Synthesis and Characterization of New Thioxanthone Derivatives

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Abstract:

This work comprises the synthesis of new thioxanthone derivatives containing C-substituted thioxanthone. To obtain these derivatives, the o-mercapto benzoic acid was chosen as the starting material, which was reacted with dry benzene in sulfuric acid (98 %) to produce the thioxanthone (**1**). The 2,7-(disulfonyl phosphine imine) thioxanthone (**4-8**) were prepared from reaction of compound (**1**) with chlorosulfonic acid gave 2,7-(disulfonyl chloride) thioxanthone (**2**). Treatment of (**2**) with sodium azide to produce 2,7-(disulfonyl azide) thioxanthone (**3**). Condensation of (**3**) with phosphorus compounds afforded compounds (**4-8**). The 2,7-(disulfonamide) thioxanthone (**9-21**) was obtained when compound (**2**) condensed with different aromatic amines, it gave the expected amides (**9-21**).

Keywords: Thioxanthone, Chlorosulfonation, Sulfonyl phosphineimine.

Introduction:

Thioxanthone and derivatives are an important class of molecules and are a common heterocyclic scaffold in biologically active and medicinally significant compounds [1,2]. The thioxanthone and derivatives are the core structure of a wide variety of naturally occurring and synthetic compounds that exhibit extraordinary anti-tumor [3,4,5], anti-parasitic [6,7], anti-cancer activity [8,9], anti-hypertensive, anti-oxidative, anti-thrombotic [10,11] and are potential anti-cancer drugs and some thioxanthones containing plant extract are directly used in traditional medicine [4,5]. The thioxanthone [12,13] possess a number of interesting pharmacological activities [14,15]. Certain members of these classes of compounds exhibit significant anti-tumor and cytotoxic effects [16,17].

Materials and Methods:

General

All reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm pre-coated silica-gel F254 plates, spots were detected with iodine vapour. The IR spectra were recorded on (SHIMDZU) FT-IR 8400 spectrophotometer; solid samples were run in KBr discs, Liquid samples were run as smears. UV spectra were recorded with UV-Visible spectrophotometer (CARY) UV-100 Conc. Melting points were determined on a Gallenkamp meting point apparatus with sample contained in open capillary glass tube in an electrically heated metal block apparatus and were un corrected. ^{1}H-NMR spectra were recorded on ultra shield 300 MHz

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NMR spectrophotometer in acetone-d_6 solutions and with tetra methylsilane (TMS) as an internal standard.

Preparation of thioxanthone (1)

This compound was prepared according to the reported in literature [21,22]; m.p. 209-211°C (lit. m.p. 209°C [21,22]).

Preparation of 2,7-(disulfonyl chloride) thioxanthone (2)

Compound (**1**) (2.12 g, 0.01 mol) was added in portions to (10 ml) cold chlorosulfonic acid. The mixture was heated and maintained (70-80)°C for (7 hrs). The reaction mixture was poured into an ice - water, then the solid product was filtered and recrystallized from methanol or ethanol. A brown crystal was formed.

Preparation of 2,7-(disulfonyl azide) thioxanthone (3)

Compound (**2**) (4.1 g, 0.01mol) was added in portions to a suspension of sodium azide (1.3 g, 0.02 mol) in acetone (50 ml). The mixture was stirred at room temperature for (24 hrs). The solid NaCl and excess NaN_3 were filtered off and the solvent was distilled and a white solid was formed, recrystallized from methanol.

Preparation of 2,7-(disulfonyl phosphineimine) thioxanthone (4-8)

A solution of (trimethyl phosphite/ triphenyl phosphine/ diphenyl methyl phosphine/ dimethyl phenyl phosphine/ diethyl phenyl phosphine) (0.05 mol) in (5 ml) of dry diethyl ether was added to a solution of compound (**3**) (10.56 g, 0.025 mol) in (5 ml) of dry THF. Complex was first formed which then decomposed with evolution of nitrogen, on standing over night in the refrigerator. The solution deposited crystals which was recrystallized from a suitable solvent. Table (1) represents the physical data of compounds (1-8). Characteristic absorption bands of FT-IR and U.V spectra of compounds (1-8) are listed in Table (2). Table (5) represent the ^{1}H-NMR spectra for compounds (1,4,6,8).

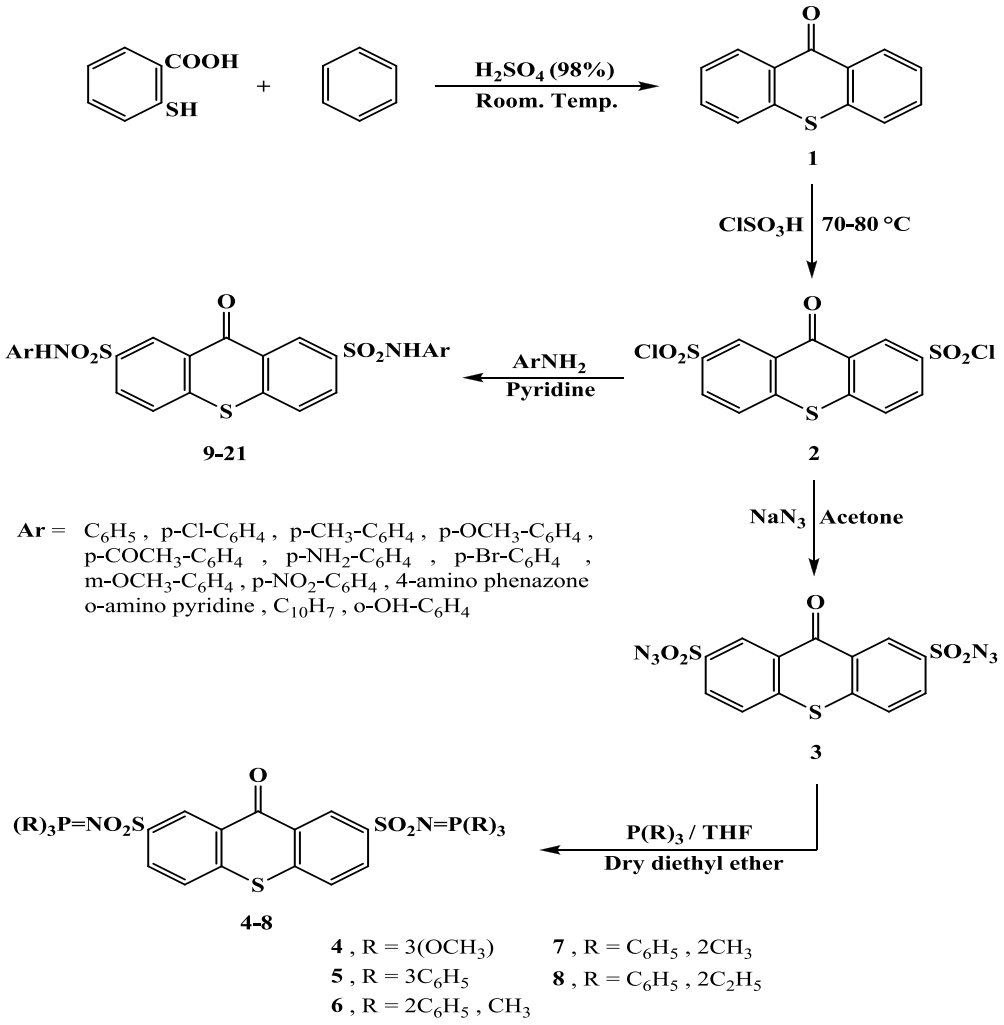
Preparation of 2,7-(disulfonyl amide) thioxanthone (9-21)

Aniline (1.8 ml, 0.01mol) was dissolved in (15 ml) of dry pyridine, (2.04 g, 0.005 mol) of compound (**2**) was added in portions with stirring and keeping temperature below (40)°C, the mixture was refluxed for (3 hrs) with stirring. After cooling at room temperature, the mixture was poured into cold water with stirring, a brown precipitate was afforded, then recrystallized from a suitable solvent. Table (3) represents the physical data of compounds (9-21). Characteristic absorption bands of FT-IR and U.V spectra of compounds (9-21) are listed in Table (4). Table (5) represent the ^{1}H-NMR spectra for compounds (13,14).

Results and Discussion:

The new phosphorus compound derivatives were prepared following the reaction sequences depicted in Scheme. The starting material for the synthesis of targeted compounds is o-mercapto benzoic acid, which was reacted with dry benzene in the presence of sulfuric acid (98 %) to give thioxanthone (**1**) according to the reported method [18-19]. Reaction between (**1**) and excess of chlorosulfonic acid at (70)°C for several hours afforded 2,7-(disulfonyl

chloride) thioxanthone (**2**). Treatment of (**2**) with sodium azide in acetone media it gave after the usual work up the expected 2,7-(disulfonyl azide) thioxanthone (**3**). IR spectra showed the azide (N_3) stretching absorption at 2138 cm^{-1}. When compound (**3**) was reacted with trimethyl phosphite, triphenyl phosphine, diphenyl methyl phosphine, dimethyl phenyl phosphine and diethyl phenyl phosphine at room temperature, a moderate reaction concerned with evolution of nitrogen to produce the imino phosphorus (**4-8**) via intermediate complexes [20-23]. The conversion to the intermediate could be effected in five minutes at room temperature in dry ether and dry THF, but incubation of the reaction mixture in refrigerator for (24 hrs). It gave a good yield (60-70)% of phosphine imine and phosphite imine. Condensation of compound (**2**) with different aromatic amines gave the expected 2,7-(disulfonamide) thioxanthone (**9-21**).



Scheme: **Synthesis of thioxanthone derivatives**.

The structures of all derivatives the thioxanthone (**1**) were proven on the basis of melting points (m.p.), thin layer chromatography (T.L.C) and spectral data.

Table (1): Represent the physical data of compounds (1-8)

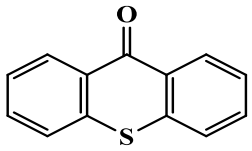
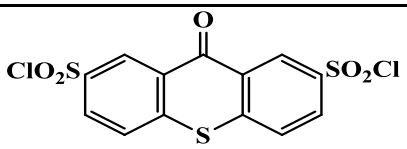
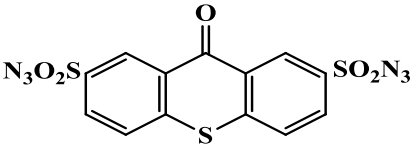
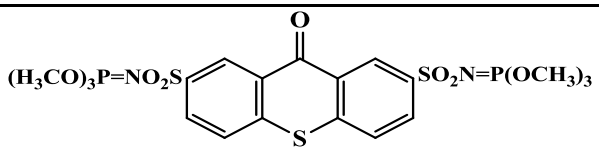
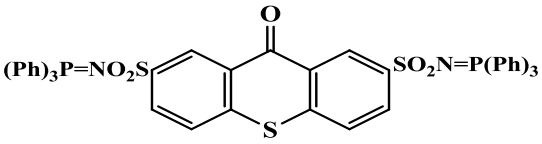
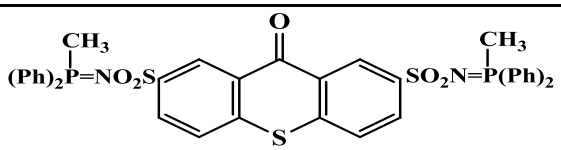
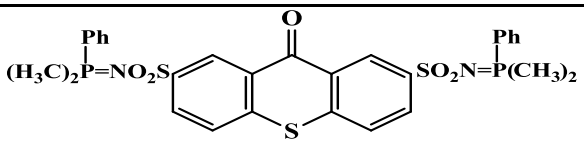
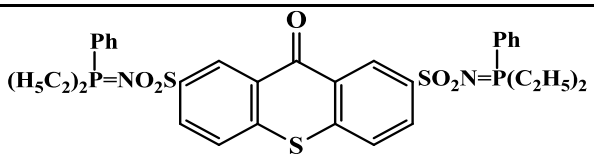
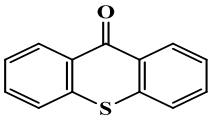
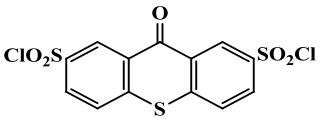
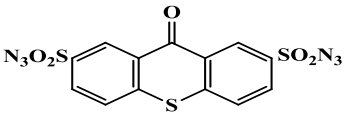
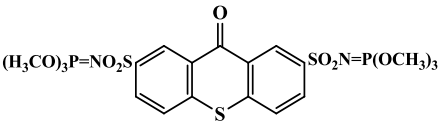
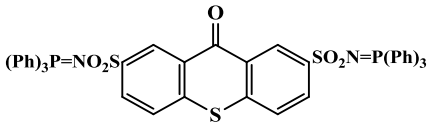
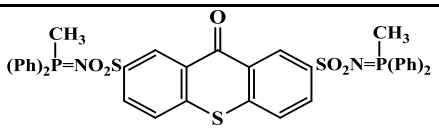
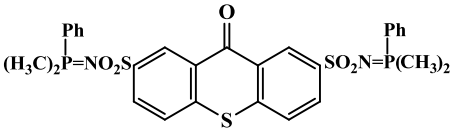
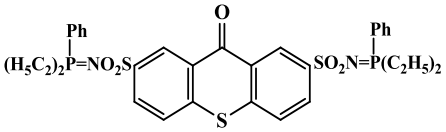
Comp. No.	Compound structure	Color of crystal	m.p. °C	Yield %	Recrystallization Solvent
1		Yellow	209-211	90	Glacial acetic acid
2		Brown	141-143	74	Ethanol or Methanol
3		White	126-128	76	Methanol
4		Green	130-132	70	Dioxane
5		Yellow	70-72	61	Dioxane
6		Red	191-193	64	Chloroform
7		Reddish -yellow	225-227	69	Dioxane
8		Yellow	197-199	67	Chloroform

Table (2): Characteristic absorption bands of FT-IR and U.V spectra of compounds (1-8)

Comp. No.	Compound structure	FTIR spectral data cm^{-1}						U.V. (λ_{max}) nm
		υ(C-H) Aromatic	υ(C-H) Aliphatic	υ(C=C) Aromatic	υ(C=O) Ketone	υ(SO_2) asym. sym.	Others	
1		3069	-	1589 1444	1643	-	-	391
2		3042 3011	-	1583 1447	1664	1380 1180	-	393
3		3084 3033	-	1589 1443	1638	1374 1179	υ(N_3) 2138	406
4		3069 3032	2891 2962	1591 1451	1641	1368 1169	υ(N=P) 1120 1036 740 υ(POC) 1080	397
5		3077 3038	-	1437 1477 1587	1640	1374 1176	υ(N=P) 1118 1090 746	398
6		3056	2898 2961	1441 1478 1591	1640	1379 1173	υ(N=P) 1117 1042 748	388
7		3054 3022	2899 2989	1440 1589	1641	1374 1165	υ(N=P) 1106 1051 750	396
8		3059 3024	2877 2912	1459 1588	1637	1371 1162	υ(N=P) 1112 1019 747	380

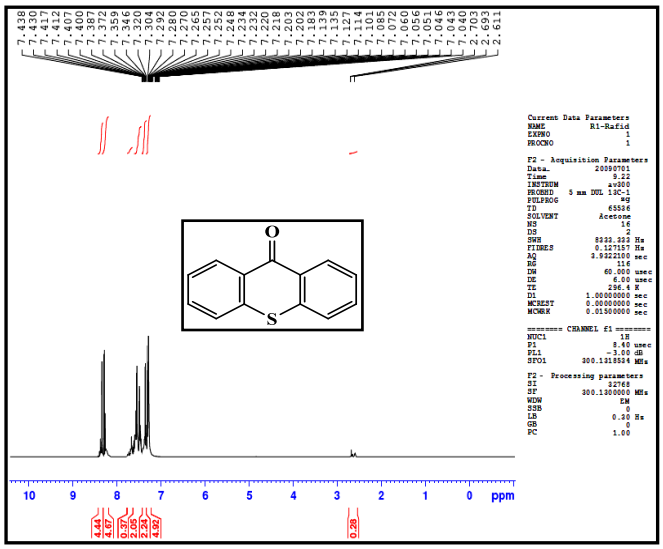


Fig.(1): ^{1}H-NMR spectrum for compound (1)

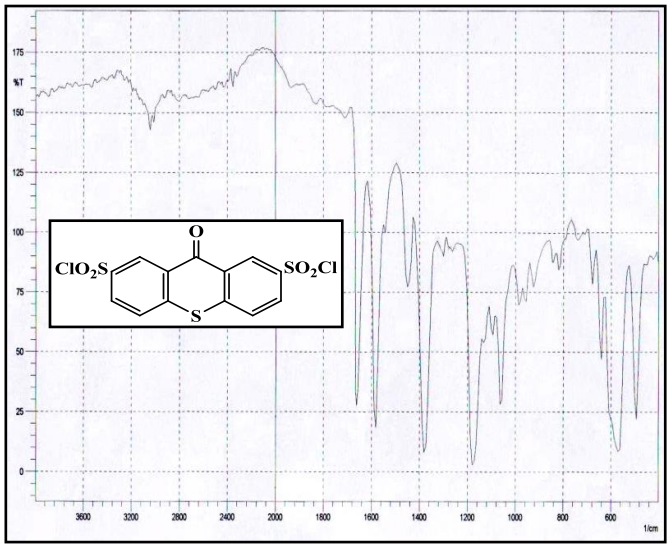


Fig.(2): FT-IR spectrum for compound (2)

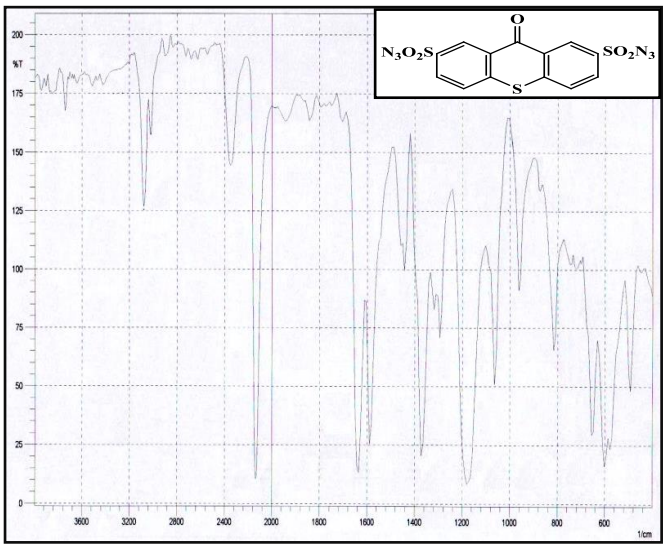


Fig.(3): FT-IR spectrum for compound (3)

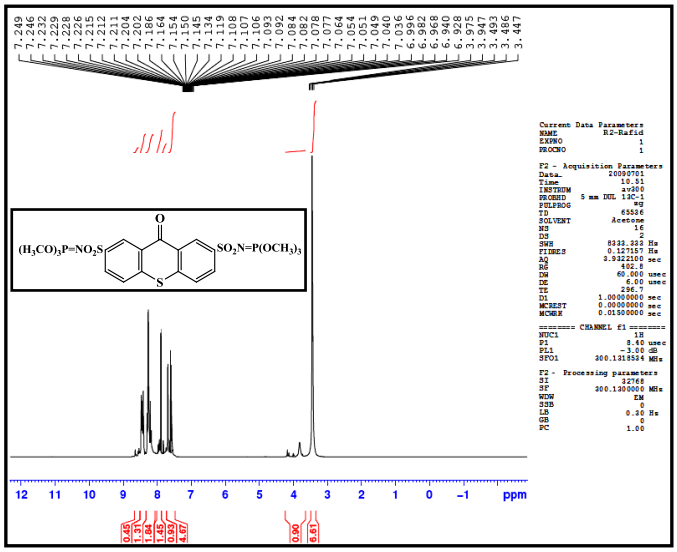


Fig.(4): ^{1}H-NMR spectrum for compound (4)

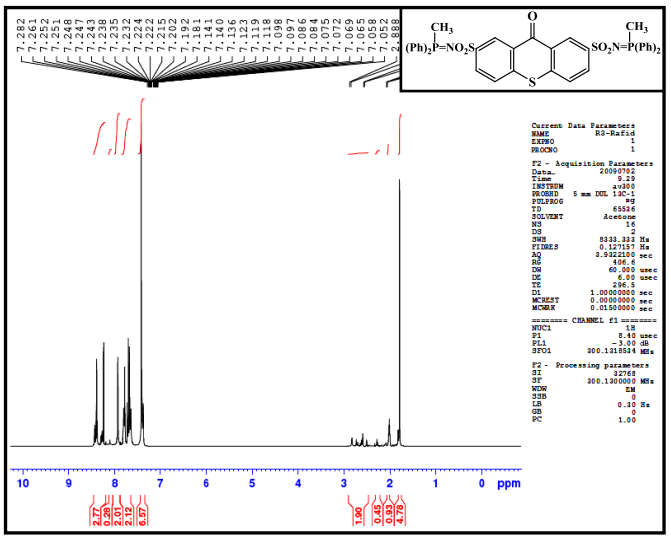


Fig.(5): ^{1}H-NMR spectrum for compound (6)

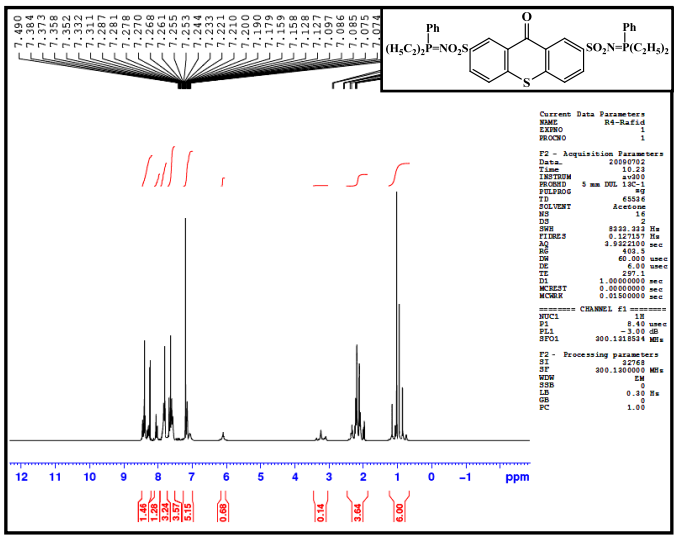


Fig.(6): ^{1}H-NMR spectrum for compound (8)

Table (3): Represent the physical data of compounds (9-21)

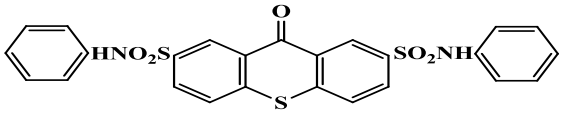
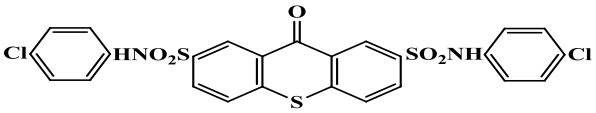
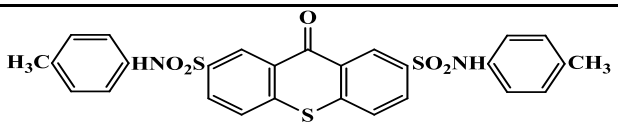
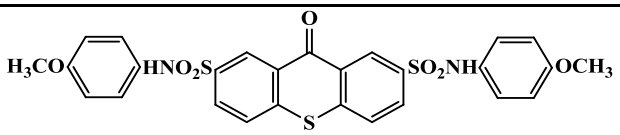
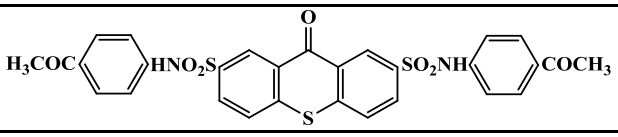
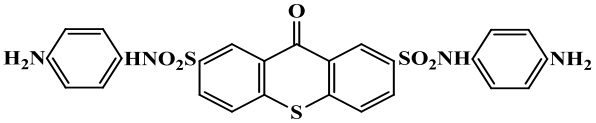
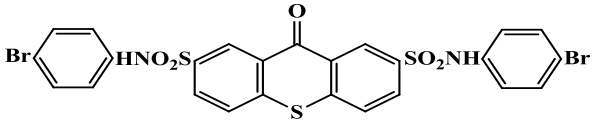
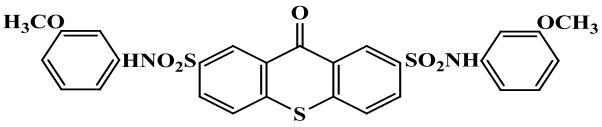
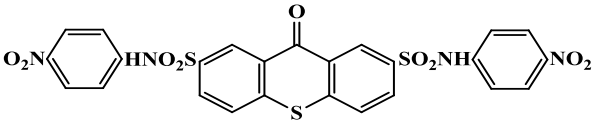
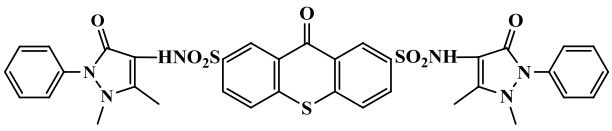
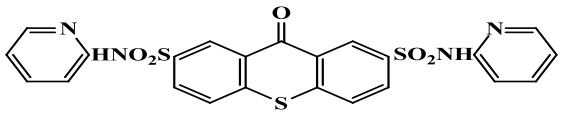
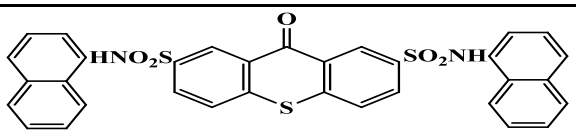
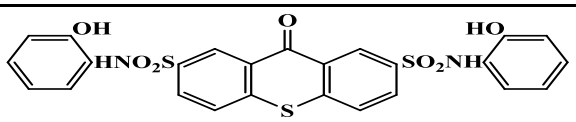
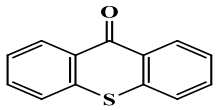
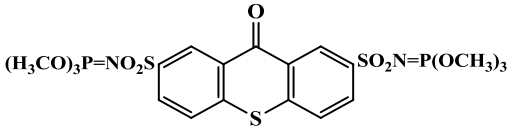
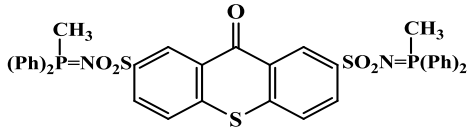
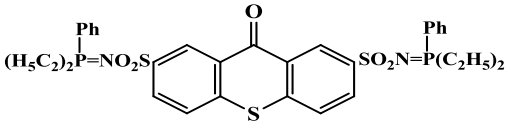
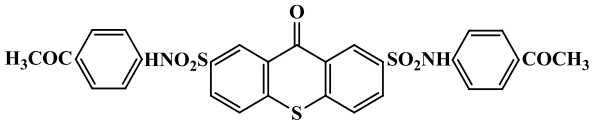
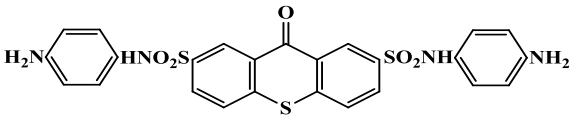
Comp. No.	Compound structure	Color of crystal	m.p. °C	Yield %	Recrystallization Solvent
9		Brown	67-69	76	Ethanol
10		Pale yellow	210-212 dec	68	Dioxane
11		Black	154-156 dec	72	Dioxane
12		Yellow	168-170 dec	67	Chloroform
13		Brown	258-260	43	Dioxane
14		Light yellow	244-246	69	Benzene
15		Yellow	280-282	63	Ethanol
16		Brown	137-139	51	Benzene
17		Deep yellow	106-108	45	Dioxane
18		Dark yellow	236-238 dec	39	Benzene
19		Reddish yellow	222-224	47	Hexane
20		Pale brown	204-206	44	Toluene
21		Black	114-116 dec	34	Ethanol

Table (4): Characteristic absorption bands of FT-IR and U.V spectra of compounds (9-21)

Comp. No.	FTIR spectral data cm^{-1}								U.V. (λ_{max}) nm
	υ(N-H) sulfonyl amide	υ(C-H) Aromatic	υ(C-H) Aliphatic	υ(C=C) Aromatic	υ(C=O) Ketone	υ(C-N) Amine	υ(SO_2) asym. sym.	Others	
9	3237	3088	-	1491 1587	1643	1273	1348 1162	-	390
10	3239	3090	-	1458 1488 1589	1638	1272	1342 1157	P-substituted 826 υ(C-Cl) 1094	382
11	3281	3052	2861 2909	1453 1512 1589	1644	1269	1384 1160	P-substituted 818	381
12	3248	3084	2832 2903	1458 1506 1588	1639	1277	1386 1181	P-substituted 824 υ(C-O-C) 1247 (asym), 1102 (sym)	397
13	3161	3028 3059	2859 2919	1459 1509 1596	1658	1268	1364 1156	P-substituted 834	396
14	3257	3067	-	1512 1589	1635	1274	1326 1157	P-substituted 833 υ(NH_2) amine 3429 (asym), 3378 (sym)	380
15	3200	3058	-	1445 1504 1591	1637	1269	1340 1164	P-substituted 822 υ(C-Br) 1091	379
16	3196	3073	2882 2916	1517 1541 1581	1627	1273	1371 1184	M-sub 750, 782 υ(C-O-C) 1234 (asym), 1097 (sym)	378
17	3281	3079	-	1495 1590	1640	1274	1382 1172	P-substituted 844 υ(N-O) 1544 (asym), 1346(sym)	388
18	3151	3057	2878 2937	1474 1496 1589	1652	1279	1376 1157	-	394
19	3204	3072	-	1527 1588	1635	1271	1379 1152	O-substituted 755 υ(C=N) 1475	391
20	3182	3078 3040	-	1458 1589	1643	1272	1371 1156	-	393
21	3247	3093	-	1491 1590	1644	1274	1337 1161	υ(O-H) Phenolic 3412 υ(C-O) 1226 O-substituted 742	388

Table (5): ^{1}H-NMR spectra for some compounds

Comp. No.	Compound structure	δH aromatic ppm	δH other bands ppm
1		(7.2-8.4) (m,8H)	_
4		(7.5-8.5) (m,6H)	3.4 (s,18H) CH_3 group protons
6		(7.4-8.4) (m,26H)	1.8 (s,6H) CH_3 group protons
8		(7.2-8.4) (m,16H)	[(0.8,0.9,1,1.1) (q,4H) CH_2 group protons (1.9,2,2.1,2.2) (q,6H) CH_3 group protons]
13		(7.0-8.2) (m,14H)	2.4 (s,6H) acetyl protons 9.4 (s,2H) sulfonamide protons
14		(6.7-8.3) (m,14H)	3.4 (s,4H) amine protons 9.8 (s,2H) sulfonamide protons

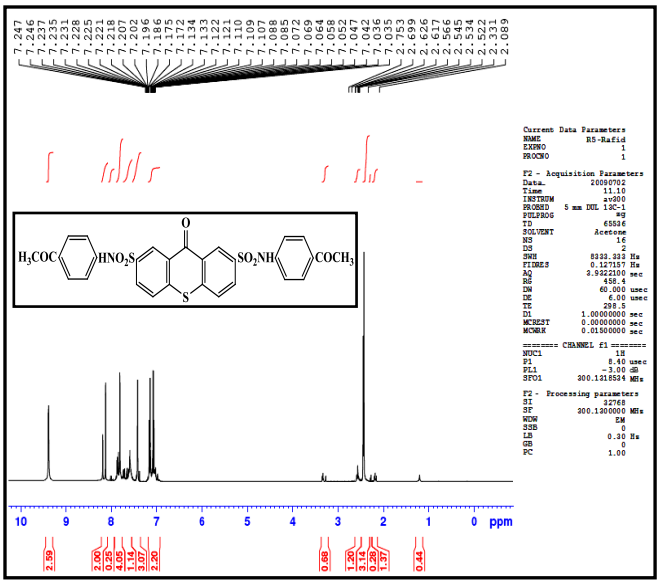


Fig.(7): ^{1}H-NMR spectrum for compound (13)

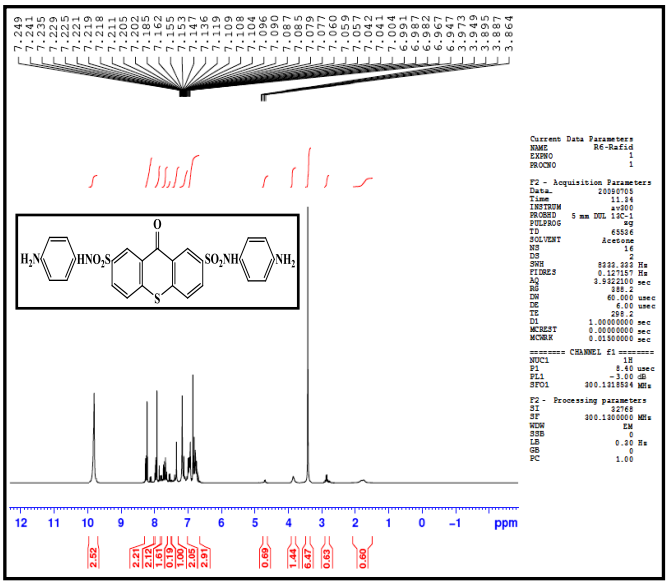


Fig.(8): ^{1}H-NMR spectrum for compound (14)

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تحضير وتشخيص مشتقات جديدة للثايوكسانثون

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الخلاصة: يتضمن البحث تحضير مشتقات جديدة للثايوكسانثون المعوضة على ذرة الكاربون. وقد اعتبرت المادة الاولية وهي اورثو مركبتوبنزويك اسيد لتحضير هذه المشتقات من خلال تفاعلها مع البنزين الجاف بوجود حامض الكبريتيك المركز وبتحريك لمدة اربعة ساعات بدرجة حرارة الغرفة لاعطاء الثايوكسانثون (1). تحضير 7,2-(ثنائي سلفونيل فوسفين امين) ثايوكسانثون (4-8) وقد تم ذلك بمفاعلة الثايوكسانثون مع حامض كلورسلفونك ليعطي مركب 7,2-(ثنائي سلفونيل كلورايد) ثايوكسانثون (2) والذي بدوره يتفاعل مع ازيد الصوديوم ليعطي مركب 7,2-(ثنائي سلفونيل ازيد) ثايوكسانثون (3)، وعند معاملة (3) مع مركبات الفسفور الثلاثية تحول الى مشتق 7,2-(ثنائي سلفونيل فوسفين امين) ثايوكسانثون (4-8). تحضير 7,2-(ثنائي سلفونيل مايد) ثايوكسانثون (9-21) وقد تم ذلك بمفاعلة 7,2-(ثنائي سلفونيل كلورايد) ثايوكسانثون (2) مع أمينات أروماتية مختلفة تحول الى مشتق 7,2-(ثنائي سلفونيل مايد) ثايوكسانثون (9-21).