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Synthesis and Anti-Denaturation Activity of Some Substituted Quinazolinone Analogs

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Abstract : In recent years there is a tremendous increase of inflammatory cases, leading to the design and development of newer anti-inflammatory agents. The reaction of 2-substituted phenyl-3-chloroacetamido quinazolin-4(3*H*)-ones with various 5-phenyl-1,3,4-oxadiazole-2-thiol and 5-(pyridine-4-yl)-1,3,4-oxadiazole-2-thiol gave N-(4-Oxo-2-substituted phenylquinazolin-3(4H)-yl)-2-[(5-aryl-1,3,4-oxadiazol-2-yl)sulfanyl] acetamides derivatives. The reaction of 2-phenyl-3-chloroacetamido quinazolinone with various heteroaryl thiols and amines gave N-(4-oxo-2-phenyl quinazolin-3(4*H*)-yl)-2-[(substituted amino/thiol] acetamide derivatives**.** The structure of all the compounds has been confirmed by IR, ^{1}HNMR, Mass spectral data and elemental analysis. *Invitro* anti-inflammatory activity was performed by bovine serum albumin method. Some of the compounds have shown good antibacterial activity and few have shown moderate antioxidant activity compared to the standard drug.
Key words: Quinazolin-4(3*H*)-one, antibacterial activity, antioxidant activity.

Introduction

Recently developed non acidic or weakly acidic NSAIDs like celecoxib, rofecoxib and so on have drawn the attention of medicinal chemists as they preferentially act by inhibiting COX-II enzyme and possessed lower incidence of gastric ulcers than the acidic NSAIDs which inhibit both COX-I and COX-II enzyme like indomethacin, aspirin, naproxen and so on. Furthermore, a large number of quinazolinones have been reported to possess potent anti-inflammatory and analgesic activities[1-3]. However, the substitution pattern in the quinazolinone nucleus at 2/3 position by different aryl or heteoaryl moieties markedly modulates its anti-inflammatory activity.

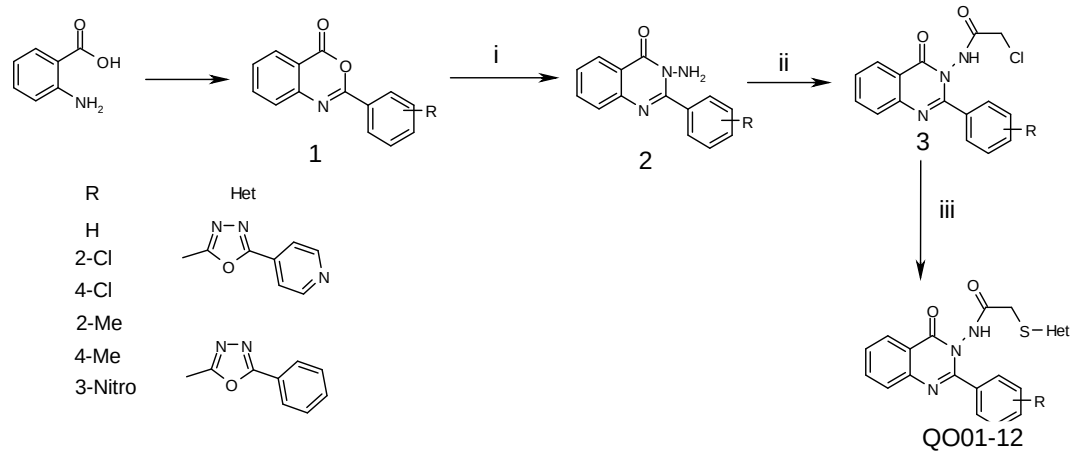
There are very few reports in the literature that quinazolinones derivatives reduce the inflammation in different inflammatory disorders by inhibiting the COX-II enzyme. Hence, it was thought worthwhile to synthesize some new 2,3disubstituted quinazolinone derivatives with the hope to possess better anti-inflammatory property.

Chemistry

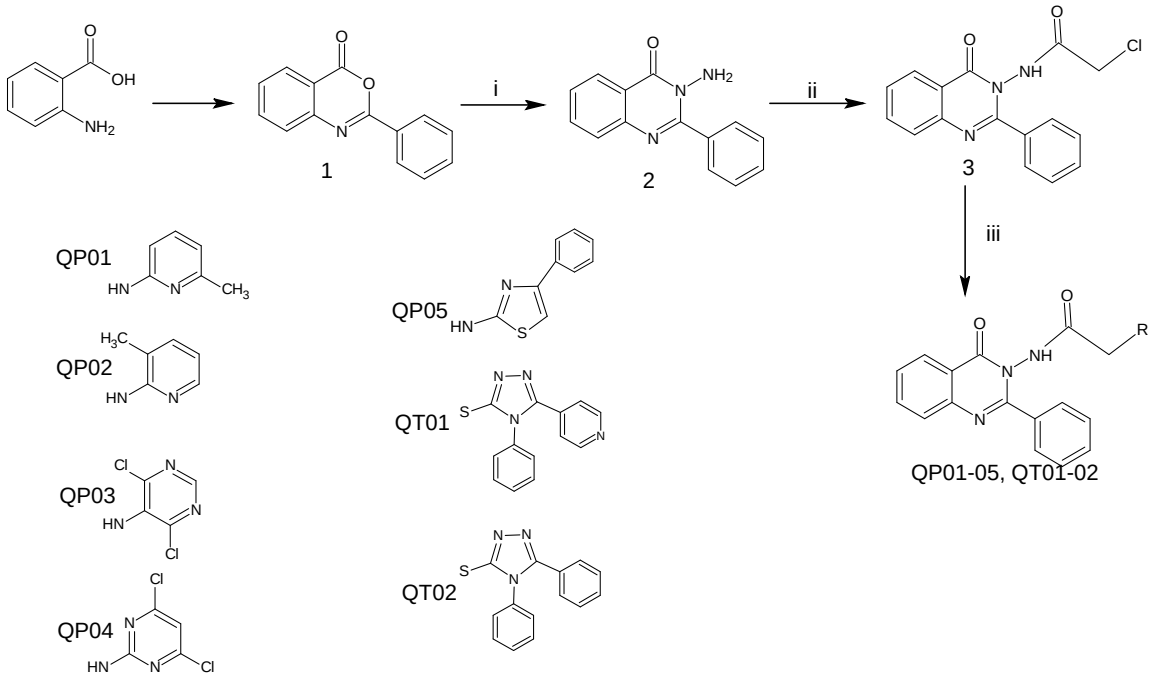
The compound 2-aryl benzoxazinone (**1**) and 3-amino-2-aryl quinazolin-4(3*H*)one (**2**) were prepared according to reported method. Compound **2** was reacted with chloroacetyl chloride in presence of pyridine in dry benzene to obtain 2-chloro-*N*-(4-oxo-2-substituted phenylquinazolin-3(4*H*)-yl)acetamide (**3**). 5-phenyl-1,3,4-oxadiazole-2-thiol and 5-(pyridine-4-yl)-1,3,4-oxadiazole-2-thiolwere reacted

with compound **3** to obtain N-(4-Oxo-2-substitutedphenylquinazolin-3(4H)-yl)-2-[(5-aryl-1,3,4-oxadiazol-2-yl)sulfanyl] acetamides derivatives. The compound 2-chloro-*N*-(4-oxo-2-substituted phenylquinazolin-3(4*H*)-yl)acetamide (**3**) was reacted with various heteroaryl amines and thiols to obtain N-(4-oxo-2-phenyl quinazolin-3(4*H*)-yl)-2-[(substituted amino/thiol] acetamide derivatives. Scheme of synthesis is given in Fig 1**.**

Fig 1: **Scheme**



Scheme of synthesis [i) NH_2NH_2, absolute alcohol ii) $ClCOCH_2Cl$, dry benzene, pyridine iii) substituted oxadiazole]



i) NH_2NH_2 , absolute alcohol ii) $ClCOCH_2Cl$,dry benzene,pyridine iii) various heteroaryl amine/thiol,dry DMF

Materials and Methods

Melting points were measured in open capillary tubes and are uncorrected. IR (KBR) spectra were recorded in film or in potassium bromide disks on a Perkin-Elmer 39 spectrophotometer (υ max in cm-1) and 1H NMR spectra on a DPX 300 MHz Bruker FT-NMR spectrophotometer. The chemical shifts were reported as parts per million (δ ppm) tetramethyl silane (TMS) as internal standard. Mass spectra were obtained on a JEOL-SX-102 instrument using fast atom bombardment (FAB positive). Elemental analysis was performed on a Perkin–Elmer 2400 C,H,N analyzer. The progress of the reaction was monitored on a readymade silica gel plates (Merck) using n-hexane: ethyl acetate as a solvent system. Spectral data (IR, 1HNMR, Mass spectra and elemental analysis) confirmed the structure of the synthesized compounds and the purity of these compounds were ascertained by microanalysis. Elemental (C,H,N) analysis indicated that the calculated and observed values were within the acceptable limits (±0.4%).

The compounds 2-phenyl-4*H*-3,1-benzoxazin-4-one (**1**), 3-amino-2-phenylquinazolin-4(3*H*)-one (**2**), 2-chloro-*N*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl) acetamide (**3**), N-(4-Oxo-2-substituted phenyl quinazolin-3(4H)-yl)-2-[(5-aryl-1,3,4-oxadiazol-2-yl)sulfanyl] acetamides derivatives (QO01-12) and N-(4-oxo-2-phenyl quinazolin-3(4*H*)-yl)-2-[(substituted amino/thiol] acetamide derivatives (QP01-05, QT01-QT02) were synthesized and reported[4,5].

Biological Activity

Anti-denaturation activity of the compounds[6]

Bovine serum albumin assay seeks to eliminate the use of live specimens as far as possible in the drug development process. When BSA is heated, it undergoes denaturation and expresses antigens with type III hypertensive reaction which are related to diseases such as serum sickness, glomerulonephritis, rheumatoid arthritis and systemic lupus erythematous. Thus the assay is applied for the discovery of those drugs which can stabilize the protein from denaturation process[7]. A solution of 0.2% w/v was prepared in 0.1ml tris buffer saline and pH was adjusted to 6.8 using glacial acetic acid. Stock solutions of 10,000µg/ml for all compounds were prepared by using methanol as solvent. From these stock solutions two different concentrations of 100 and 200µg/ml were prepared by using methanol as solvent. A 50 µl (0.1ml) of each compound was transferred to volumetric flask using 1ml micropipette. 5ml of 0.2% w/v BSA was added to all the volumetric flasks.

The control consists of 5ml of 0.2% BSA solution with 50 µl methanol. The standard consists of 100 µg/ml of diclofenac sodium in methanol with 5ml of 0.2% w/v solution The volumetric flasks were heated at 72ºC for 5min and then cooled for 10 min, the absorbance of this solution was determined by using spectrophotometer at a wavelength of 660 nm. The percentage inhibition of precipitation (denaturation of protein) was determined as % relative to the control using the following formula:

$$\% \text{ inhibition of denaturation} = \frac{(\text{Abs. of}_{\text{control}} - \text{Abs. of}_{\text{sample}})}{\text{Abs. of}_{\text{control}}} \times 100$$

Table 1: Anti-inflammatory activity of the compounds QO01-QO12:

Comp.Code	% inhibition	
	100 µg/ml	200 µg/ml
QO01	23.84	27.77
QO02	1.25	3.20
QO03	6.62	10.27
QO04	20.14	34.16
QO05	24.80	59.40
QO06	3.87	14.18
QO07	4.54	17.51
QO08	2.54	5.92
QO09	7.33	11.03
QO10	16.66	30.89
QO11	27.77	37.60
QO12	11.03	16.66
Diclofenac	57.84	79.08

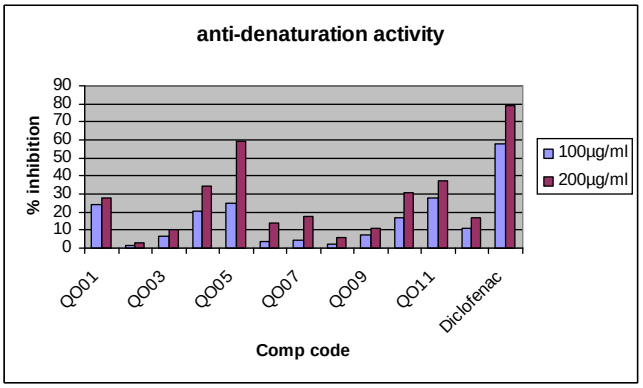
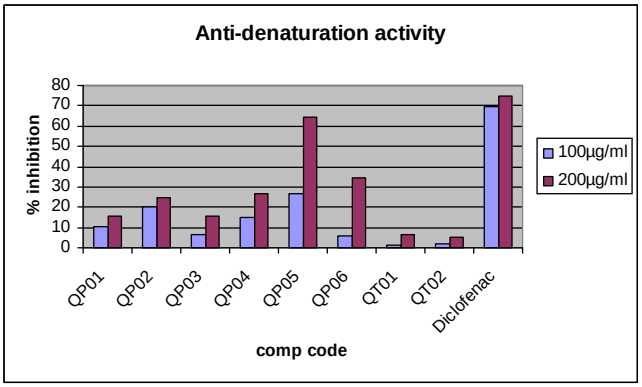


Table 2: Anti-inflammatory activity of the compounds QP01-QP6, QT01 and QT02:

Comp.Code	% inhibition	
	100 µg/ml	200 µg/ml
QP01	10.27	15.82
QP02	20.14	24.80
QP03	6.62	15.82
QP04	14.84	26.77
QP05	26.77	64.28
QP06	5.92	34.16
QT01	1.25	6.62
QT02	1.89	5.22
Diclofenac	69.56	74.53



Results & Discussion

The compounds possessing phenyl, 4-methyl phenyl substitution at 2nd position and pyridyl oxadiazole, phenyl oxadiazole, substituted thiazole at 3rd position have shown good anti-inflammatory activity (>50% inhibition) compared with the standard drug and the compounds with 2-methyl, 3-nitro phenyl substitution at 2nd position and pyridyl, phenyl oxadiazole, substituted pyridyl group at 3rd position of quinazolinone moiety have shown moderate activity (<50% inhibition)and all other compounds have shown negligible anti-inflammatory activity. Hence these compounds shall be exploited further for anti-inflammatory activity to attain a potential pharmacophore.

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