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Studies of synthesis and structure of some Quinazolones

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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, 1H-NMR and 13C-NMR.

Keywords: Quinazolones, synthesis and structure, characterized

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, quinazolinone 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], anti-inflammatory [6], anticonvulsant [7], Antide-Pressant [8], hypolipidemic [9], antiulcer [10], analgesic [11] or Immunotropic activites [12] and also known to act as thymidylate 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]. Anilin-quinazoline, 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].

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 take up the environmentally begin and economic synthesis of some new heterocyclic compounds.

Experimental Instruments
Melting points were determined on Gallen Kamp 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. 1H-NMR and 13C-NMR spectra were

recorded at 300.13 and 75.47 MHz, respectively, in DMSO-d6 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).

Synthesis of 2-phenyl-4(3H)-3,1-benzoxa-zinone (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 ^{0}C, Yield 83%.

Synthesis of 3-amino-2-phenyl-4(3H)-quina-zolinone (2)
To a stirred solution of 1 (0.05mol) in pyridine (20ml), 80% N2H4.H2O (0.15mol) was added. The reaction mixture was stirred and refluxed for 2h at 117 ^{0}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 ^{0}C, Yield 88%.

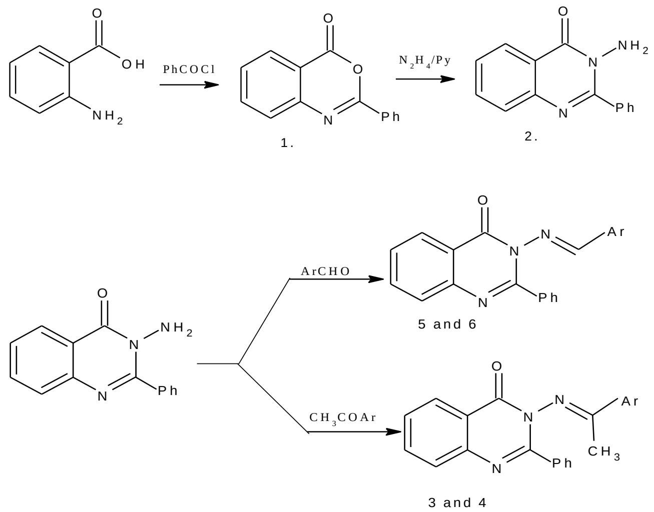
Synthesis of 3-[(1-naphthalen-2-ylethy-lidene) amino]-2-phenylquinazolin-4(3H)-one (3)
To a solution of 2-acetyl naphthalene (0.01 mol) in abs. ethanol (15 ml), were added the 3-amino-2-phenyl-4(3H)-quinazolinone (2) (0.01 mol) and a few drops of glacial acetic acid. The reaction mixture was refluxed 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) ethy-lidene] 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) ethy-lidene] amino}-2-phenylquinazolin-4 (3H)- one (5)
A mixture of 2 (0.01 mol), 4-methylbe-nzaldehyde (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) ethy-lidene] amino}-2-phenylquinazolin-4(3H)-one (6)
The same method described for synthesis of compound 5 but used 4-methoxybe-nzaldehyde instead of 4-methylbenzaldehyde. M.P. 182-184 ˚C, Yield 80%.

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 simult-aneous 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 1180 cm^{-1} for C-O stretching in IR spectrum. On condensation of 2-phenyl-4(3H)-3,1-benzoxa-zinone (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) according to following scheme.



Structural elucidation of compounds 3-6 was accompanied by IR, 1H-NMR and 13C-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 1H- and 13C-NMR data are in agreement with the results obtained from IR analysis.

Table 1: The Molecular Formula FTIR 1H-NMR 13C-NMR

Compd. No.	Molecular Formula	FTIR	1H-NMR	13C-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(NH2), 3037(C-H aromatic), 1679(C=O), 1596 (C=N)	6.67(s, 2H, NH2)(D2O 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, CH3), 7.11-8.30(m, 16H, Ar-H)	14.2(1C, CH3), 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, CH3), 6.75(s, 1H, NH) (D2O exchange, disappeared), 7.21-8.05 (m, 13H, Ar-H)	13.3(1C, CH3), 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)

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, CH3), 5.89(s, 1H, N=CH), 6.91-7.78(m, 13H, Ar-H)	12.8(1C, CH3), 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, -OCH3), 5.60(s, 1H, N=CH), 6.78-7.96(m, 13H, Ar-H)	15.2(1C, -O**C**H3), 102.4, 105.5(2C, 2**C**=N), 126.1-135.6(18C, aromatic carbons), 173.2(1C, C=O)

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