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SYNTHESIS AND SOME CHEMICAL STUDIES ON 2-(4-TOLUENESULPHONYLOXY PHENYL)-3,1-BENZOXAZINE-4-ONE

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ABSTRACT

2-(4-Toluenesulphonyloxy phenyl)-3,1-benzoxazine-4-one was prepared and reacted with some nitrogen nucleophiles, e.g., ammonia, *o*- phenylendiamine, some heterocyclic amines, hydrazine hydrate and hydroxylamine hydrochloride, and sulfur nucleophile, e.g., phosphorous pentasulphide. The structure of these new products has been elucidated by elemental and spectral data .

Keywords: *Benzoxazinone, Quinazolinone, Benzothiazine, Thiazolidinone, Imidazole.*

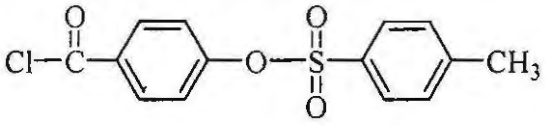
1. INTRODUCTION

Substituted benzoxazinone and quinazolinone derivatives have become of great importance due to their wide range of biological activity. **[Farghaly et al., (1990) and Gilmore et al., (1996)]**. Previous studies have been reported that, they exhibit antitubercular **[Shirodkar et al., (2000)]** antihypertensive, anticancer, anti-HIV **[Shah et al., (1995)]** antiviral **[Parkanyi et al., (1992)]** anti-inflammatory **[Saxena et al., (1991)]** and antifungal activities. **[Pandey et al., (1994)]** Besides, they were used as analgesics **[Bansal et al., (2002)]** inhibitors for cathepsin G **[Gutschow et al., (1997)]** Human leukocyte elastase **[Krantz et al., (1990)]** dual selective serotonin reuptake **[Zhou et al., (2006)]** and potent as activators of C_{1r} serine protease **[Hays et al., (1998)]**.

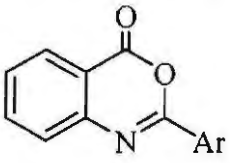
On the other hand, it has been stated that compounds containing aromatic sulfonate or sulfonamide moieties possess high acaricidal as well as insecticidal activity **[Habib et al., (1990) and Kassem et al., (1982)]**.

2. DISCUSSION

The biological importance of benzoxazinones , quinazolones and also aryl sulphonates prompted us to synthesize 2-(4-toluene sulphonyloxy phenyl)-3,1-benzoxazine-4-one **II** and study its reactions. Thus, treatment of anthranilic acid with two moles of the acyl chloride **I** in the presence of dry pyridine affords **II**.

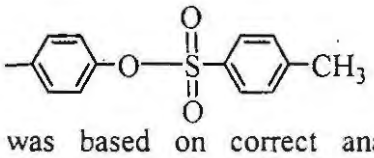


I



II

Ar =



Structure of **II** was based on correct analytical data and spectroscopic measurements. The infra-red spectrum revealed absorption bands at 1766, 1627 and 1370 cm^{-1} characteristic for the carbonyl of lactone, -C=N and $-SO_3$ groups, respectively. ^{1}H-NMR spectrum showed signals at δ 7.0-8.3 (m, 12H, aromatic) and at δ 2.4 (s, 3H, $-CH_3$), and the mass spectrum showed the molecular ion peak at *m/z* 393 (M^+) (29.24%).

Fusion of **II** with ammonium acetate at 160-170°C afforded 4–(4–oxo–3,4–dihydroquinazolin–2–yl)phenyl–4'–methylbenzenesulfonate **III**. The infra-red spectrum revealed stretching frequencies at 3336, 3173, 1661, 1604 and 1377 cm^{-1} characteristic for the –OH, -NH, C=O, C=N and SO_3 groups, respectively. This illustrates that quinazolone **III** exists in a lactam- lactim tautomeric equilibrium.^{1}H-NMR spectrum showed signals at δ 7.0-8.3 (m, 12H, aromatic) , δ 2.4 (s, 3H, $-CH_3$), and δ 3.5 (s, 1H, NH), and the mass spectrum showed the molecular ion peak at *m/z* 392 (M^+) (67.35%).

The reaction of 2–aryl–3,1–benzoxazin–4–one **II** with *o*-phenylenediamine is interesting since the reaction products depend upon the conditions of the reaction **[Gay et al., (1957)]**. Thus, reaction of benzoxazinone **II** with *o*-phenylenediamine in absolute ethanol under

reflux afforded 4–[2–[(N-2-aminophenyl)benzoyl]carbamoyl]phenyl–4'–methylbenzenesulfonate (**IV**).

Structure **IV** was confirmed by its correct elemental analysis and spectroscopic data. The infra-red spectrum showed stretching frequencies at 3332-3410, 3240, 1665 and 1375 cm^{-1} attributable to the $-NH_2$, NH, C=O and $-SO_3$ groups, respectively, and its mass spectrum showed the molecular ion peak M^+ as the base peak at *m/z* 501 (4.13%). ^{1}H-NMR showed signals at δ 2.4 (s, 3H, $-CH_3$), δ 7.1-8.1 (m, 16H, aromatic), δ 8.4(s, 2H , $-NH_2$) and δ 8.6(s, 2H, -2NHCO).

Moreover, fusion of compound **II** with *o*- phenylenediamine in the presence of freshly fused sodium acetate at 100°C and 180°C gives different products. When fusion was carried out at 100°C, 4–(3–(2–aminophenyl)–4–oxo–3,4–dihydroquinazolin–2–yl)phenyl–4-methyl benzene sulfonate (**V**)was obtained. On the other hand, fusion at 180°C leads to the formation of 4–(4–benzo[4,5]imidazo[1,2–c]quinazolin–6–yl)phenyl–4–methylbenzene sulfonate (**VI**).

Structures **V** and **VI** were based on correct analytical results and spectroscopic data. The infra-red spectrum of **V** showed stretching frequencies at 3332-3425, 1665, 1600 and 1360 cm^{-1} attributable to the $-NH_2$, CON, C=N and $-SO_3$ groups, respectively, ^{1}H-NMR showed signals at δ 2.4 (s, 3H, $-CH_3$), δ 7.2-8.2 (m, 16H, aromatic), δ 3.3 (s,2H,NH_2), and the mass spectrum showed the molecular ion M^+ as the base peak at *m/z* 483 (7.19%). The infra–red spectrum of **VI** revealed absorption bands at 1600 and 1360 cm^{-1} attributable to –C=N, $-SO_3$ groups, respectively. The bands characteristic for the C=O and $-NH_2$ groups disappeared, and the mass spectrum of **VI** showed the molecular ion [M^++2] as the base peak at *m/z* 467 (0.96%).

On the other hand, compound **II** reacted with some heterocyclic amines, e.g., 3-aminopyridine, 2-aminothiazole and 4-aminoantipyrine afforded **VII**, **VIII** and **IX** respectively.

The infra-red spectrum of **VII** showed absorption bands at 1684, 1597 and 1374 cm^{-1} corresponding to CON, C=N and $-SO_3$ groups, respectively, and the mass spectrum showed the molecular ion peak at *m/z* 469 (M^+) (3.24%).

The infra-red spectrum of **VIII** showed stretching frequencies at 1666, 1610, 1580, 1380 and 666 cm^{-1} corresponding to CON, C=N, C=C, $-SO_3$ and C-S groups, respectively. The mass spectrum showed the molecular ion peak at *m/z* 475 (M^+) (0.5%).

The infra-red spectrum of **IX** showed stretching frequencies at 1665, 1613 and 1380 cm^{-1} corresponding to CON, C=N and $-SO_3$ groups, respectively, and the mass spectrum showed the molecular ion peak at *m/z* 578 (M^+) (4.00%).

With the aim of expanding the synthetic potential of the quinazolones formed, we also studied the reaction of benzoxazinone **II** with both hydrazine hydrate and hydroxylamine hydrochloride **[Sammour et al., (1971) and Gupta et al., (1988)]**. Thus, reaction of **II** with hydrazine hydrate in boiling ethanol affords 4–(3-amino–4–oxo–3,4–dihydriquinazolin–2–yl)phenyl-4–methyl benzene sulfonate (**X**).

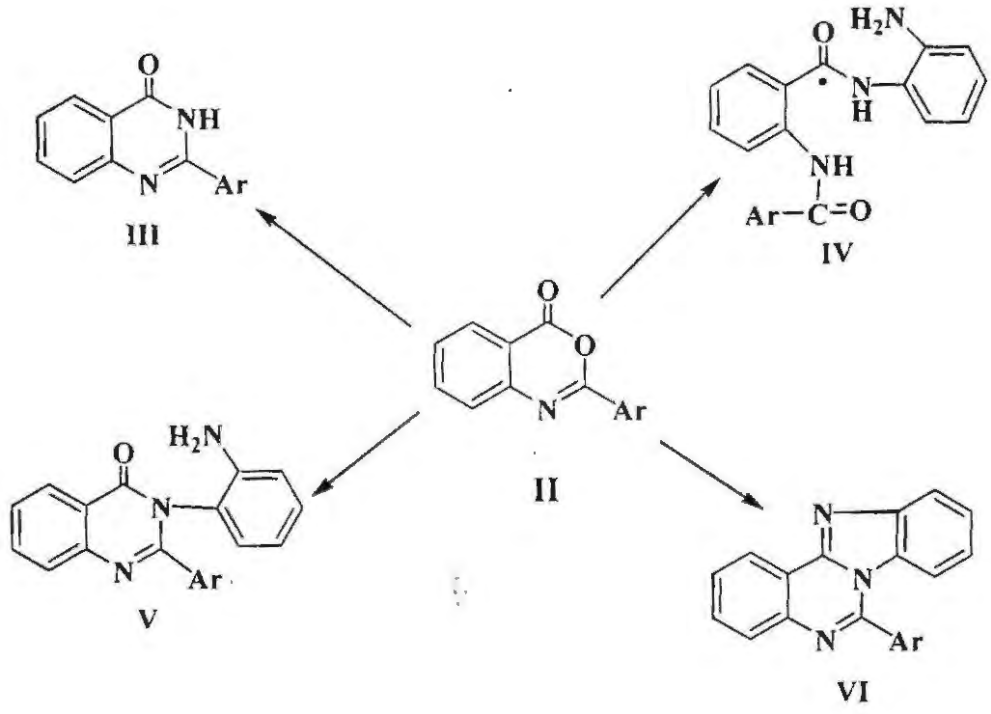
The structure of **X** was based upon correct elemental analysis and spectroscopic data. The infra-red spectrum showed strong absorption bands at, 3332-3425, 1653, 1597 and 1360 cm^{-1} that could be assigned to the $-NH_2$, C=O, C=N and $-SO_3$ groups, respectively, and the mass spectrum showed the molecular ion peak at *m/z* 407 (M^+) (100%). ^{1}H-NMR spectrum showed signals at δ 2.4 (s, 3H, $-CH_3$), δ 4.9 (s, 2H, $-NH_2$) and δ 7.0-8.3 (m, 12H, aromatic).

On the other hand, the reaction of **II** with hydroxylamine hydrochloride in boiling ethanol in presence of sodium acetate gives 4–(3-hydroxy–4–oxo–3,4–dihydroquinazolin–2–yl)phenyl–4–methyl benzene sulfonate (**XI**).

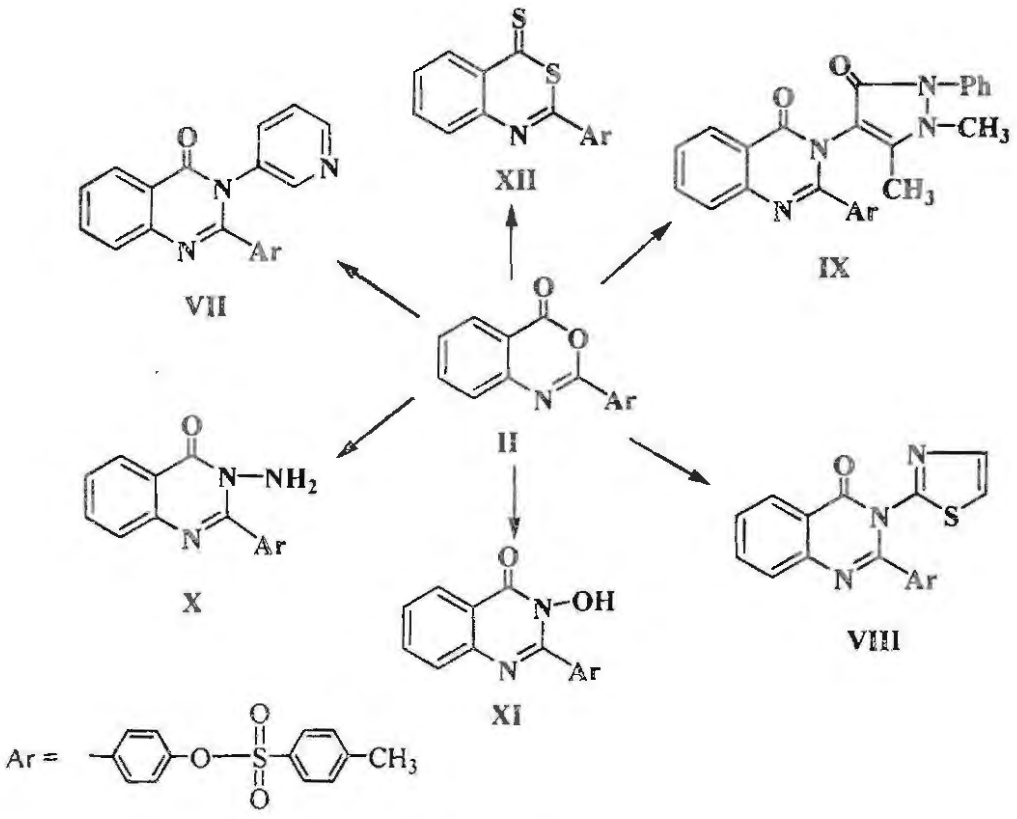
Structure **XI** was confirmed from correct elemental analysis and infra-red spectrum which showed stretching frequencies at 3220, 1665, 1613 and 1380 cm^{-1} assigned to –OH (chelated), C=O, C=N and $-SO_3$ groups, respectively. The mass spectrum showed the molecular ion M^+ as the base peak at *m/z* 408 (5.70%).

By analogy with the previously reported reaction of benzoxazin-4-one with phosphorous pentasulfide **[Fahmy et al., (1978)]**. benzoxazone **II** reacts with phosphorous pentasulfide in refluxing dry xylene to afford 4-(4-thioxo-4*H*-3,1-benzothiazin-2-yl)phenyl-4-methylbenzenesulfonate (**XII**).

Structure **XII** was confirmed by correct elemental and spectroscopic data. The infra-red spectrum showed stretching bands at 1323, 1595 and 1364 cm^{-1} attributable to the C=S, C=N and $-SO_3$ groups, respectively and the mass spectrum showed the molecular ion M^+ as the base peak at *m/z* 425 (24.46%).



Scheme 1



Scheme 2

3. EXPERIMENTAL

3.1 General

All melting points (uncorrected) are in degree centigrade and were determined on Gallenkamp electric melting point apparatus, FTIR spectra (KBr disk) were recorded on a Nicolet Magna. IR model 550 spectrophotometers, ^{1}H-NMR spectra in DMSO, were determined on Brucker Wpsy 200 MHZ spectrometer with TMS as internal standard and the chemical shifts are in σ ppm. Mass spectra were recorded at 70 ev with a varian MAT 311. C, H and N elemental analyses are satisfactory for all synthesized compounds, all analysis were carried out in Faculty of Science, Cairo University, Egypt.

Synthesis of 2-(4-toluene sulphonyloxy phenyl)-3,1-Benzoxazine-4-one (II).

To a solution of anthranilic acid (1.371 gm : 0.01 mole) in dry pyridine (30 ml), the acid chloride **I** (6.21 gm : 0.02 mole) was added portionwise with stirring at room temperature. The reaction mixture was poured onto cold water (100 ml) and the precipitated solid was filtered off, washed with cold water, dried and recrystallized from ethanol to give benzoxazinone **(II)**.

Yellow crystals; Yield 50%; m.p. 140-141°C

Anal. For $C_{21}H_{15}NO_5S$ (393.41)

Calcd.;	C 64.11;	H 3.84;	N 3.56
Found;	C 64.12;	H 3.77;	N 3.51

Synthesis of 4-(4-oxo-3,4-dihydroquinazolin-2-yl) phenyl-4-methyl benzenesulfonate(III).

A mixture of benzoxazinone **II** (3.93 gm : 0.01 mole) and ammonium acetate (2.68 gm : 0.01 mole) was fused in an oil bath at 160-170 °C for 3 hours. The reaction mixture was left to cool, washed with water several times, filtered off, dried and recrystallized from ethanol to give **(III)**.

Grey crystals; Yield 55%; m.p. 215-217°C

Anal. For $C_{21}H_{16}N_2O_4S$ (392.43)

Calcd.;	C 64.27;	H 4.11;	N 7.14
Found;	C 64.15;	H 4.06;	N 7.06

Synthesis of 4–[2–[(N-2-aminophenyl)benzoyl]carbamoyl] phenyl–4'–methylbenzenesulfonate (IV).

A mixture of benzoxazinone **II** (1.18 gm : 0.003 mole) and o-phenylenediamine (0.32 gm : 0.003 mole) in absolute ethanol (20 ml) was refluxed for 8 hours. The solid product that separated on cooling was filtered off and recrystallized from ethanol to give **(IV)**.

White crystals; Yield 33%; m.p. 225-227°C

Anal. For $C_{27}H_{23}N_3O_5S$ (501.55)

Calcd.;	C 64.66;	H 4.62;	N 8.38
Found;	C 64.42;	H 4.54;	N 8.45

Synthesis of 4-(3–(2-aminophenyl)–4–oxo–3,4–dihydroquinazolin–2–yl)phenyl-4-methylbenzenesulfonate (V) and 4-(4–benzo[4,5] imidazo[1,2-c]quinazoline-6-yl)phenyl-4-methylbenzenesulfonate (VI).

A mixture of benzoxazinone **(II)** (1.18 gm : 0.003 mole), *o*-phenylenediamine (0.32 gm : 0.003 mole) and freshly fused sodium acetate (0.2 gm) was fused at 100°C and/or at 180°C for 3 hours. In each case, the reaction mixture was cooled, washed with dil. HCl. The separated solid product was dried and recrystallized from a mixture of ether-ethanol and methanol to give **(V)** and **(VI)** respectively.

Compound (V)

Brown crystals; Yield 55%; m.p. 170-172°C

Anal. For $C_{27}H_{21}N_3O_4S$ (483.54)

Calcd.;	C 67.07;	H 4.38;	N 8.69
Found;	C 67.00;	H 4.28;	N 8.34

Compound (VI)

Brown crystals; Yield 61%; m.p. 291-293°C

Anal. For $C_{27}H_{19}N_3O_3S$ (465.52)

Calcd.;	C 69.66;	H 4.11;	N 9.03
Found;	C 69.33;	H 4.00;	N 9.00

Synthesis of 4- (4-oxo-3-(pyridine-3-yl)-3,4–dihydroquinazolin-2-yl) phenyl 4-methyl benzenesulfonate (VII).

A mixture of benzoxazinone **(II)** (3.93 gm : 0.01 mole) and 3-aminopyridine (0.94 gm : 0.01 mole) was fused in an oil bath at 150-155 °C in presence of anhydrous $ZnCl_2$ (1gm) for 4 hours. The reaction mixture was triturated with ice/HCl. The formed solid product was filtered off, washed with water several times, dried and recrystallized from methanol to give **(VII)**.

White crystals; Yield 79%; m.p. 112-114°C

Anal. For $C_{26}H_{19}N_3O_4S$ (469.51)

Calcd.;	C 66.51;	H 4.08;	N 8.95
Found;	C 66.22;	H 3.96;	N 8.87

Synthesis of 4-(4-oxo-3-(thiazol-2-yl)-3,4-dihydroquinazolin-2-yl) phenyl-4-methyl benzenesulfonate (VIII).

A mixture of **(II)** (0.79 gm : 0.002 mole) and 2-aminothiazole (0.20 gm : 0.002 mole) in glacial acetic acid (20 ml) was refluxed for 4 hours. The reaction mixture was concentrated and then poured onto ice-

water. The solid that separated out was filtered off, washed with water several times, dried and then recrystallized from ethanol to afford **(VIII)**.
Grey crystals: Yield 69%; m.p. 200-202°C
Anal. For $C_{24}H_{17}N_3O_4S_2$ (475.54)

Calcd.;	C 60.62;	H 3.60;	N 8.84
Found;	C 59.87;	H 3.63;	N 8.87

Synthesis of 4-(3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihyhro-1H-pyrazol-4-yl)-4-oxo-3,4-dihydroquinazolin-2-yl)phenyl-4-methylbenzenesulfonate (IX).

A mixture of **II** (0.79 gm : 0.002 mole) and 4-aminoantipyrin (0.41 gm : 0.002 mole) in glacial acetic acid (20 ml) was refluxed for 6 hours then cooled. The reaction mixture was poured onto ice water, the precipitated product was filtered off and recrystallized from the acetic acid yielding the product **(IX)**.
White crystals; Yield 83%; m.p. 195-197°C
Anal. For $C_{32}H_{26}N_4O_5S$ (578.64)

Calcd.:	C 66.42;	H 4.53;	N 9.68
Found:	C 66.33;	H 4.48;	N 9.63

Synthesis of 4-(3-amino-4-oxo -3,4-dihydroquinazolin-2-yl)phenyl -4 -methylbenzenesulfonate (X).

A solution of benzoxazinone **(II)** (3.93 gm : 0.01 mole) and hydrazine hydrate (1.0 gm : 0.02 mole) in absolute ethanol (30 ml) was refluxed for 6 hours. The solid product that separated on cooling was filtered off, dried and recrystallized from ethanol to afford quinazolinone **(X)** .
Yellow crystals; Yield 60%; m.p. 156-158°C
Anal. For $C_{21}H_{17}N_3O_4S$ (407.44)

Calcd.:	C 61.90;	H 4.21;	N 10.31
Found:	C 61.80;	H 4.20;	N 10.22

Synthesis of 4-(3-hydroxy-4-oxo-3,4-dihydroquinazolin-2-yl)phenyl -4-methylbenzenesulfonate (XI).

To a solution of benzoxazinone **(II)** (2.35 gm : 0.006 mole) in ethanol (30 ml), hydroxylamine hydrochloride (0.417 gm : 0.006 mole) and sodium acetate (0.49 gm : 0.006 mole) dissolved in the least amount of water was added. The reaction mixture was refluxed for 8 hours,

cooled and then concentrated. The solid product that separated on cooling was filtered off and recrystallized from ethanol to give **(XI)**.
Yellow crystals; Yield 62%; m.p. 170-172°C
Anal. For $C_{21}H_{16}N_2O_5S$ (408.43)

Calcd.;	C 61.76;	H 3.95;	N 6.86
Found;	C 61.66;	H 4.00;	N 6.84

Synthesis of 4-(4-thioxo-4H-3,1-benzothiazin -2-yl)phenyl -4-methyl benzenesulfonate(XII).

A mixture of benzoxazinone **II** (3.93 gm : 0.01 mole) and phosphorous pentasulphide (8.9 gm : 0.02 mole) in dry xylene (40 ml) was refluxed for 8 hours. The reaction mixture was filtered off while hot, concentrated and the solid that separated on cooling was washed with petroleum ether (b.p. 80-100°) then recrystallized from ethanol to give **XII** .
Yellow crystals; Yield 38%; m.p. 135-137°C
Anal. For $C_{21}H_{15}NO_3S_3$ (425.54)

Calcd.;	C 59.27;	H 3.55;	N 3.29
Found;	C 59.18;	H 3.50;	N 3.24

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تحضير وبعض الدراسات الكيميائيه على ٢-(٤- تولوين سلفونيل أوكسى فينيل)-٣و١- بنزوأوكزازين-٤-أون

عثمان محمد عثمان حبيب - حسين محمد حسن- أحمد المكباتى محمد

قسم الكيمياء-كليه العلوم-جامعه المنصوره

تم تحضير ٢-(٤- تولوين سلفونيل أوكسى فينيل)-٣و١- بنزوأوكـــزازين-٤-أون وتم تفاعل هذا المركب مع بعض النيوكليوفيلات النيتروجينيه مثل الامونيا ،أورثوفينيلين داى أمين &بعض الامينات غير متجانسه الحلقه &الهيـــدرازين هيـــدرات والهيدروكـــسيل أمـــين هيدروكلوريد وكذلك نيوكليوفيلات الكبريت مثل خامس كبريتيد الفوسفور.وتم اثبات التركيب الكيميائى لهذه المركبات بواسطه التحليل الكمى للعناصر وكذلك باستخدام التحليل الطيفى.