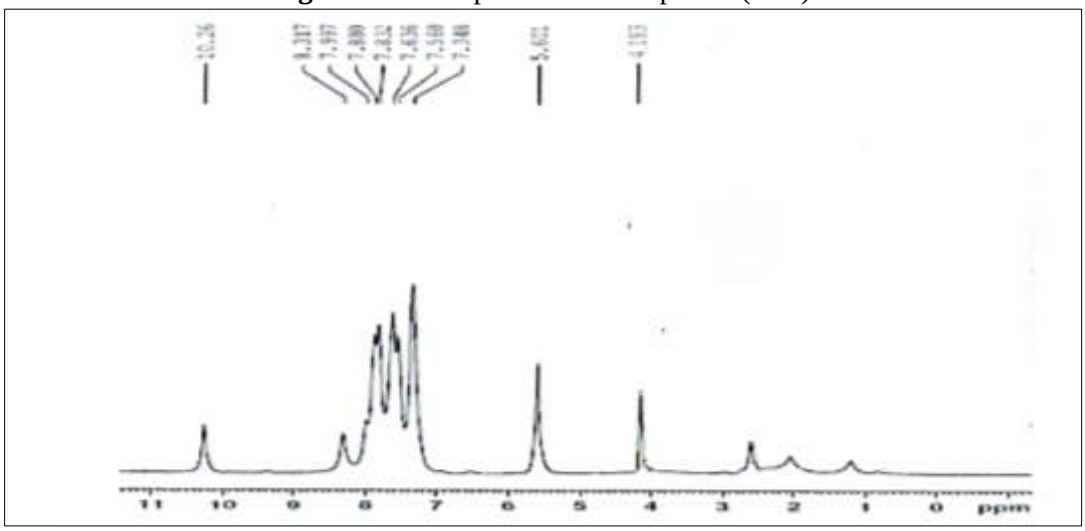


Figure 10-[1]H NMR Spectrum of compound (**A18**)

References

1. Isloor, A. M., Kalluraya, B. and Shetty, P. **2009**. Regioselective reaction: synthesis, characterization and pharmacological studies of some new Mannich bases derived from 1,2,4-triazoles. *Eur. J. Med. Chem*, **44**: 3784–3787.

2. Sakata, M., Shirakawa, Y., Kamata, N., Hiroshino, Y. S. and Jie, O. Y. **2000.** Synthesis and antibacterial activity of some new *s*-triazolo[3,4-*b*]-1,3,4- thiadiazine derivatives. *J. Heterocycl. Chem.*, **37:** 269–271.

3. Holla, B. S., Rao, B. S., Sarojini, B. K., Akberali, P. M. and Kumari, N. S. **2006**. Synthesis and studies on some new fluorine containing triazolothiadiazines as possible antibacterial, antifungal and anticancer agents. *Eur. J. Med. Chem.*, **41**: 657–663.

4. Jain, K., Sharma, S., Vaidya, A., Ravichandran, V. and Agrawal, R. K. **2013**. 1,3,4-Thiadiazole and its derivatives: a review on recent progress in biological activities. *Chem Biol Drug Des*., **81**: 557–576.

5. Kushwaha, N., Kushwaha, S. K. S. and Rai, A. K. **2012**. Biological activities of thiadiazole derivatives: a review. *Inter J Chem Res*., **4**: 517–531.

6. Gomha, S. M., Salah, T. A. and Abdelhamid, A. O. **2015.** Synthesis, characterization, and pharmacological evaluation of some novel thiadiazoles and thiazoles incorporating pyrazole moiety as anticancer agents. *Monatsh Chem*., **146**: 149-158.

7. Siddiqui, N., Ahuja, P., Ahsan, W., Pandeya, S. N. and Alam, M. S. **2009**. Thiadiazoles: progress report on biological activities. *J Chem Pharm Res*., **1**: 19-30.

8. Kumar, D., Kumar, N. M., Chang, K. H. and Shah, K. **2010**. Synthesis and anticancer activity of 5-(3-indolyl)-1,3,4-thiadiazoles. *Eur J Med Chem*., **45**: 4664-4668.

9. Sharma, B., Verma, A., Prajapati, S. and Sharma, U. K. **2013**. Synthetic methods, chemistry, and the anticonvulsant activity of thiadiazoles. *Int J Med Chem*., **34**: 8948.

10. Mohammed, J. A., Vikram, P. S., Ramdayal, S., Surender, S. J., Sabina, Y. and Pradeep, K. **2013.** Synthesis, anticancer, and molecular docking studies of 2-(4-cholorophenyl)-5-aryl-1,3,4-oxadiazole analogues. *Med. Chem. Res*., **3**: 294-297.

11. Murthy, M. S. R., Ramalingeswara, R. B., Maohana, R. K., Lekshmi, N. R. and Ruby, J. A. **2013.** Synthesis of piperazinyl benzothiazole/benzoxazole derivatives coupled with 1,3,4-oxadiazole-2-thiol: Novel hybrid heterocycles as anticancer agents. *Med. Chem. Res*., **22**: 4980-4991.

12. Bereket, M., Xin, Q., Suresh, E., Donald, S., Neelly, M. K. and Soliman, F. **2016.** Design and evaluation of novel oxadiazole derivatives as potential prostate cancer inhibitors. *Bioorg. Med. Chem. Lett.*, **26**: 2847-2851.

13. Rajesh, A. R., Shweta, G. D. and Niteshkumar, S. **2012.** Synthesis and evaluation of novel 1,3,4-oxadiazole derivatives of marine bromopyrrole alkaloids as antimicrobial agent. *Bioorg. Med. Chem. Lett*., **22**: 6429-6432.

14. Shrihar, M., Arun, I. M., Peethambar, S. K. and Hoong, K. F. **2014**. Synthesis and biological evaluation of newer analogues of 2,5-disubstituted 1,3,4-oxadiazole containing pyrazole moiety as antimicrobial agents. *Arabian J. Chem*., **7**: 1185-1191.

15. Desai, N. C., Kotadiya, G. M., Triveni, A. R. and Khedkar, V. M. **2016**. Synthesis, biological evaluation and QSAR studies of novel pyrazole bearing pyridyl oxadiazole analogues as potential antimicrobial agents. *Med. Chem. Res*., **25**: 712-727.

16. Wenneng, W., Qin, C., Anqi, T., Guangqi, J. and Guiping, O. **2015**. Synthesis and antiviral activity of 2-substituted-methylthio-5-(4-amino-2-methylpyrimidin-5-yl)-1,3,4-oxadiazole derivatives. *Med. Chem. Lett.*, **25**: 2243-2246.

17. Tashfeen, A., Shahid, H., Najim, A., Roberta, L. and Paolo, L. C. **2005**. In vitro antitumor and antiviral activities of new benzothiazole and 1,3,4-oxadiazole-2-thione derivatives. *Acta. Pharm.*, **58**:135.

18. Dabholkar, V. V. and Ansari, F. Y. **2008.** Synthesis and biological studies of bis (thiadiazole / triazole) by sonication. *Acta Poloniae Pharmaceutica*., **65** (5): 521-526.

19. Dolman, S. J., Gosselin, F., O'shea, P. D. and Davies, I. W. **2006**. Superior reactivity of thiosemicarbazide in the synthesis of 2-amino-1,3,4-oxadizaoles. *J. Org. Chem.*, **71**: 9548–9551.

20. Bodke, Y. D., Biradar, S. A. and Kenchappa, R. **2016**. Synthesis, characterization, and biological evaluation of 2-(2-substituted)-5-phenyl-1,3,4-oxadiazole and 3,6-

diphenyl[1,2,4]triazole[3,4-][1,3,4]thiadiazole derivatives. *Indian Journal of Advances in Chemical Science*, **4**(3): 269-275.

21. Tomi, I. H. R., Al-Qaisi, A. H. J. and Al-Qaisi, Z. H. J. **2010**. Synthesis, characterization and effect of bis-1,3,4-oxadiazole containing glycine moiety on the activity of some transferase enzymes. *Ibn Al-Haitham Journal for Pure and Applied Science*, **23**: 33.

22. Moorthy, N. S. H. N., Vittal, U. B., Karthikeyan, C., Thangapandian, V., Venkadachallam, A. P., and Piyush, T. **2017**. Synthesis, antifungal evaluation and in silico study of novel Schiff bases derived from 4-amino-5-(3,5-dimethoxy-phenyl)-4H-1,2,4-triazol-3-thiol. *Arabian Journal of Chemistry*, **10**: S3239–S3244.

23. El-Naggar, M., Sallam, A. H., Shaban, S. S., Abdel-Wahab, S. S., Amr, A. E., Azab, M. E., Nossier, E. S., and Al-Omar, M. A. **2019.** Design, synthesis, and molecular docking study of novel heterocycles incorporating 1,3,4-thiadiazole moiety as potential antimicrobial and anticancer agents. *Molecules*, **24**: 1066.

24. Selvaraj, K., Zulfareen, N. and Kulanthai, K. **2019**. Synthesis and biological evaluation of sulfonamide-based 1,3,4-oxadiazole derivatives. *Bull. Chem. Soc. Ethiop.*, **33**(2): 307-319.

25. Ayyash, A. N., Jaffer, H. J., and Tomma, J. H. **2014.** Synthesis and characterization of some novel 4-thiazolidinones and isoxazolines derived from thiosemicarbazones. *American Journal of Organic Chemistry*, **4**(2): 52-62.

26. Silvrstein, R. M., Welster, F. X. and Kienle, D. J. **2005**. Spectrometric Identification of Organic Compounds. 7th edition, New York. John Wiely and Sons Inc.

27. Sharma, Y. R. **2009**. *Elementary Organic Spectroscopy*. 5th Ed. New Delhi. S. Chand and Company Ltd.

28. Kumar, A., Jayaroopa, P. and Kumar, V. **2012**. Comprehensive review on the chemistry of 1,3,4-oxadiazoles and their application. *International Journal of ChemTech Research*, **4**(4):1782-1788.

29. Arthington-Skaggs, B., Motley, M. and Morrison, C. J. **2000**. Comparative evaluation of PASCO and national committee for clinical laboratory standards m-27-a broth microdilution methods for antifungal drug susceptibility testing of yeast. *J. Clin. Microbiol.*, **38**: 2254-2260.