SYNTHESIS AND EVALUATION OF THE BIOLOGICAL ACTIVITY FOR SOME OF CARBAZOLE DERIVATIVES

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Abstract

This research includes preparing of some carbazole derivatives .The (3,6-Disulfonylchloride-9H- carbazole (1) was achieved by the reaction of carbazole with chloro sulfonic acid in cold condition, reaction of compound (1) with sodium azide in acetone as a solvent to give (3,6-Disulfonyl azide-9H- carbazole) (2), then reaction of compound (2) with different phosphine and phosphate compounds(1mole and 2 mole) yielded the (3,6-Disulfonyl -6- azide-3-(phosphine or phosphate imine)-9H- carbazole) derivatives (3-8) and (3,6-Disulfonyl (phosphine or phosphate imine)-9H- carbazole) derivatives respectively (9-14).Some of physical properties have determined for the prepared compound, and identified by spectral methods (FTIR, ^{1}H-NMR, ^{13}C-NMR), furthermore evaluation of the biological activity for some of the prepared compounds on two type of bacteria Bacillus and E.Coli.

Introduction

Carbazole is one of organic hetero cyclic compounds containing a dibenzopyrrole, also known as 9-azo fluorine.Carbazole was synthesized by Borsche-Drechsel Cyclization[1]. Carbazoles are a large and an interesting group of organic compounds which one can find pharmaceutical activity[2], dyestuffs, plastics[3-5], and known to possess mutagenic and toxice activities and also to be arecalcitrant molecule[6].

Carbazole derivatives showed anticancer[7], antifungal[8], anti malarial [9], anti tumor (leuckemia, renal, colon), anti inflammatory, antiallergic antiviral, and anti hypertensive properties [10-12].Due to their extensive biological activity carbazole derivatives and their chemistry have been studies at length. Keeping the above facts, we aimed to synthesize new carbazole derivatives to thus obtain new hetero cyclic system which is expected to possess characteristic of biological activites.

Experimental

-Instruments

Melting Point were determined on a Gllenkamp FB.600-olof. melting point apparatus.

FTIR Spectra were recorded using solid KBr dises by tests scan Shimadzu FIIR 8400Series. The ^{1}H-NMR and ^{13}C-NMR Spectra were recorded on a make Bruker model ultrashield 300MHz, NMR at Al-Albyt university, Jordan .DMSO-d^{6} was used as solvent and TMS as internal reference.

Materials

All starting chemical compounds were obtained from Fluka or Aldrich.

Preparation of (3,6-Disulfonyl chloride- 9H-carbazole)(1)[13]

Carbazole(0.04 mole, 6.68 gm) was added in portions to 40 ml. cold chloro sulfonic acid.The mixture was heated and maintained at 60-70 C° for 3 hrs.The reaction of mixture was poured on to ice-water, and the solid product was filtered and recrystallized from ethanol. Physical properties of the product is listed in Table (1).

Preparation of (3,6-Disulfonylazide-9H-carbazole) (2) [13]

(3,6-Disulfonylchloride-9H-carbazole)(1) (0.01 mole, 3.64 gm) was added in portion to a suspension of sodium azide (1.3 gm,0.02 mole) in acetone (100 ml.).

The mixture was stirred at room temperature for 24 hrs. A white solid was formed, the solid NaCl and excess NaN_3 were filtered off and the solvent was distilled. The physical properties of prepared compound is shown in Table (1).

Preparation of [3,6-Disulfonyl-6-azide (phosphine or phosphite imines) -9H-carbazole(3-8) [14]

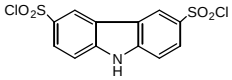
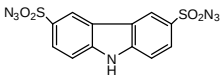
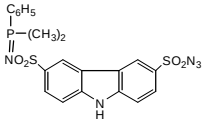
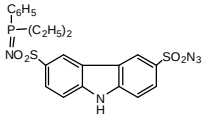
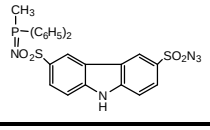
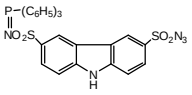
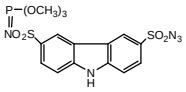
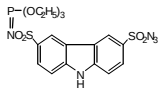
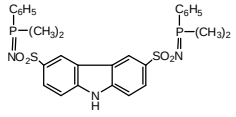
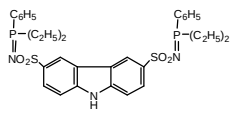
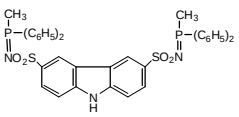
To a solution of dimethyl phenyl phosphine , diethyl phenyl phosphine, methyl diphenyl phosphine, tri phenyl phosphine, tri methyl phosphite or tri ethyl phosphate (0.001 mole) in 5 ml of dry ether was added to a solution of (3,6-Disulfonyl azide-9H-carbazole) (0.001 mole, 0.37 gm) (2) in 5 ml of dry THF.A complex was first formed then decomposed with evolution of nitrogen on standing over night in the refrigerator, the solution deposited crystals derivatives respectively (3-8) were recrystallized from different solvents.

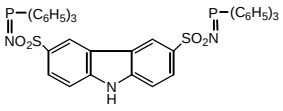
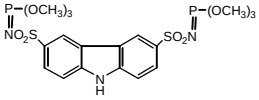
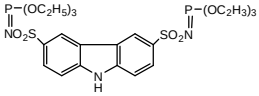
The physical properties of prepared compounds (3-8) are shown in Table (1).

Preparation of [3,6-Disulfonyl (phosphine or phosphiteimines) -9H- carbazole] (9-14)[14]

To a solution of dimethyl phenyl phosphine, diethyl phenyl phosphine, methyl diphenyl phosphine, tri phenyl phosphine, tri methyl phosphate or tri ethyl phosphite (0.002 mole) in 5 ml of dry ether was added to a solution of (3,6-Disulfonyl azide-9H-carbazole) 0.001mole, 0.37 gm) (2) in 5 ml of dry THF. A complex was first formed then decomposed with evolution of nitrogen on standing over night in the refrigerator, the solution deposited crystals derivatives respectively (9-14) were recrystallized from different solvents. The physical properties of prepared compounds (9-14) are shown in Table (1).

Table (1)
Physical properties of the prepared compounds.

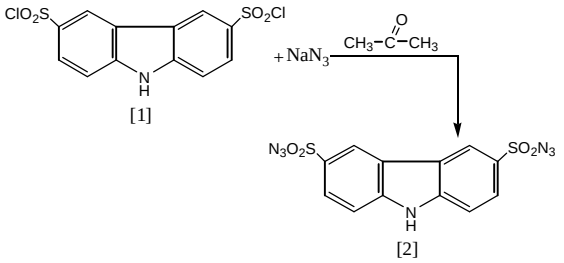
Comp. No.	*Molecular formula (M.wt.)*	*Comp. Structure*	*m.p. ℃*	*Yield %*	*Colour*	*Recryst. solvent*
1	$C_{12}H_7NO_4S_2Cl_2$ 364		222 decomp.	80	Pale green	Ethanol
2	$C_{12}H_7N_7O_4S_2$ 377		177-179	77	White	Methanol
3	$C_{20}H_{18}N_5O_4S_2P$ 487		180 decomp.	70	Pale yellow	Ethanol
4	$C_{22}H_{22}N_5O_4S_2P$ 515		160-164 decomp.	50	Pale yellow	Ethanol-water
5	$C_{25}H_{20}N_5O_4S_2P$ 549		122-125	40	Dark yellow	Ethanol-water
6	$C_{30}H_{22}N_5O_4S_2P$ 611		110-120	90	White	Ethanol
7	$C_{18}H_{25}N_3O_{10}S_2P$ 569		220 decomp.	65	dusty	Ethanol-water
8	$C_{18}H_{22}N_5O_7S_2P$ 515		250 decomp.	60	White	Ethanol-water
9	$C_{28}H_{29}N_3O_4S_2P_2$ 597		205 decomp.	80	Yellow	Ethanol-water
10	$C_{32}H_{37}N_3O_4S_2P_2$ 653		210-215	50	White	Methanol
11	$C_{38}H_{33}N_3O_4S_2P_2$ 721		245 decomp.	88	White	Ethanol-water

Comp. No.	Molecular formula (M.wt.)	Comp. Structure	m.p. ℃	Yield %	Colour	Recryst. solvent
12	$C_{48}H_{37}N_3O_4S_2P_2$ 845		120-125	90	Yellow	Methanol
13	$C_{15}H_{16}N_5O_7S_2P_2$ 473		230 decomp.	78	Pale green	Ethanol
14	$C_{24}H_{37}N_3O_{10}S_2P_2$ 653		242	45	dusty	Ethanol-water

Results and Discussion

In the present work we synthesized some carbazole derivatives where achieved from carbazole, the synthetic route used is shown in Scheme (1).

(3,6-Disulfonylchloride-9H-carbazole)(1) was prepared by chloro sulfonation of carbazole . The reaction was carried in cold condition and excess chloro sulfonic acid. FTIR spectra showing the absorption at 3420 cm^{-1} for νN-H and at 1370 cm^{-1}, 1174 cm^{-1} for asymmetric and symmetric stretching band of sulfonyl chloride νSO_2Cl group respectively .This increase in frequency ,compared with the sulfones, results from the electronegativity of the chlorine atom.The compound (1) react with sodium azide in acetone as solvent to give (3,6-Disulfonylazide-9H-carbazole) (2) according to the following equation:

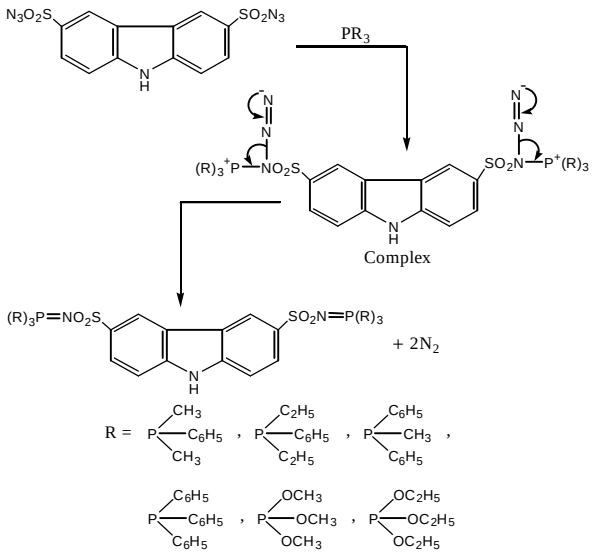


FTIR spectra of compound (2) showing the absorption at 3430 cm^{-1} for νN-H and stretching band at 2135 cm^{-1} for (–N3 group)[15] , 3064cm^{-1} for aromatic(C-H) , two bands at 1365 cm^{-1} and 1164 cm^{-1} for SO_2 group.

Compound (2) treatment with one equivalent from phosphine or phosphite compounds were synthesized [3,6-Disulfonyl -6- azide-3-(phosphine or phosphate imine)-9H- carbazole] (3-8). The structures of compounds(3-8) were confirmed by physical properties which are listed in Table (1), FTIR spectra of compounds (3-8) showing the absorption at ν(3390-3438) cm^{-1} for νN-H; ν(720-760) cm^{-1}, ν(1060-1089) cm^{-1}, ν (1110-1164) cm^{-1} for ν(N=P) [14,16];ν[(1150-1170)-(1340-1370)]cm^{-1} for asymmetric and symmetric stretching band of νSO_2 respectively .In the same time, we found absorption at ν (2130-2136) cm^{-1} for –N3 in positin C-6 in carbazole. While the ^{1}H-NMR spectra data of compound (3,7)[17] δppm in DMSO-d6 solvent:2.47 (S, 6H, $-CH_3$); 7.4-7.6 (S, 5H, p-Ar-H); 7.5-7.9 (m, 6H, p-Ar-H);12.9 (broad, 1H,NH) for compound(3] while compound(7) δppm in DMSO-d6 solvent:3.4-3.6 (S, 9H, $-OCH_3$); 7.2-7.7 (m, 6H, C-Carbazole);13.1 (broad, 1H,NH).

^{13}C-NMR spectra for compounds (3,7) showed results were listed in Table (4).

When compound (2) treatment with two equvelant from phosphine or phosphite compound were synthesized [3,6-Disulfonyl (phosphine or phosphate imine)-9H-carbazole] derivatives (9-14). At room temperature. A moderate reaction concerned with evolution of nitrogen and produces the imino phosphorus Via intermediate complexes according to the following equation:



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. FTIR Spectra of compound (9-14) are shown absorption in Table (2). All compounds (9-14) showed disappearance of the absorption of N3 group. FTIR Spectra of P 1330 cm^{-1}, 1168cm^{-1} for asymmetric and symmetric stretching band of SO_2 group respectively, While the ^{1}H-NMR spectra data of compound (10) δppm in DMSO-d6 solvent: 1.2-1.9 (t, 12H, -CH_3); 2.5-2.52 (q, 8H,p-CH2-); 7.4-7.7 (m, 6H, C-Carbazole);7.6-8.1(m,10H,P-aromatic); 12.8 (broad, 1H,NH).^{13}C-NMR spectra for compound (3) is shown the results in Table (4).

FTIR Spectra of compound (13) shows the absorption at 1348cm^{-1},1170cm^{-1} for asymmetric and symmetric stretching band of SO_2 group respectively , 1039cm^{-1} for (νP-O-C) , 2944cm^{-1} for (ν C-H aliph.) and disappearance the absorption of (–N_3 group).

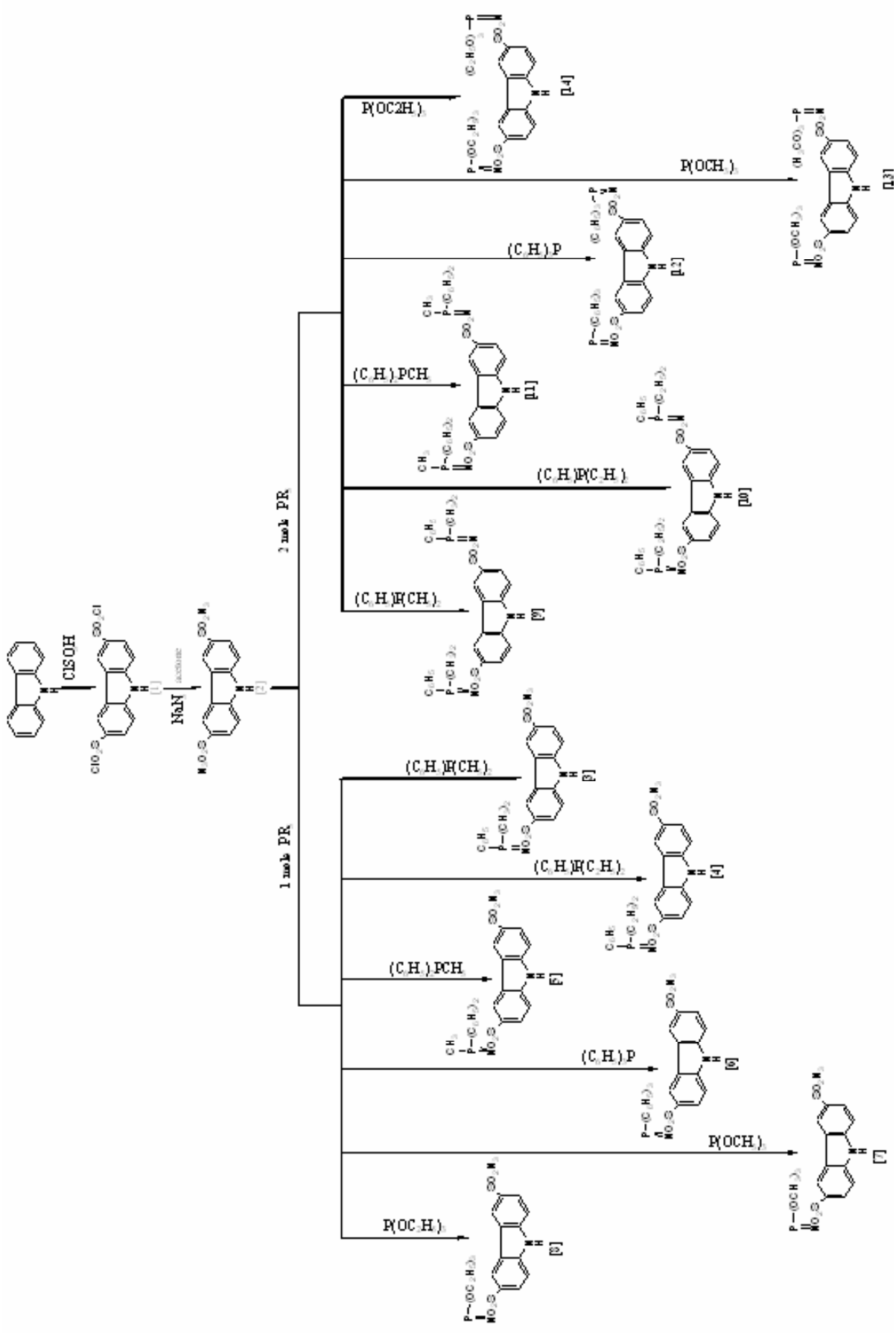
Antimicrobial Activity Test

The test was performed according to the d isk diffusion method[18]. The some of the prepared compounds were tested against one strain of Gram +ve Bacillus, and one strain of Gram -ve Escherichia .Coli .Whatman No.1 filter paper disk of 5 mm diameter were sterilized by autoclaving for 15 min at 121˚C. The sterile disks were impregnated with different compounds (700 µg\disk).Agar plates were surface inoculated uniformly with 100 µl from the broth culture of the tested microorganisms. The impregnated disks were placed on the medium suitably spaced apart and the plates incubated at 5˚C for 1hr.to permit good diffusion and then transferred to an incubator at 37 ˚C for 24hrs. The inhibition zones caused by the various compounds on the microorganisms were examined .The results are listed in Table (5). From the data it is clear that compounds (1 and 3) possess highly activity against two types of bacteria, compounds (9 and 10) possess between moderate and less activity against two types of bacteria. Compound (13) possess moderate specific activity against for E. Coli and have no effect on other strains while compounds (6 and 12) were found inactive against two types of bacteria.

Table (5)
Results of antimicrobial activity of the tested prepared compounds*.

Comp. No.	*E. Coli*	*Bacillus*
1	+++	+++
3	+++	+++
5	+	++
6	-	-
9	++	+
10	++	+
12	-	-
13	+	-

**** Solvent: DMSO, [C] = 2 mg/ml***
Key to symbols:
Highly active = +++ (inhibition zone 15-20 mm)
Moderately active = ++ (inhibition zone 10-14 mm)
Slightly active = + (inhibition zone 6-9 mm)
Inactive = - (inhibition zone < 6 mm)


ClSO3H
NaN
2 mole PR
1 mole PR
P(OC2H5)3
P(OCH3)3
(C2H5)3P
(C2H5)2PCH2
(C2H5)2P(C2H5)
(C2H5)2P(CH3)
(C2H5)2P(CH3)
(C2H5)2P(C2H5)
(C2H5)2PCH2
(C2H5)3P
P(OCH3)3
P(OC2H5)3

Scheme (1).

Table (2)
FTIR absorption spectra data (cm)$^{-1}$ of the prepared compounds.

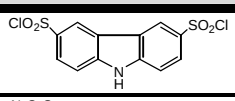
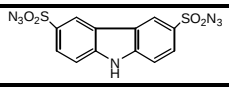
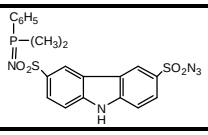
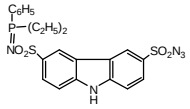
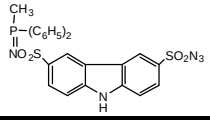
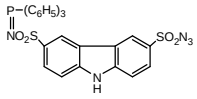
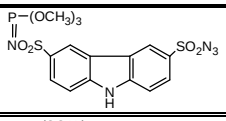
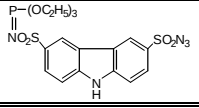
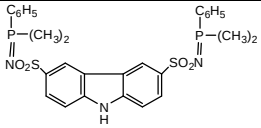
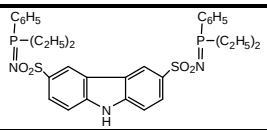
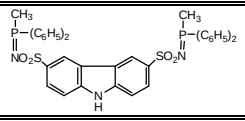
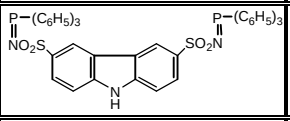
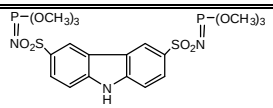
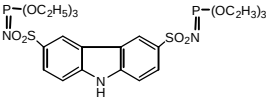
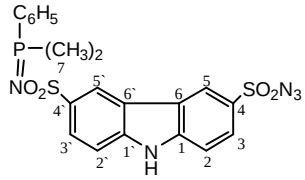
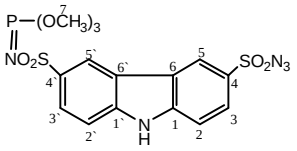
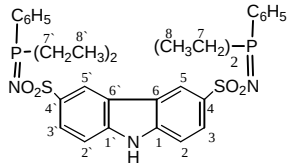
Comp. No.	*Comp. Structure*	*νN-H*	*νC-H arom.*	*νC-H aliph.*	*νC=C*	*νSO_2 asym. Sym.*	*νN=P*	*Other band ν*
1		3420	3080	-	1600 1580	1370 1174	-	-
2		3430	3064	-	1602 1585	1365 1164	-	-N3 2135
3		3390	3082	2980	1605 1580	1370 1157	748 1074 1110	-N3 2130
4		3450	3080	2900	1596 1590	1365 1157	740 1085 1124	-N3 2130
5		3438	3055	2977	1589 1583	1370 1160	760 1070 1115	-N3 2135
6		3380	3062	-	1596 1592	1365 1176	758 1089 1110	-N3 2136
7		3425	3082	2954	1602 1585	1365 1150	753 1074 1124	-N3 2136 P-O-C 1045
8		3420	3087	2980	1622 1600	1340 1150	720 1065 1134	-N3 2130 P-O-C 1041
9		3450	3055	2985 2916	1595 1585	1344 1164	750 1086 1164	-
10		3425	3051	2977 2947	1600 1589	1330 1168	732 1079 1126	-
11		3450	3065	2977 2869	1602 1589	1360 1176	744 1060 1150	-
12		3450	3055	-	1600 1598	1340 1160	758 1064 1120	-
13		3415	3082	2944	1600 1595	1348 1170	755 1077 1163	P-O-C 1039
14		3420	3064	2947	1600 1610	1365 1165	740 1079 1110	P-O-C 1041

Table (3)
^{1}H-NMR spectra for selected compounds.

Comp. No.	*^{1}H-NMR parameters (ppm) δ-H*
3	2.47 (S, 6H, -CH_3); 7.4-7.6 (S, 5H, Ar-H); 7.5-7.9 (m, 6H, Ar-H);12.9 (broad, 1H,NH)
7	3.4-3.6 (S, 9H, -OCH_3); 7.2-7.7 (m, 6H, C-Carbazole);13.1 (broad, 1H,NH).
10	1.2-1.9 (t, 12H, -CH_3); 2.5-2.52 (q, 8H,p-CH2-); 7.4-7. 7(m, 6H, C-Carbazole);7.6-8.1(m,10H,P-aromatic);12.8 (broad, 1H,NH)

Table (4)
^{13}C-NMR spectra for selected compound.

Comp. No.	*Structure*	*C_1,C_1`*	*C_2,C_2`*	*C_3,C_3`*	*C_4,C_4`*	*C_5,C_5`*	*C_6,C_6`*	*C_7,C_7`*	*C_8,C_8`*	*P-C6H5*
3		133.54	131.88	132.52	135.17	130.38	129.60	40.79	-	(126.71-125.20)
7		139.63	126.90	136.99	141.04	124.51	120.13	66.80	-	-
10		126.75	125.95	124.51	129.73	120.06	113.41	41.78	40.78	(120-86-126.75)

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الخلاصة

تم في هذا البحث تحضير مشتقات للكاربيزول. (6,3–ثنائي كلوريد السلفونيل -9H –كاربيزول) (1) كمركب رئيسي ينتج من تفاعل الكاربيزول مع كلورو حامض السلفونيك في ظروف باردة. تم تفاعل المركب (1) مع ازيد الصوديوم بوجود الاسيتون كمذيب يعطي (6,3 – ثنائي سلفونيل ازيد -9H –كاربيزول(2) ، ثم يتفاعل المركب (2) مع مختلف مركبات الفوسفين والفوسفيت (امول و2 مول) لينتج [6,3 – ثنائي سلفونيل -6- ازيد(فوسفين او فوسفيت ايمين) -9H –كاربيزول] (3-8) و[6,3 – ثنائي سلفونيل (فوسفين او فوسفيت ايمين) -9H – كاربيزول] (9-14) على التوالي . المركبات المحضرة تم تعيين بعض خواصها الفيزيائية وشخصت المركبات المحضرة بالطرق الطيفية [FTIR، ^{1}H-NMR، ^{13}C-NMR] وقيمت الفعالية البايولوجية لبعض هذه المركبات على نوعين من البكتيريا الباسلوس وايكولاي.