SYNTHESIS OF SOME NEW QUINAZOLIN-4(3H)-ONE DERIVATIVES AND STUDY OF THEIR SOME ANTIBACTERIAL ACTIVITY

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Abstract

In this work, 2-phenyl-4(3H)-3,1-benzoxazinone (1) was synthesized from benzoylation with simultaneous cyclization of anthranilic acid and benzoyl chloride. Compound 1 was treated with hydrazine hydrate to yield 3-amino-2-phenyl-4(3H)-quinazolinone (2). Reaction of compound 2 with aromatic aldehydes/ketones resulted Schiff bases 3-6. Furthermore, treated of compound 1 with thiosemicarbazide yield compound 7, which on reaction with chloroacetic acid in the presence of sodium acetate gave 3-[(4-oxo-1,3-thiazolidin-2-yliden)amino]-2-phenylquinazolin-4(3H)-one (8). On the other hand, 2-substitutedquinazolin-4(3H)-one (9-12) were also synthesized from the reaction of anthranilic acid with different substituted amides in acetic acid.

All newly synthesized compounds were characterized using different methods of spectroscopy such as IR, ^{1}H-NMR and ^{13}C-NMR. The antibacterial activity of all of the synthesized compounds was also reported. All synthesized compounds have been found to be active against both Gram-positive and Gram-negative bacteria but compounds 4 and 8 were the most active one.

Introduction

Quinoxaline derivatives are the subject of considerable interest from both academic and industrial perspective[1]. Among the various classes of nitrogen containing heterocyclic compounds, quinoxalines are important components of several pharmacologically active compounds[2].

Although rarely described in nature, synthetic quinoxaline ring is a part of a number of antibiotics which are known to inhibit the growth of Gram-positive bacteria and are also active against various transplantable tumors[3]. Furthermore, quinazolinones and their derivatives occupy an important position in medicinal and pesticide chemistry, presenting a wide range of bioactivities. As medicines, many of them display anti-HIV[3],antitubercular[3], anticancer[5], antiinflammatory[6], anticonvulsant[7], antidepressant[8], hypolipidemic[9], antiulcer[10], analgesic[11] or immunotropic activites[12] and also known to act as thymidyalate synthase[13], poly(ADP-ribose) polymerase (PARP)[14], and protein tyrosine kinase inhibitors[15]. As pesticides, they are used as insecticides[16], fungicides[17], and antiviral agents[18]. Anilinoquinazolines, in particular, are potent inhibitors of Growth Factor Receptor (GFR) tyrosine kinase and have found clinical applications in Epidermal and Vascular Endothelial GFR targets[19] Fig. (1) :-

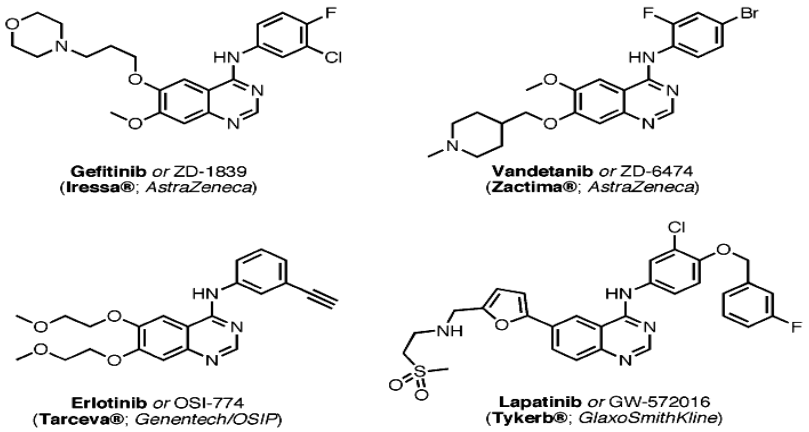


Fig.(1) : Growth Factor Receptor tyrosine kinase-targeting anti-cancer drugs[19].

4-Thiazolidinones have been synthesized and used for the treatment of cardiac diseases. Modification on 2, 3, 4 and 5 positions of 4-thiazolidinone give out antidiabetic drugs and potent aldose reductase inhibitors. Significant antiparkinsonian activity against tremor, rigidity, hypokinesia and catatonia has been evaluated in "*vivo*" in rats and mice in quinazolinyl- thiazolidinone[20].

In light of the growing number of applications in recent years there has been an enormous increase in the interest among biologists and chemists in their synthesis and bioactivity of thiazolidinone derivatives.

Expecting an enhancement of biological activity I have placed two potential bioactive sites, a quinazolone moiety as well as a Schiff base or 4-thiazolidinones ring in my systems. Beside this, in order to taken up the environmentally begin and economic synthesis of some new heterocyclic compounds.

Experimental

Instruments:

Melting points were determined on GallenKamp melting point apparatus and were uncorrected. The IR spectra of the compounds were recorded on Shimadzu FTIR-8300 spectrometer as KBr disc; results are given in cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 300.13 and 75.47 MHz, respectively, in DMSO-d_6 for all compounds on a Bruker AMX-400 NMR spectrometer. The chemical shifts are reported in part per million (ppm) downfield from internal tetramethylsilane (TMS) (chemical shift in δ values). ^{1}H- and ^{13}C-NMR were made at Medicinal and Health Analytical Center, Peking University, China.

Synthesis of 2-phenyl-4(3H)-3,1-benzoxazinone (**1**)

To a stirred solution of anthranilic acid (0.05 mol) in pyridine (25 ml), benzoyl chloride (0.05 mol) was added dropwise, maintaining the temperature near 0-5 ˚C for 1h. The reaction mixture was stirred for another 2h at room temperature until a solid product was formed. The reaction mixture was neutralized with saturated sodium bicarbonate solution and the pale yellow solid which separated was filtered, washed with water and recrystallized from ethanol. M.P. 113-115 ˚C, Yield 83%.

Synthesis of 3-amino-2-phenyl-4(3H)-quinazolinone (**2**)

To a stirred solution of 1 (0.05mol) in pyridine (20ml), 80% $N_2H_4.H_2O$ (0.15mol) was added. The reaction mixture was stirred and refluxed for 2h at 117 ˚C. After cooling, the crude product was obtained by filtration and the crude product was recrystallized from ethanol to afford 2 as a white product. M.P. 177-178 ˚C, Yield 88%.

Synthesis of 3-[(1-naphthalen-2-ylethylidene)amino]-2-phenylquinazolin-4(3H)-one (**3**)

To a solution of 2-acetyl naphthalene (0.01 mol) in abs. ethanol (15 ml), were added the 3-amino-2-phenyl-4(3H)-quinazolinone (**2**) (0.01 mol) and a few drops of glacial acetic acid. The reaction mixture was refluxed for 12h. The resulting mixture was cooled and poured into ice water. The separated solid was filtered, washed with and recrystallized from 95% ethanol to give title compound. M.P. 120-122 ˚C dec., Yield 70%.

Synthesis of 3-{[1-(1H-indol-3-yl) ethylidene]amino}-2-phenylquinazolin-4(3H)-one (**4**)

The same method described for synthesis of compound 3 but used 3-acetylindol instead of 2-acetylnaphthalene. M.P 218-220 ˚C, Yield 77%.

Synthesis of 3-{[1-(4-methyl-phenyl) ethylidene]amino}-2-phenylquinazolin-4 (3H)-one (**5**)

A mixture of 2 (0.01 mol), 4-methylbenzaldehyde (0.01 mol) and abs. ethanol (20 ml) were refluxed for 7h. The resulting mixture was cooled and poured into ice water. The separated solid was filtered, washed with water and recrystallized from ethanol. M.P. 144-146 ˚C, Yield 85%.

Synthesis of 3-{[1-(4-methoxyphenyl) ethylidene]amino}-2-phenylquinazolin-4(3H)-one (6)

The same method described for synthesis of compound 5 but used 4-methoxybenzaldehyde instead of 4-methylbenzaldehyde. M.P. 182-184 ˚C, Yield 80%.

Synthesis of Ǹ-[2-phenyl-4(3H)-oxoquinazolin-3-yl] thiourea (7)

Compound 1 (0.01 mol) was dissolved in ethanol and thiosemicarbazide (0.01 mol) in ethanol was added to it with a catalytic amount of pyridine. Reaction mixture was refluxed for 4h and after cooling a crystalline product was obtained. It was filtered and recrystallized from ethanol to yield needle shaped shining white crystals. M.P. 193-195 ˚C, Yield 70%.

Synthesis of 3-[(4-oxo-1,3-thiazolidin-2-yliden) amino]-2-phenylquinazolin-4(3H)-one (8)

A mixture of 7 (0.01 mol), chloroacetic acid (0.01 mol) and anhydrous sodium acetate (0.02 mol) in abs. ethanol was refluxed for 12h. Excess of solvent was distilled off and the reaction mixture was poured on crushed ice. The solid obtained was filtered, washed with water and recrystallized from DMF to get white crystals. M.P. 260-262 ˚C, Yield 71%.

Synthesis of 2-aminoquinazolin-4(3H)-one (9)

To a mixture of anthranilic acid (0.02 mol) and urea (0.02 mol) was added (20 ml) of abs. ethanol, and the mixture was heated under reflux for 24h. After the reaction was finished, the resulting mixture was cooled and stirred for 30 min. The precipitate was filtered and washed with water to yield target molecule. M.P. 163-165 ˚C, Yield 67%.

Synthesis of 2-methylquinazolin-4(3H)-one (10)

The same method described for the synthesis of compound 9 but using acetamide instead of urea. M.P. 100-102 ˚C, Yield 75%.

Synthesis of 2-phenylquinazolin-4(3H)-one (11)

The same method described for the synthesis of compound 9 but using benzamide instead of urea. M.P. 200-202 ˚C, Yield 67%.

Synthesis of quinazolin-4(3H)-one (12)

The same method described for the synthesis of compound 9 but using formamide instead of urea. M.P. 78-80 ˚C, Yield 82%.

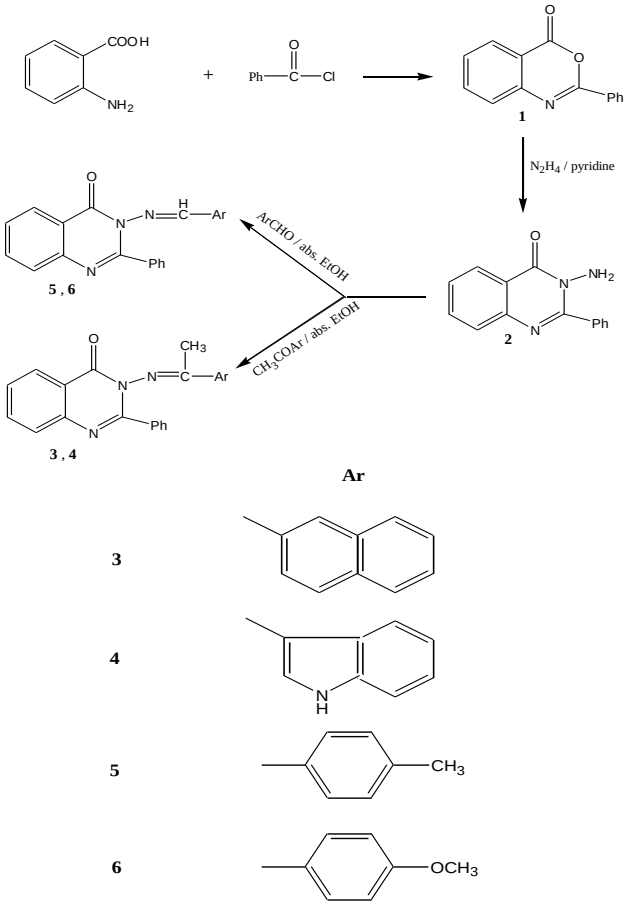
Antibacterial Studies:

All synthesized compounds were test for their in *vitro* growth inhibitory activity against a standard strain of pathogenic microorganism including Gram-positive bacteria (*Bacillus subtilis*), Gram-negative bacteria (*Escherichia coli*). The primary screening was carried out using the agar disc-diffusion method using Müller-Hinton agar medium. Bacteria including *Bacillus subtilis* and *Escherichia coli were* grown in nutrient broth at 37 ˚C for 24h. Sterile filter paper disc (5 mm) were moistened with the compound solution in dimethylsulphoxide of specific concentration (200 μg/disc). The plates were incubated at 37 ˚C, and the diameter of the growth inhibition zones were measured after 24h. Antibiotic discs for Ampicilline were additionally tested as positive control.

Results and Discussion

In the present work, an attempt has been made to undertake the synthesis of quinazolin-4(3H)-one derivatives through a multi steps process. For this purpose, the required 2-phenyl-4(3H)-3,1-benzoxazinone (1) was prepared through benzoylation with simultaneous cyclization of anthranilic acid and benzoyl chloride using pyridine as a solvent and also as a base. Formation of the product was confirmed by a sharp band at 1721cm^{-1} for C=O group along with a band at 1180cm^{-1} for C-O stretching in IR spectrum. On condensation of 2-phenyl-4(3H)-3,1-benzoxazinone (1) with hydrazine hydrate yielded 3-amino-2-phenyl-4(3H)-quinazolinone (2). Compound 2 was then treated with different substituted aldehydes/ ketones in abs. ethanol to form the corresponding 3-(arylidene-amino)-2-phenyquinazolin-4(3H) –one (3-6).

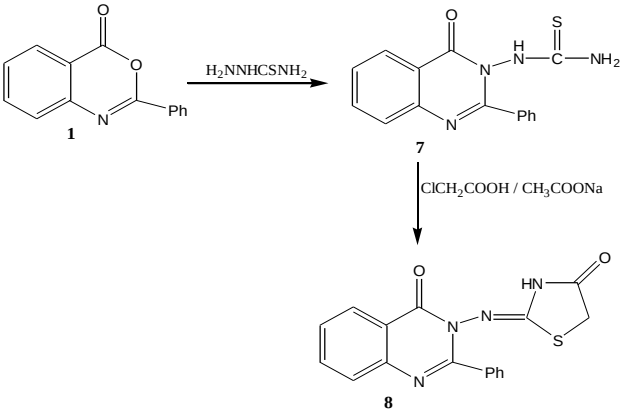
The synthetic route is summarized in Scheme I.



Scheme I

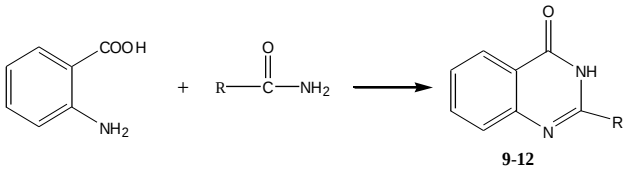
Structural elucidation of compounds 3-6 was accompanied by IR, ^{1}H-NMR and ^{13}C-NMR. The strong absorption at about 1670cm^{-1} is due to the C=O stretching vibration and the moderate intensity absorption at 1625-1605cm^{-1} corresponds to a C=N stretching vibration. The ^{1}H- and ^{13}C-NMR data are in agreement with the results obtained from IR analysis.

Furthermore, benzoxazine 1 was converted to quinazolinyl- thiourea **7** by its nucleophilic substitution reaction with thiosemicarbazide. Insertion of nitrogen in the ring was characterized by disappearance of band at 1180cm^{-1} of C-O and shift of carbonyl band from1721 to 1692cm^{-1}. Appearance of new bands near 3400 and 3260cm^{-1} for N-H stretching also helped in assigning the structure of **7**. ^{1}H- and ^{13}C-NMR were confirmed the structure of compound **7**. When **7** was treated with chloroacetic acid in the presence of sodium acetate as base, nucleophilic reaction took place at the thiourea site of molecule and thiazolidinone ring was formed as a result, to yield a new heterocyclic compound 8 having two free different heterocyclic rings namely quinazolone and thiazolidinone in it, Scheme II. New band in IR at 2983cm^{-1} and a singlet in ^{1}H-NMR at δ3.50 for methylene protons and a singlet at δ5.30 for NH proton together with the signal at 171.5 in ^{13}C-NMR were in accordance with the structure of thiazolidinone ring.



Scheme II

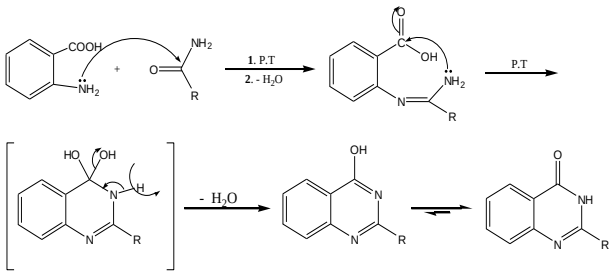
Moreover, condensation of anthranilic acid with different amides afforded corresponding 2-substitutedquinazolin-4(3H)-one derivatives (9-12), equation I.



9: R=NH$_2$; **10**: R=CH$_3$; **11**: R=Ph ; **12**: R=H

equation I

Mechanistically, the reaction may proceed via an *o*-amidine intermediate as illustrated in Scheme III. The first step in this reaction involves the reaction of amino group in anthranilic acid with the carbonyl group of the amide, followed by the nucleophilic attack of the nitrogen nucleophile at the carboxylic carbonyl group to produce the target molecules upon elimination of water molecule :-



Scheme III

Formation of compounds 9-12 were confirmed by appearance of carbonyl band near 1680cm^{-1} due to the quinazolinone ring. Furthermore, appearance of singlet at δ 6.53 and 1.80, in the ^{1}H-NMR spectrum, due to the $-NH_2$ and CH_3 groups also confirmed the formation of compounds 9 and 10, respectively. While the formation of compounds 11 and 12 were confirmed through their ^{13}C-NMR spectra which showed multiple signals at 128.4-134.6 for twelve aromatic carbons, and at 126.1-131.4 for six aromatic carbons, respectively. Table (2) summarized the spectral data of synthesized compounds.

Antibacterial Activity

Synthesized compounds 1-12 were tested for their antibacterial activity against Gram-positive bacteria (*Bacillus subtilis*) and Gram-negative bacteria (*Escherichia coli*). The compounds 1, 7, 10, 11 and 12 showed moderate antibacterial activity toward *Bacillus subtilis*, while 3 and 6 were more active against *Bacillus subtilis*.

The compounds 4 and 8 showed high activity against *Bacillus subtilis* and *Escherichia coli*. Other compounds exhibited moderate to weak antibacterial activity towards both species. The biological activity results are summarized in Table (1).

Table (1)
Antibacterial activity of compounds (1-12).

Comp. No.	Gram +ve	Gram -ve
	Bacillus subtilis	***Escherichia coli***
1	++	+
2	+	++
3	+++	+
4	+++	+++
5	+	+
6	+++	+
7	++	++
8	+++	+++
9	+	+
10	++	+++
11	++	+
12	++	+
Ampicilline	+++	+++

\+ = ***slightly active***
++ = ***moderately active***
+++ = ***highly active***

Table (2)
Spectral data of compounds (1-12).

Comp. No.	Molecular Formula	FT-IR	^{1}H-NMR	^{13}C-NMR
1	$C_{14}H_9NO_2$	3030(C-H aromatic), 1764 (C=O), 1598 (C=N), 1182(C-O)	7.61(m, 9H, Ar-H)	100.2(1C, **C**=N), 130.4-137.0(12C, aromatic carbons), 172.1(1C, C=O)
2	$C_{16}H_{11}N_3O$	3448, 3342(NH_2), 3037(C-H aromatic), 1679(C=O), 1596 (C=N)	6.67(s, 2H, NH_2)(D_2O exchange,disappeared), 7.48-8.19(m, 9H, Ar-H)	110.5(1C, C=N), 126.6-140.3(12C, aromatic carbons), 167.4(1C, C=O)
3	$C_{24}H_{19}N_3O$	3088(C-H aromatic), 2930, 2870(C-H aliphatic), 1678 (C=O), 1625, 1590 (C=N), 777 (aromatic *ortho* substituted)	1.88(s, 3H, CH_3), 7.11-8.30(m, 16H, Ar-H)	14.2(1C, CH_3), 112.3, 118.6(2C, 2**C**=N), 130.4-145.2(22C, aromatic carbons), 170.0(1C, C=O)
4	$C_{23}H_{18}N_4O$	3065(C-H aromatic), 2900, 2850(C-H aliphatic), 1670 (C=O), 1622, 1585 (C=N), 1545(C=C), 778(aromatic *ortho* substituted)	1.62(s, 3H, CH_3), 6.75(s, 1H, NH) (D_2O exchange, disappeared), 7.21-8.05 (m, 13H, Ar-H)	13.3(1C, CH_3), 103.5, 107.0 (2C, 2**C**=N), 110.3, 113.7(2C, 2**C**=N), 128.1-135.4(18C, aromatic carbons), 168.8(1C, C=O)

Comp. No.	Molecular Formula	FT-IR	^{1}H-NMR	^{13}C-NMR
5	$C_{21}H_{17}N_3O$	3030(C-H aromatc), 2910, 2820(C-H aliphatic), 1673 (C=O), 1610, 1590 (C=N), 848(aromatic *para* substituted)	1.57(s, 3H, CH_3), 5.89(s, 1H, N=C**H**), 6.91-7.78(m, 13H, Ar-H)	12.8(1C, CH_3), 104.1, 107.8(2C, 2**C**=N), 127.9-132.5(18C, aromatic carbons), 172.1(1C, C=O)
6	$C_{21}H_{17}N_3O_2$	3020(C-H aromatic), 2920, 2870(C-H aliphatic), 1675 (C=O), 1605, 1585 (C=N), 855(aromatic *para* substituted)	2.38(s, 3H, -OCH_3), 5.60(s, 1H, N=C**H**), 6.78-7.96(m, 13H, Ar-H)	15.2(1C, -O**C**H_3), 102.4, 105.5(2C, 2**C**=N), 126.1-135.6(18C, aromatic carbons), 173.2(1C, C=O)
7	$C_{14}H_{12}N_3OS$	3345-3260(NH, NH_2), 3028(C-H aromatic), 1692 (C=O), 1585(C=N), 1270(C=S)	5.67(s, 1H, NH) (D_2O exchange,disappeared), 6.18(s, 2H, NH_2) (D_2O exchange,disappeared), 6.35-7.62(m, 9H, Ar-H)	98.7(1C, C=S), 110.2(1C, **C**=N), 127.4-135.8 (12C, aromatic carbons), 167.6(1C, C=O)
8	$C_{16}H_{10}N_4O_2$	3345-3260(NH, NH_2), 3028(C-H aromatic), 1692 (C=O), 1585 (C=N), 1270 (C=S)	5.67(s, 1H, NH) (D_2O exchange, disappeared), 6.18(s, 2H, NH_2) (D_2O exchange, disappeared), 6.35-7.62(m, 9H, Ar-H)	98.7(1C, C=S), 110.2 (1C, **C**=N), 127.4-135.8 (12C, aromatic carbons), 167.6 (1C, C=O)
9	$C_8H_7N_2O$	3390-3253(NH, NH_2), 3037(C-H aromatic), 1680 (C=O), 1588 (C=N), 779 (aromatic *ortho* substituted)	5.81(s, 1H, NH) (D_2O exchange,disappeared), 6.53(s, 2H, NH_2) (D_2O exchange,disappeared), 7.05-7.98(m, 4H, Ar-H)	104.4(1C, **C**=N), 121.5-134.7(6C, aromatic carbons), 165.2(1C, C=O)
10	$C_9H_8N_2O$	3180(NH), 3033(C-H aromatic), 2910, 2820 (C-H aliphatic), 1685 (C=O), 1590 (C=N), 772 (aromatic *ortho* substituted)	1.80(s, 3H, CH_3), 5.76(s, 1H, NH) (D_2O exchange,disappeared), 6.62-7.50(m, 4H, Ar-H)	14.5(1C, CH_3), 102.3(1C, **C**=N), 127.1-135.4(6C, aromatic carbons), 168.7(1C, C=O)
11	$C_{14}H_{10}N_2O$	3133(NH), 3050 (C-H aromatic), 1687 (C=O), 1588 (C=N), 769 (aromatic *ortho* substituted)	5.70(s, 1H, NH) (D_2O exchange,disappeared), 6.06-7.85(m, 9H, Ar-H)	100.2(1C, **C**=N), 128.4-134.6(12C, aromatic carbons), 170.5(1C, C=O)
12	$C_8H_6N_2O$	3185(NH), 3030(C-H aromatic), 1683 (C=O), 1590 (C=N)	5.49(s, 1H, NH) (D_2O exchange, disappeared), 6.87-7.25(m, 5H, quinazolinone-H, Ar-H)	105.0(1C, **C**=N), 126.1-131.4(6C, aromatic carbons), 168.7 (1C, C=O)

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الخلاصة

لقد تم في هذا البحث تحضيرالمركب 2-فنيل-4(3H)-1,3-بنزوأوكزازينون (1) من تفاعل الأنثرانلك أسد مع البنزوايل كلورايد. عومل المركب (1) مع الهيدرازين هيدرايد لينتج 3-أمينو-2-فنيل- 4(3H)-كوينازولينون (2). تفاعل المركب (2) مع الألديهايدات/الكيتونات الأروماتية لينتج قواعد شف (3-6). ان معاملة المركب (1) مع الثايوسميكاربازايد أعطى المركب (7) تفاعل المركب (7) مع كلوروأستيك أسد بوجود الصوديوم أستيت أعطى 3-[(4-أوكسو-1،3-ثايازوليدين-2-يليدين)أمينو]-2-فنيل كوينازولين 4-(3H)-أون (8). لقد تم أيضا تحضير كوينازولين-4(3H)-أون المعوض في الموقع 2 (9-12) من تفاعل الأنثرانلك أسد مع أمايدات مختلفة التعويض بستخدام حامض الخليك كمذيب. قد تم تشخيص جميع المركبات المحضرة باستخدام تقنيات الـــ FT-IR ^{1}H-NMR ^{13}C-NMR وكذلك تم دراسة الفعالية البايولوجية لجميع المركبات المحضرة. لقد أظهرت جميع المركبات المحضرة فعالية ضد بكتريا الـــ Gram-positive والـــ Gram-negative لكن المركبان 4 و 8 كانا الأكثر فعالية.