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REVIEW ON QUINAZOLINE DERIVATIVES

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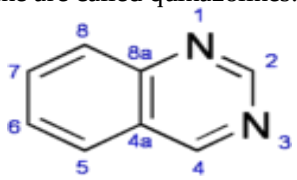
ABSTRACT

Alkaloids with a quinazoline ring system are known as natural compounds having a wide spectrum of biological effects. About one fifth of them are biological active. Moreover, many synthetic derivatives of quinazolines are pharmacologically interesting compounds as well. This type of compounds shows for example antinflammatory, antihypertonic, CNS, antibacterial, analgetic, spasmolytic activity or in the some cases may be characterized as antagonists of adenosine.

Key words: quinazolines, pharmacologically activities

INTRODUCTION:

Quinazolines is a heterocyclic compound made up of two fused six-membered simple aromatic rings, a benzene ring and a pyrimidine ring. Its chemical formula is $C_8H_6N_2$. Quinazoline is yellow solid. It is isomeric andother naphthyridines including qui noxaline, phthalazine and cinnoline. Derivatives of quinazoline are called quinazolines.



IUPAC name:
Benzopyrimidine &Phenmiazine &benzo-1, 3-diazine.

Quinazoline (1) is a fused bicycle compound earlier known as benzo-1 3-diazine was first prepared in the laboratory by Gabriel1 in 1903, although one of its derivatives was known much earlier(2). The name quinazoline (German : Chinazolin) was first proposed for this compound by Weddige3, on observing that this was isomeric with the compounds cinnoline (2) and quinoxaline (3).

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CHEMISTRY:

The significance of this tautomeric interaction can also be seen when a 4(3H)-quinazolinone containing a methyl in the 3-position is subjected to chlorination with POCl3 , the methyl group is lost and chlorination proceed; and when the methyl group is present in the 2-position,the tautomeric effect is extended generating an exomethylene carbon, this compound can be condensed with aldehydes producing 2-styryl-4(3H)-quinazolinones. The significanceof these extended tautomeric effects is that they enhance reactivity of the substituted4 (3H)-quinazolinones.

Paal and Bush4 suggested the numbering of quinazoline ring system, which is currently used. The other less commonly used names for this ring system are ‘phenmiazine’ and 5,6-benzopyrimidine. However, the name quinazoline is now universally accepted. The many derivatives of quinazoline system known so far, keto-quinazolines also called as quinazolinones, are the most important compounds. Depending upon the position of the keto or oxo group, these compounds may be classified into two types: 2-(1H) quinazolinones (or) 1,2-dihydro-2-oxo quinazolines (4) and 4(3H)-quinazolines or 3,4-dihydro-oxoquinazolines (5). These systems (4&5) exhibit lactam-lactim tautomerism and undergo hydroxy group replacement reactions. 2-

Cyano-4(3H)-quinazolinone was the first quinazolinone derivative to be synthesized5.

Brief Account of reactivity of 4(3H)-Quinazolinones:

Reactions associated with tautomeric nature of the quinazolinones are often quite complex and generally unpredictable. The recorded chemical investigation on the subject is voluminous. The amide linkages in quinazolinones should not be looked on as predominantly the keto or the enol form but as true keto-enol tautomers, showing reaction characteristic of both the forms. Quinazolinones are always high melting crystalline solids, insoluble in water and in most organic solvents but soluble in aqueous alkali. They are generally insoluble in dilute acids but are sometimes soluble in concentrated acids. Simple 4(3H)-quinazolinones, although insoluble in dilute acids, are soluble in 6N hydrochloric acid. 4(3H)-quinazolinones form stable monohydrochlorides, chloroplatinate, chloroaurates and picrates6 and their metal salts of silver, mercury, zinc, copper, sodium and potassium7.

Stability of the ring system:

The ring system in quinazolinone is exceedingly stable in oxidation, reduction, hydrolysis reactions and other treatment designed to break the ring. There is no report of degradation of quinazolinone by simple chemical oxidation.

Aromatization:

When a simple and 2-substituted- 4(3H)-quinazolinone is heated with an equivalent amount of phosphorous pentachloride in phosphorous oxychloride, the corresponding 4-chloroquinazoline (6) is obtained. If a methyl group is present at 3-position, prohibiting the usual tautomerism, the methyl group is lost during the chlorination8.

Alkylation:

The position of alkylation of quinazolinones is similar to all the aromatic nitrogen heterocyclic systems in which a hydroxyl group is found ortho or para to the nitrogen position. Such compounds exist in tautomeric mixture (7), the two structures being inter-convertible by the shift of one proton and one pair of electrons. In alkaline solution the ions of such compounds exist as resonance hybrids of the two major forms differing only by the position of two pairs of electrons, as shown. Thus in alkylation of such hydroxyl derivatives of pyridine, pyrimidine and similar heterocycles, the entering group may become attached to either the nitrogen atom, thus giving for instance, an N-alkyl-pyridine or to the oxygen atom, giving an alkoxy pyridine. Alkylating agent9 and the conditions of alkylation but not the hetercyclic nucleus, were the factors determining the course of alkylation.

Nitration:

Quinazolinone on boiling with nitric acid undergoes substitution to give 6-nitro-4 (3H)-quinazolinone (8). On further nitration it has been observed that the second nitro group enters the 8-position to give 6,8-dinitro derivatives (9). 2-Substituted-4(3H)-quinazolinones were also found to behave similarly, under such conditions10-13.

Reduction:

2&3-Dihydro-3-methyl- 4(1H)-quinazolinone (10) could be obtained on reduction of 3-methyl-4(3H)-quinazolinone with Lithium Aluminium Hydride (LiAIH4) in benzene14.

Reactivity of the 2-methyl group:

The methyl group in 2-position of 4(3H)-quinazolinone system was found to be quite reactive since it is linked to an azomethine carbon and condenses with aldehydes to give the styryl compounds (11)15, 16 .These studies, interestingly, revealed that quite a few of such quinazolinone derivatives possess a wide variety of pharmacological activities.

The summary of methods of preparation of 4(3H)-Quinazolinones:

Most of the methods employed for the synthesis of 4(3H)-quinazolinones make use of anthranilic acid or one of their functional derivatives as the starting materials. Based on this factor, the general methods of synthesis are:

Condensation of anthranilic acid with acid amides:

When anthranilic acid is heated in a open container with excess of formamide at 120°C, water is expelled and a nearly quantitative (90%) conversion to 4(3H)-quinazolinones (12)17 is achieved.

Condensation of acetanilides with urethanes:

A number of attempts have been made to condense a urethane derivative with aniline to give 4(3H)-quinazolinone, directly. Urethane and acetanilide, heated for 3 hours with phosphorus pentoxide in toluene, give 2-methyl-4(3H)-quinazolinone (13)18.

Condensation of N-acylanthranilic acids with primary amines:

3(4H)-Quinazolinones may also be synthesized directly from the corresponding N-acylanthranilic acid by heating with ammonia or substituted amines. Bogert and Steiner19 have prepared 2-methyl-3-alkyl-6-nitro- 4(3H)-quinazolinones (14) from N-acyl-5-

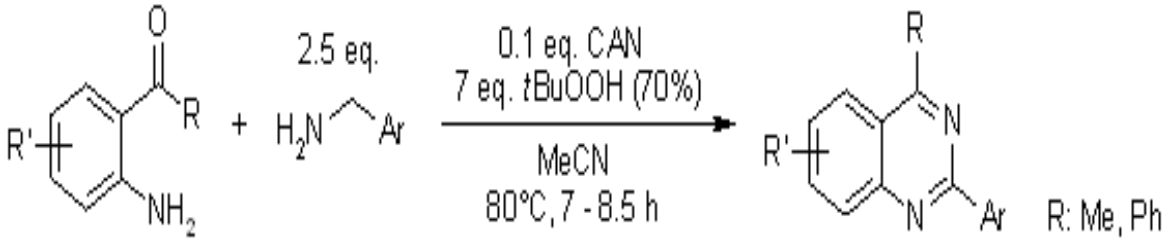
nitroanthranilic acid and a variety of primary amines.

Biological importance of 4(3H)-Quinazolinones

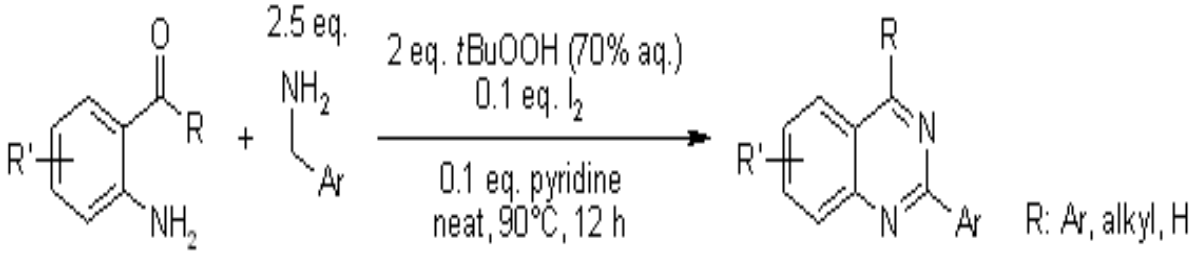
The quinazolinone skeleton is a frequently encountered heterocycle in medicinal chemistry literature with applications including antibacterial20, analgesic21, anti-inflammatory22,23.antifungal24, antimalarial25, antihypertensive26, CNS depressant27, anticonvulsant28, antihistaminic & local anaesthetic29, antiparkinsonism30, antiviral and cancer activities31. Little number of quinazolinones was reported as potent chemotherapeutic agents in the treatment of tuberculosis. For example 3-aryl-6,8-dichloro-2H-1,3-benzoxazine-2,4(3H)-diones and 3-arylquinazoline-2,4(1H,3H)-diones32 as antimycobacterial agents, quinazolinone derivatives33 as antitubercular agents.

Synthesis of quinazolines:

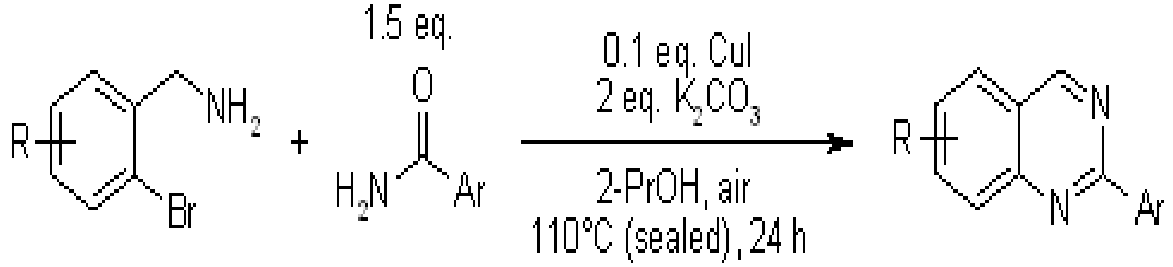
A facile and efficient method for the synthesis of 2-phenylquinazolines from 2-aminobenzophenones and benzylamines us catalyzed by ceric ammonium nitrate (CAN)-TBHP in acetonitrile. The corresponding 2-phenylquinazolines were obtained in good to excellent yields.



A facile approach allows the synthesis of 2-phenylquinazolines via a tandem reaction following sp3 C-H functionalization. Twenty-five examples of 2-phenylquinazolines were obtained from easily available 2-aminobenzophenones and benzylic amines with good to excellent yields. J. Zhang, D. Zhu, C. Yu, C. Wan, Z. Wang, Org. Lett., 2010, 12, 2841-2843.

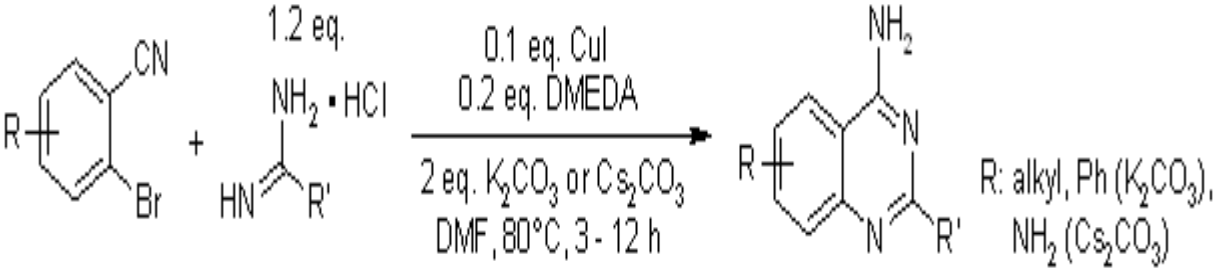


A simple and efficient, ligand-free copper-catalyzed approach to quinazoline derivatives uses readily available substituted (2-bromophenyl)methylamines and amides as starting materials. The cascade reaction includes a sequential Ullmann-type coupling and aerobic oxidation and provides a convenient and practical strategy for the synthesis of quinazoline derivatives. C. Wang, S. Li, H. Liu, Y. Jiang, H. Fu, J. Org. Chem., 2010, 75, 7936-7938.

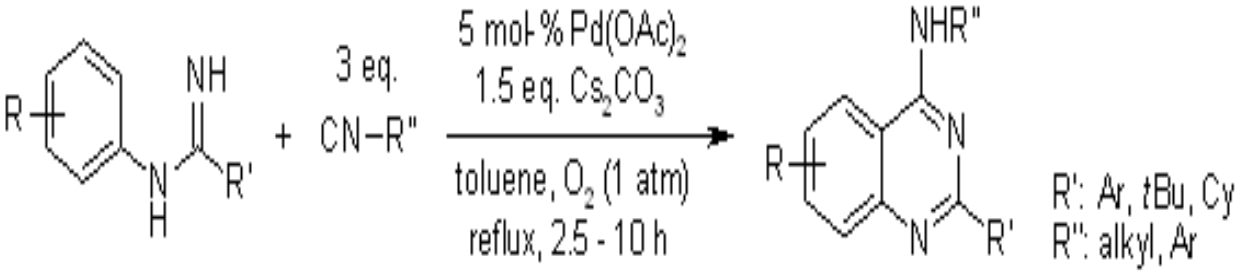


CuCl/DABCO/4-HO-TEMPO as the catalysts and oxygen as the terminal oxidant enabled an efficient aerobic oxidative synthesis of 2-substituted quinazolines and 4H-3,1-benzoxazines

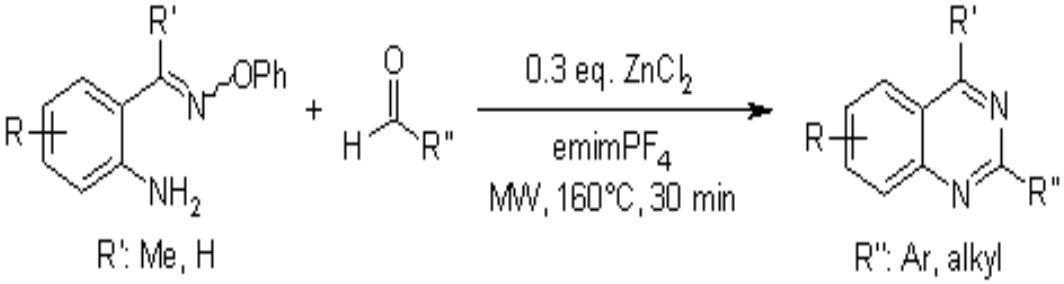
from the one-pot reaction of aldehydes with 2-aminobenzylamines and 2-aminobenzyl alcohols, respectively. B. Han, X.-L. Yang, C. Wang, Y.-W. Bai, T.-C. Pan, X. Chen, W. Yu, J. Org. Chem., 2012, 77, 1136-1142.



An efficient copper-catalyzed reaction of substituted 2-bromo-benzonitriles with amidines or guanidine allows an economical and practical synthesis of 4-aminoquinazoline and 2,4-diaminoquinazoline derivatives. X. Yang, H. Liu, R. Qiao, Y. Jiang, Y. Zhao, Synlett, 2010, 101-106.



An efficient method enables a synthesis of 4-amino-2-aryl(alkyl)quinazolines from readily available N-arylamidines and isonitriles via palladium-catalyzed intramolecular aryl C-H amidination by isonitrile insertion. Y. Wang, H. Wang, J. Peng, Q. Zhu, Org. Lett., 2011, 13, 4596-4599.



A rapid and convenient free-radical-based synthesis of functionalized quinazolines relies on microwave-promoted reactions of O-phenyl oximes with aldehydes in the presence of ZnCl2. The method worked well with alkyl, aryl, and heterocyclic aldehydes and for a variety of substituents in the benzenic part of the molecule. F. Portela-Cubillo, J. S. Scott, J. C. Walton, J. Org. Chem., 2009, 74, 4934-4942

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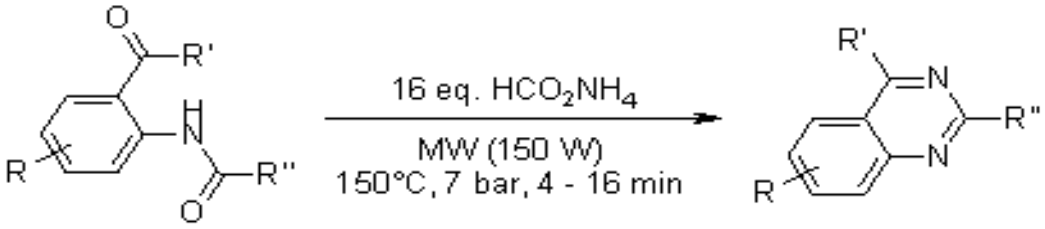
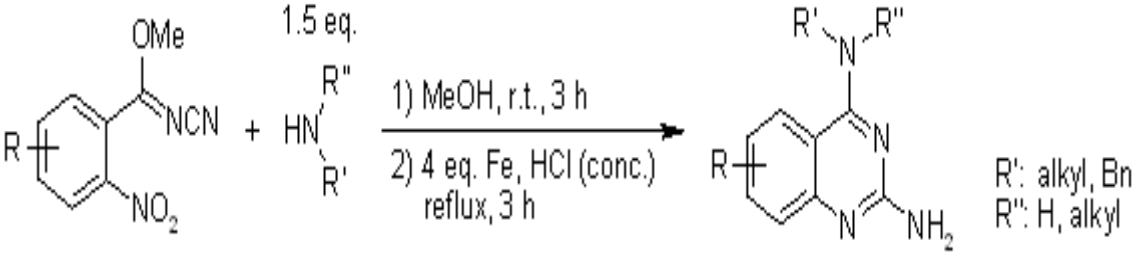
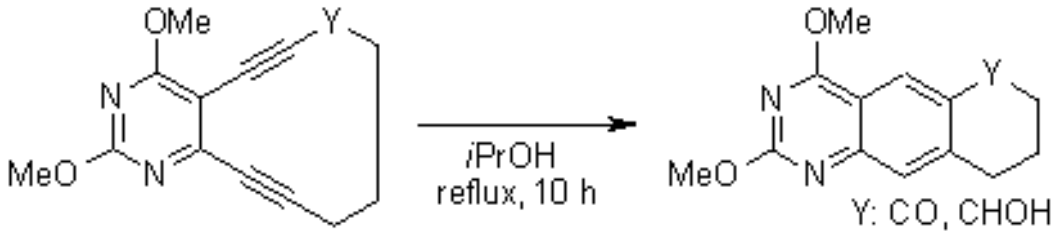


A photochemically induced Fries rearrangement of anilides gave several ortho-aminoacylbenzene derivatives that were acylated. These acylamides underwent rapid microwave-assited cyclization to 2,4-disubstituted quinazolines (and benzoquinazolines) in the presence of ammonium formate.

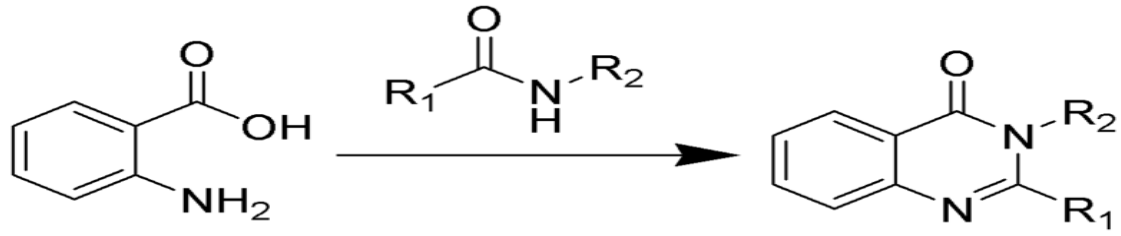
S. Ferrini, F. Ponticelli, M. Taddei, Org. Lett., 2007, 9, 69-72.



A tandem condensation of a cyanoimidate with an amine followed by reductive cyclization in an iron-HCl system enables an efficient route to N4-substituted 2,4-diaminoquinazolines. An additional N-alkylation can produce two fused heterocycles in a one-pot procedure.



Novel 10-membered pyrimidine enediynes were synthesized in seven and eight steps, respectively. These compounds were compared for their abilities to undergo Bergman cyclization both thermally and photochemically and to cleave dsDNA under the appropriate conditions. N. Choy, B. Blanco, J. Wen, A. Krishan, K. C. Russel, Org. Lett., 2000, 2, 3761-3764.

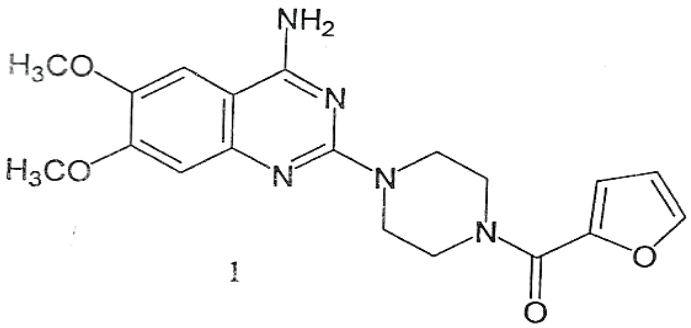


The Niementowski quinazoline synthesis is the chemical reaction of anthranilic acids with amides to form 4-oxo-3, 4-dihydroquinazolines.[1][2][3] The Niementowski quinazoline synthesis.

Biological Activities of Quinazolines

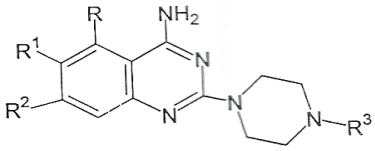
Diverse Biological activities were attributed to compounds possessing a quinazoline ring system.

1-Cardiovascular activity: Quinazolines were found to possess a pronounced cardiovascular activity, in 1968, Scariabine and his co-workers [(5)] investigated the antihypertensive activity of prazosin (1) which is an antihypertensive drug Minipress®.



1

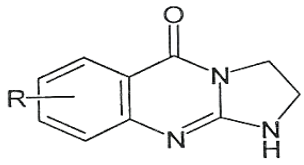
Prazosin is the prototype of several quinazoline based antihypertensive drugs[6], terazosin (2) Hytrin®, doxazosin (3) Caradura®, trimazosin (4) Cardovar®.



	Compound	R	R^1	R^2	R^3
2	Terazosin	H	OCH_3	OCH_3	
3	Doxazosin	H	OCH_3	OCH_3	
4	Trimazosin	OCH_3	OCH_3	OCH_3	

Qiunazolinones were reported to have excellent diuretic activity. In 1970, Shetty and his group[7] reported the synthesis of 2-methyl -6-chloro-3-(o-tolyl)-l,2-dihydro-4(3H)-quinazolinone-7-sulphonamide (Metolazone (5)which is a diuretic drug used under the trade name Zaroxolyn.

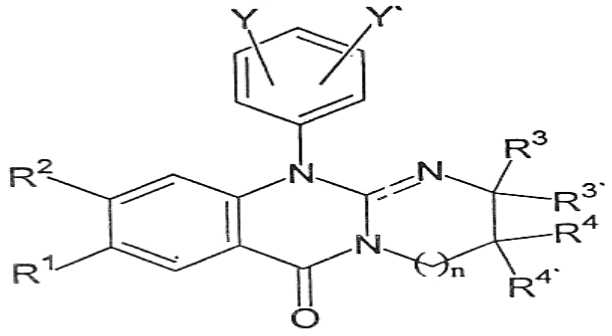
Furthermore, in 1972, Jen, and his team synthesized a series of tetrahydroimidazo[2,l-b]quinazolinone 6 which exhibited a promising antihypertensive activity.



6

R= -H, 6-Cl, 7-Cl, 7-OCH_3,7-OH, 8-Cl or 9-CH_3

After four years, Hardtmann(9), prepared a series of alkyl substituted fused quinazolinone derivatives of the class of imidazo[2,l-b] quinazolin-5-one and pyrimido[2,l-b]quinazolin-6-one 7. Some of the prepared compounds possessed antihypertensive activity as well as a bronchodilator activity.



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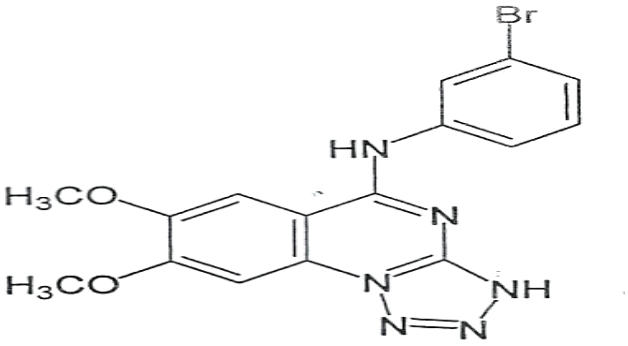
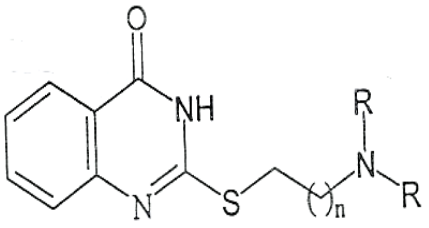


14

R^1 and R^2 are independently, hydrogen and halogen or lower alkyl of 1 to 3 carbon atoms, or either both hydroxy or lower alkoxy of 1 to 2 carbon atoms; or one is hydrogen and the other bromo, hydroxy or lower alkoxy of 1 to 2 carbon atoms. n = 0 or 1 R3, R3, R4 and R4 are hydrogen or lower alkyl of 1 to 5 carbon atoms. Y and Y' are independently, hydrogen or halogen.

2-Anticancer activity:

Quinazoiincs were reported to have anticancer activity. In 1997, Benctenx and his co-workers[16] synthesized 7,8-dimethoxy-5-(3-bromo-anilino) tetrazoline(14) as a highly selective inhibitor of tyrosine kinase activity of the Epidermal Growth Factor receptor[16] which is known to be over expressed in a high percentage of cancers. Moreover, in 2003, Kulscar and his co-workers[20] synthesized 4-quinazolinones 18and evaluated them for anticancer activity. The following compounds exhibited a remarkable inhibitory effect on PARP enzyme, *in vitro.*



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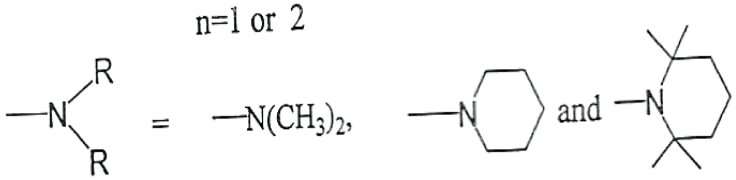

3-Centeral nervous system activities:

The effect of quinazolines on the central nervous system (CNS) was confirmed by Gujral and his group[21]. They found that some 4-quinazolinones exhibited a potent hypnotic action on experimental animals. In addition, 2-methyl- 3-(o-tolyl) - 4(3H) - quinazolinone (methaqualone) (19) and 2- methyl- 3- (o-chlorophenyl)- 4(3H)-quinazolinone (mecloqualone)(20) [22] have been utilized in therapy as a hypnotics

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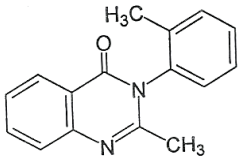

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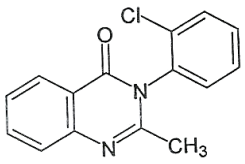
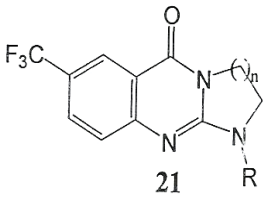


20

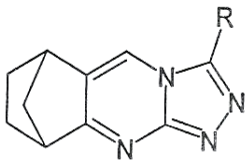
In 1984, the effect of quinazoline on central nervous system (CNS) was also confirmed by Hardtmann and his group [23]. They synthesized imidazo[2,l-b]quinazolin-5-one and pyrimido[2,l-b]quinazolin-6-one derivatives 21 exhibiting a central nervous system depressant effect on mammals and were also useful as tranquilizers.



21

R is alkyl groups from 1 to 8 carbon atoms and
n= 1 or 2

In 1998, Nagai and others [24] reported the synthesis of 5,8-methanoquinazolines fused with 1,2,4-triazole 22 and 1,2,4-triazine 23. The synthesized compounds exhibited central nervous system stimulant activity.



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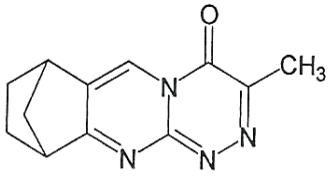
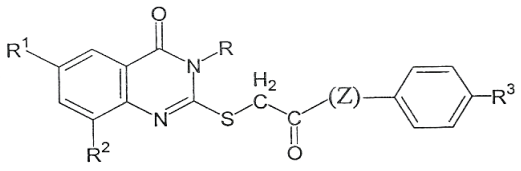


23

R = H, NH_2 or CO_2Et

In 2003, Elhelby and Abdel-Wahab [25] synthesized new derivatives of 4(3H)-quinazolinone 24 with promising anticonvulsant activity.



24

A

Z: NH
R: C_6H_5

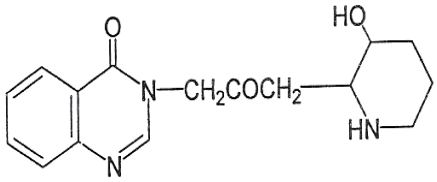
B

Z: O
R: CH_3, C_2H_5 or C_6H_5

For A and B
R^1,R^2: H or Br
R^3: H, C_6H_5-, C_6H_{11}-, 4-$CH_3C_6H_4$-
and 1-Naphthyl

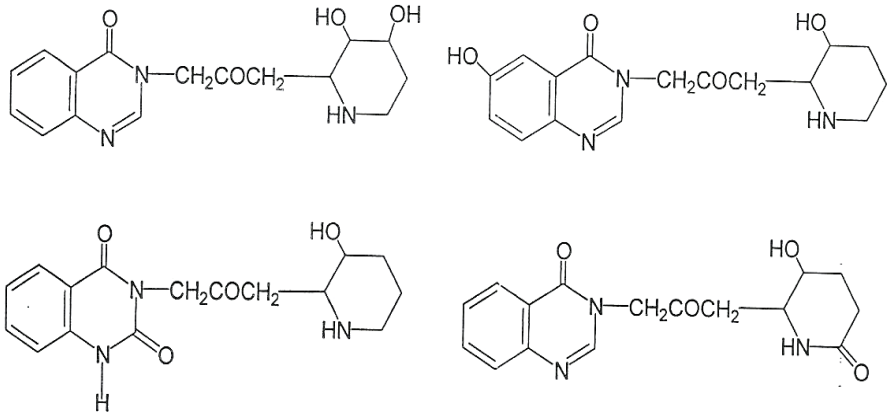
4-Antimalarial activity :

In 1950, Koepfli and other researchers[26] reported that the quinazolinone type alkaloid febrifugine 25 was isolated from Dichorea febrifuga and showed a powerful antimalarial activity, unfortunately, its emetic effect and other undesirable side effects precluded its clinical use for malaria.



25

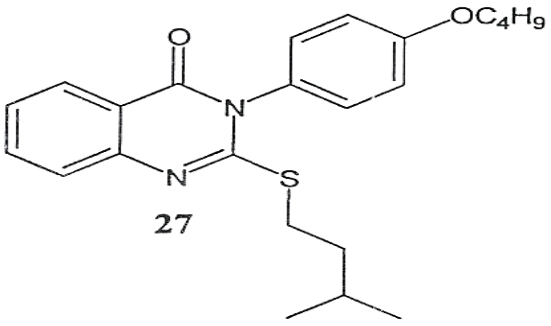
Recently, in 2003, Hirai and others [27], reported that the metabolites of febrifugine 26 posses a powerful antimalarial activity with a spectacular decrease of side effects.



26

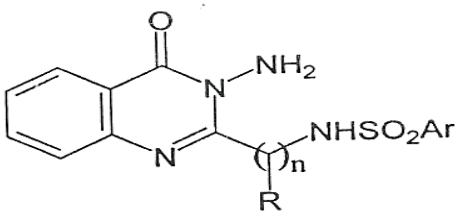
5- Antibacterial activity:

4-Quinazolinones were found to possess broad antibacterial activity against a variety of organisms in vitro. In 1967, Murav'eva and other researchers [28] found that compound 27 possesses a very high tuberculostatic activity..OC4H9



27

In 2001, El-Sharief and others[29] synthesized 4-quinazolinone derivatives 28, where the N-amino compound 28d was found to possess antimicrobial activity against Bacillus cereus ,compound 28c possesses a high antimicrobial activity against Staphylococcus aureus , Bacillus cereus and Proteus merabitis and compound 28f possesses antimicrobial activity towards Staphylococcus aureus, Serratia marcesens and Proteus merabitis



28_{a-f}

№	R	Ar	n
28_a	H	C_6H_5	1
28_b	$CH_2CH(CH_3)_2$	p-CH_3-C_6H_4	1
28_c	$CH_2C_6H_5$	p-CH_3-C_6H_4	1
28_d	H	p-CH_3-C_6H_4	2
28_e	$CH(CH_3)_2$	p-CH_3-C_6H_4	1
28_f	C_6H_5	p-CH_3-C_6H_4	1

In 2003, Kubicova [()]and his co-workers synthesized several 2,2 dimethyl-3-aryl-l,2-dihydroquinazoline-4(3H)-thiones (29) and 2-methyl-3- arylquinazoline – 4 (3H) - thiones (30) and tested them for antimycobacterial and photosynthesis - inhibiting activities. Antimycobacterially active compounds were found among the 6-chloro substituted compounds. 6-Chloro-3-(4-isopropylp:nenyl)-2-methyl-4(3H)-quinazolinethione (31) exhibited higher activity than the isoniazid standard against Mycobacterium^ avium and Mycobacterium kansasii. Most of the synthesized compounds possessed photosynthesis- inhibiting activity.

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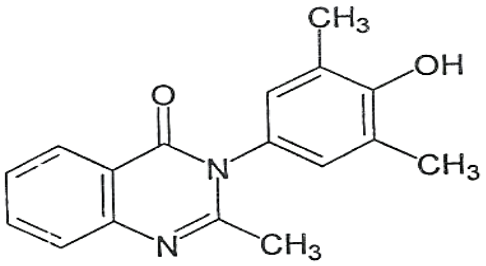
7- Antiinflammatory activity.

Antiinflammatory activity was ascribed to compounds containing 4(3H)-quinazolinone skeleton. In 1976, Parikh and his group[(33)] examined the analgesic and antiinflammatory activities of compound 34 on dogs, where it was found to be four folds more potent than aspirin



34

Pharmacological action of Quinazoline

Quinazoline derivatives with antitubercular activity:

4-Quinazolinol was prepared by the reaction of anthranilic acid and formamide .

The hydroxy group was converted into the thiol function by treatment with phosphorus(V)sulfide, and the subsequent alkylation of the thiol group was carried out with alkylhalides under the conditions of phase-transfer catalysis. The structure of the substances was confirmed by 1H, 13C NMR, IR, and MS. Most of the synthesized compounds exhibited antimycobacterial activity against the strains of Mycobacterium tuberculosis, Mycobacerium avium, Mycobacterium fortuitum, Mycobacterium kansasii and Mycobacterium intracellulare. 4-(S-Butylthio)quinazoline (3c) was even more active than isoniazide against atypical strains of mycobacteria.

Protein kinase inhibitors of the quinazoline class exert anti-cytomegaloviral activity *In vitro and In vivo:*

Cytomegalovirus infection is associated with severe disease in immunocompromised individuals. Current antiviral therapy faces several limitations. In a search of novel drug candidates, we describe here the anti-cytomegaloviral properties of two compounds of the chemical class of quinazolines, gefitinib (Iressa) and Ax7396 (RGB-315389). Both compounds showed strong inhibitory effects in vitro against human and animal cytomegaloviruses with IC(50)s in a low

micromolar range. Cytotoxicity did not occur at these effective concentrations. The antiviral mode of action was based on the inhibition of protein kinase activity, mainly directed to a viral target kinase (UL97/M97) in addition to cellular target candidates. This was demonstrated by a high sensitivity of the respective protein kinases in vitro and by infection experiments with viral mutants carrying genomic alterations in the ORF UL97/M97 modulating viral drug sensitivity .In a guinea pig model, gefitinib showed inhibition of cytomegaloviral loads in blood and lung tissue. Importantly, the rate of mortality of infected animals was reduced by gefitinib treatment. In contrast to the in vitro data, Ax7396 showed no significant antiviral activity in a mouse model. Further in vivo analyses have to assess the potential use of gefitinib in the treatment of cytomegalovirus disease.

Induction of prostate apoptosis by alpha1-adrenoceptor antagonists:

Mechanistic significance of the quinazoline component alpha1-Adrenoceptor antagonists, have been documented to induce apoptosis and reduce prostate tumor vascularity in benign and malignant prostate cells. The quinazoline based alpha1-antagonists, doxazosin and terazosin but not tamsulosin (a sulphonamide derivative) suppress prostate growth without affecting cell proliferation. These quinazoline-mediated apoptotic effects occur via an alpha1-adrenoceptor independent mechanism potentially involving activation of the TGF-beta signal transduction pathway. This review discusses the current knowledge of the action of quinazoline-derived alpha1-adrenoceptor antagonists in the benign and malignant prostate and their potential therapeutic use in the treatment of benign prostatic hyperplasia (BPH) and prostate cancer. Finally, a molecular pathway is proposed for their observed apoptotic function against prostate cells. Increased understanding of the action of these established and clinically accepted agents would provide a basis for the design of safe, effective therapeutic regimens in the treatment of prostatic diseases. At the start of a new millennium, prostatic diseases continue to affect and account for a substantial number of lives in the USA. An estimated one in 11 men will develop a malignant neoplasm of the prostate and approximately 37 000 men will die each year from prostate cancer.1 For European Community countries, more than 35 000 annual deaths are forecast due to prostate cancer.2 Prostate cancer mortality results from metastases to the bone and lymph nodes together with progression from androgen-dependent to androgen independent disease.3 The high mortality associated with these tumors is due to the fact that more than 50% of newly diagnosed patients present with advanced, metastatic disease.4,5 Radical prostatectomy, androgen-ablation monotherapy and radiotherapy are considered to be curative for localized disease,6,7,8 but there is no effective treatment for metastatic prostate cancer that increases patient survival.6. As men approach their sixth decade of life, 50% of them will require treatment for the management of lower urinary tract symptoms (LUTS). This is clinically characterized by enlargement of the prostate and progressive bladder outlet obstruction, with 90% of them having histological evidence of benign prostatic hyperplasia (BPH)9 by the ninth decade. Hyperplasia of both stromal and glandular components of the ageing prostate is implicated in the development and pathophysiology of BPH. The high number of men who will be affected by either prostate cancer or BPH and those currently diagnosed with prostatic diseases translates into an imperative need for the immediate development of clinically effective therapeutic modalities. As loss of apoptosis is associated with the development of prostatic diseases, BPH and prostate cancer,10 re-activation of cell death pathways within the prostate represents an alternative target for pharmacological intervention. Recently, there have been increased efforts toward the design of pharmacological agents that would target the apoptotic component of prostate epithelial cells and significantly improve the therapeutic response of prostate cancer and BPH, while minimizing toxicity.11 The therapeutic significance of apoptosis in the treatment of prostate cancer emerges from evidence suggesting that like normal prostate epithelial cells, prostate cancer cells maintain sensitivity to androgens and undergo apoptosis in response to androgen withdrawal.10,12,13 The androgen-independent prostate cancer cells still contain an intact apoptotic machinery and can undergo apoptosis in response to hormone independent approaches,14 such as ionizing radiation and chemotherapeutic agents.14,15,16,17 .During the last decade, a new class of pharmacological drugs, the alpha-1adrenoceptor antagonists, has emerged as clinically useful for the long-term management of BPH. This review aims to outline the recently recognized apoptotic actions of these alpha1-antagonists against benign and malignant prostate cancer growth and to discuss potential molecular mechanisms underlying this effect that has been specifically associated with the quinazoline-based alpha1-adrenoceptor antagonists.

)1 (The alpha1-adrenoceptor connection in the human prostate

The identification of alpha1-adrenoceptors within the smooth muscle element of prostate adenomas, prostatic capsule and bladder neck18 led to the targeting of these elements for therapeutic purposes. alpha1 -Adrenoceptors belong to the superfamily of G-protein coupled adrenergic receptors which mediate actions of endogenous catecholamines (norepinephrine and epinephrine). Two types of alpha1-adrenoreceptors have been identified in the bladder19,20 and at the bladder neck and in the prostatic smooth muscle surrounding the urethra.21 Targeting these receptors as a means of preventing smooth muscle contraction gave rise to a class of medications commonly used to treat LUTS.22,23 There are currently four recognized subtypes of alpha-adrenoceptors identified in the prostate: alpha1a, alpha1b, alpha1d and alpha1L.24,25,26 Classically, alpha1-adrenoceptor antagonists have been used to target the stromal smooth muscle cells in the treatment of BPH in order to reduce their tone. The competitive inhibition of catecholamines prevents smooth muscle contraction by interfering with perpetuation of second messenger pathways and subsequently modulating cytoskeletal proteins in prostatic smooth muscle cells.27 The therapeutic efficacy of alpha1-adrenoreceptor antagonists for the treatment of BPH has been clinically documented and their safety profiles of these alpha1-blockers are now well established as a result of their long-term use as front-line antihypertensive agents.28,29,30

Recent evidence gathered at our center suggests that in addition to decreasing smooth muscle tone, two alpha1-adrenoceptor antagonists, doxazosin and terazosin, induce apoptosis in benign and malignant prostate epithelial cells, as well as prostate smooth muscle cells.31,32,33 The findings that alpha1-adrenoceptor antagonists can induce apoptosis in prostate epithelial cells in clinical specimens of BPH triggered an upsurge of investigations into the mechanism of action of these drugs against prostate cell growth. Our initial clinical observations were in full accord with experimental studies using a mouse model of prostate hyperplasia, in which doxazosin exhibited a potent apoptotic effect against oncogene-induced prostatic growth.34 In the androgen-independent prostate cancer cells, PC-3 and DU-145 pharmacologically relevant doses of the quinazoline-derived alpha1-antagonists, doxazosin and terazosin (15-25 muM) resulted in significant induction of apoptosis in vitro.33 In contrast, tamsulosin, a methoxysulphonamide derived alpha1-adrenoceptor antagonist had no effect on prostate growth.33 Furthermore, in vivo efficacy studies showed that doxazosin treatment suppressed tumorigenic growth of PC-3 prostate cancer xenografts growing in SCID mice.33 Confirming support for our data came from another independent study that was recently reported.35Although originally designed as antagonists of alpha1-adrenoceptors, recent mechanistic studies have implicated a non-alpha1-adrenoreceptor mediated mechanism of apoptotic action of doxazosin and terazosin in prostate cancer cells.33 The studies summarized in Table 1 provide a strong argument in support of a growth regulatory effect of alpha1-adrenoceptor antagonists in the prostate and raise the possibility that programmed cell death of prostate cancer cells occurs via an effect mediated by the quinazoline component of the drugs. Interestingly, both doxazosin and terazosin were found to exert a similar apoptotic effect in human breast cancer cells, but not in other human tumor cell lines (such as colon or bladder cancer cells),33,36 implying a quinazoline-driven action potentially targeted at hormone-dependent tissues. While one cannot rule out the possibility that this might be prostate specific effect, further investigation is required to establish the organ specificity of this action. In the following sections we will discuss the potential signaling pathways that may underlie such an apoptotic effect specifically directed by the quinazoline-based alpha1-adrenoceptor antagonists in prostate tumor cells.

)2 (Induction of prostate apoptosis: the TGF-beta signal transduction pathway

Transforming growth factor-beta (TGF-beta) is a multifunctional cytokine which regulates cell proliferation, extracellular matrix production and degradation, dif-ferentiation and modulation of apoptosis.37 TGF-beta is a physiological regulator of prostatic growth38,39 via its ability to inhibit prostate epithelial cell proliferation and activate apoptosis in the presence of physiological levels of androgens.38,40 Interestingly, TGF-beta is overexpressed in the malignant prostate when compared with the normal gland.41,42 A molecular basis for this TGF-beta ligand elevation in prostate cancer could be

The apoptotic process initiated by TGF-beta is mediated by complex downstream signaling events that lead to nuclear gene expression. This begins with the formation of a stable heteromeric complex of the TGF-beta ligand and its transmembrane receptors TGF-beta receptor I (TbetaRI) and TGF-beta receptor II (TbetaRII)44 which have intrinsic cytoplasmic serine-threonine kinase domains.45 TGF-beta interacts with

TbetaRII which recruits TbetaRI into the complex44 where it becomes phosphorylated, subsequently leading to downstream signaling.46 TGF-beta initiated intracellular signaling events are mediated by the Smad family of coactivators and transcription factors.47 The importance of these transcription factors in mediating apoptosis of prostate epithelial cells was demonstrated by immunohistochemical analysis of normal prostate and prostate tumors where castration induced apoptosis was associated with increased expression and nuclear accumulation of Smads 2, 3, 4, 6 and 7.48 Decreased levels of TGF-beta receptors are associated with increasing grade in prostate tumors,49,50,51 while enforced expression of TbetaRII in LNCaP cells restores sensitivity to TGF-beta, leading to growth arrest and apoptosis.52for by an increased activation of Raf.43

The apoptotic process initiated by TGF-beta is mediated by complex downstream signaling events that lead to nuclear gene expression. This begins with the formation of a stable heteromeric complex of the TGF-beta ligand and its transmembrane receptors TGF-beta receptor I (TbetaRI) and TGF-beta receptor II (TbetaRII)44 which have intrinsic cytoplasmic serine-threonine kinase domains.45 TGF-beta interacts with TbetaRII which recruits TbetaRI into the complex44 where it becomes phosphorylated, subsequently leading to downstream signaling.46 TGF-beta initiated intracellular signaling events are mediated by the Smad family of coactivators and transcription factors.47 The importance of these transcription factors in mediating apoptosis of prostate epithelial cells was demonstrated by immunohistochemical analysis of normal prostate and prostate tumors where castration induced apoptosis was associated with increased expression and nuclear accumulation of Smads 2, 3, 4, 6 and 7.48 Decreased levels of TGF-beta receptors are associated with increasing grade in prostate tumors,49,50,51 while enforced expression of TbetaRII in LNCaP cells restores sensitivity to TGF-beta, leading to growth arrest and apoptosis.52 The intracellular mediators of TGF-beta signaling pathway may also be targets for apoptosis driven-pharmacological intervention. In response to TGF-beta, the receptor activated Smads 2 and 3 are phosphorylated by the activated TbetaRI53 and these receptor activated-Smads upon association with the Co-Smad, Smad4, are subsequently translocated into the nucleus. Smad4 can only translocate to the nucleus while complexed with the R-Smads, whereas TGF-beta activated Smads can enter the nucleus independently of Smad4.54 Smad4, originally identified as a candidate tumor suppressor gene, deleted in pancreatic carcinoma locus 4 (DPC4), is lost or inactivated in approximately 40% of pancreatic carcinomas.55 Additionally, multiple defects in TGF-beta signaling pathway partly due to reduced expression and activation of Smad2 has recently been reported in head and neck squamous cell carcinomas.56

Recent findings from this laboratory link TGF-beta signaling with the quinazoline-based induction of prostate apoptosis. Increased levels of TGF-beta protein expression in prostatic stromal and epithelial cells undergoing apoptosis was observed in clinical specimens from patients treated with alpha1-blockade,57 evidence supporting TGF-beta upregulation in response to these drugs. One could thus postulate that increased secretion of TGF-beta in the response to quinazoline-mediated apoptosis prostate tissue may be attributed to dying cells releasing active TGF-beta, as has been reported in apoptotic T-cells that release TGF-beta protein without an increase in mRNA level.58 Indirect support for this concept stems from observations that doxazosin treatment of PC-3 prostate cancer cells does not yield any changes in TGF-beta mRNA expression over a 24 h timecourse of apoptosis induction.42

)3 (Antagonistic signaling pathways of TGF-beta mediated apoptotic effects

As previously discussed, several pathways impinge on the TGF-beta signaling pathway in vitro and modulate the apoptotic response. The EGFR/PI-3K pathway,59 PI-3/Akt pathway,60,61 EGFR/Ras/MAPK pathway,62 and the NF-kappaB pathway63 play key roles in cellular proliferation and cell survival. These pathways are hyperactivated in a number of human tumors including the prostate cancer.62 In BPH, increased levels of EGFR and the related HER2/neu signaling pathways have also been associated with loss of growth control.64,65,66

Downstream elements of the EGFR pathway have inhibitory effects on the Smad elements of the TGF-beta signaling, potentially pathway via a Ras mediated mechanism67 and the transcriptional co-repressor, TGIF.68 EGFR has also been implicated in the activation of the survival factor NF-kappaB69 suggesting multiple mechanisms for mediating cell survival. HER2/neu belongs to the EGFR family of receptor tyrosine kinases and has been implicated in androgen-independent prostate cancer growth by activation of the androgen receptor pathway.70,71 The HER2/neu pathway also promotes cell survival through the PI-3/Akt

pathway72 by inactivating the pro-apoptotic protein Bad.73 Interestingly, the PI-3/Akt pathway activates the NF-kappaB transcription factor which mediates several cellular processes including cell growth, inflammatory responses and apoptosis63 and inhibition of TGF-beta signaling by increasing Smad7 expression.74 NF-kappaB can be activated by pathogenic signals and proinflammatory cytokines75 involving the phosphorylation of IkappaBalpha, which is subsequently degraded via the ubiquitin pathway.76 Activation of NF-kappaB in B-lymphocytes upregulates the inhibitory Smad7 and subsequently attenuates TGF-beta induced growth inhibition and apoptosis.77

Conversely, increased IkappaBalpha stability and aberrant NF-kappaB expression mediated by TGF-beta in breast cancer cells has been associated with induced apoptosis.78 This would imply that apoptotic pathways via a crosstalk with TGF-beta can antagonize NF-kappaB activity by upregulating IkappaBalpha. Direct support for this concept is derived from studies linking apoptosis of smooth muscle cells to the deactivation of NF-kappaB.79 Furthermore, recent molecular analyses revealed that doxazosin upregulates IkappaBalpha expression in prostate cancer cells, an event that temporally precedes induction of apoptosis in this system.80 Taken together, these findings provide an interesting mechanistic insight into the apoptotic effect of quinazolines .Considering the above, it is becoming increasingly evident that there is a functional interplay between diverse intracellular signal transduction pathways and the TGF-beta signaling mechanism, that would result in inhibition of the latter. This may occur by inactivation or decreased expression of signal transduction elements, or upregulation of Smad specific inhibitory factors. Thus, removal of these repressive pathways may facilitate normal TGF-beta signaling and subsequent apoptosis activation during benign and malignant prostate growth.

4 **(**Quinazolines as antitumor agents: a molecular insight

Quinazoline based compounds have been studied intensely since they were found to compete with ATP binding to protein tyrosine kinases to inhibit various signaling pathways. The mechanism of action for quinazoline based tyrosine kinase inhibitors (TKI) involves the prevention of the transmembrane tyrosine kinase phosphorylation by competing with ATP binding site on the receptor.81 A number of quinazoline-based antitumor agents acting as TKI exhibit potent antiproliferative, antiangiogenic or apoptotic effects against several cancer cell types.

For instance, the selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, Iressa (ZD1839) inhibits tumorigenicity and angiogenic activity of several cancer cell lines including breast, colon and ovarian and colon cancer xenografts.82 Another TKI, PKI166 induces apoptosis in endothelial cells, while it decreases growth of pancreatic carcinoma cells.83 Significantly enough, we recently reported that prostate tumors from patients who underwent treatment with terazosin and doxazosin exhibited increased apoptosis and reduced tissue neovascularization.84 Considering the apoptotic and potential antiangiogenic effect of terazosin and doxazosin (but not tamsulosin) against prostate cancer cells, one may speculate that the intrinsic quinazoline component may confer partial tyrosine kinase inhibitor activity to these drugs. The chemical structures of the two quinazoline-derived alpha1-adrenoceptor antagonists, doxazosin and terazosin, and the sulphonamide-based tamsulosin are shown in Figure 1. Also shown on Figure 1, for comparative pur-poses are the structures of two characteristic quinazolines with anti-tyrosine kinase activity (EGFR antagonists).85

Quinazoline mediated apoptosis in prostate cells: a mechanistic model of a novel action

Growing evidence from this laboratory supports the concept that the mechanism of doxazosin and terazosin action against benign and malignant prostate cells occurs independently of targeting the alpha1-adrenoceptors.83,86 It is tempting to propose that the apoptotic effects of these drugs may share mechanistic similarity with other quinazoline-based agents reported in the literature. A novel class of TKI, the 4-aniloquinazolines have apoptotic inducing capabilities.87 Although the quinazoline based alpha1-adrenoceptor antagonists (Figure 1) were originally designed, to antagonize alpha1-adrenoceptors to mediate their effects, mounting evidence indicates that these agents induce apoptosis independently of an alpha1-adrenoceptor action.36,86 We therefore propose that these quinazoline-based alpha1-adrenoceptor antagonists may potentially have some tyrosine kinase activity. Such activity would interfere with the signaling of EGFR, HER2/neu, PI-3K pathways, all of which have previously been shown to have repressive effects on TGF-beta signaling. Thus, a model has been proposed to provide a mechanistic basis for the signaling of quinazoline based alpha1-adrenoceptor antagonists against prostatic cell growth (Figure 2). The rapidly induced expression of the TGF-beta regulated gene Smad7, the TGF-beta

inducible IkappaBalpha and p21 in prostate cancer cells after doxazosin treatment, implicates the TGF-beta signaling pathway in the execution of the quinazoline apoptotic effect in prostate cells. Considering the existing reports discussed above, it is conceivable that this may feature tyrosine kinase-mediated pathways that facilitate cell survival by inhibiting the TGF-beta pathway as illustrated in Figure 2. The expression of various effectors of TGF-beta signaling in prostate cells in vitro and in vivo in response to quinazoline treatment is currently being investigated. We also propose that antagonism of these overactive tyrosine kinase pathways in prostate cancer and BPH by the quinazoline-based alpha1-adrenoceptor antagonists may, in turn, uncouple the TGF-beta pathway from the mitogenic pathways initiated by tyrosine kinases. The temporal gene expression profile of key intracellular and nuclear effectors of TGF-beta transduction pathway in normal, benign and malignant prostate epithelial cells in response to quinazoline-based alpha1-adrenoceptor antagonists is currently being characterized, using microarray analysis.

SUMMARY:

With the progressive unraveling of the apoptotic processes at the molecular level, the development of pharmacological agents against prostate cancer has become the focus of intense investigations. Considering that apoptosis induction in prostate biopsies from BPH patients was observed over the normal dose range,31,32,57 effective application of these FDA-approved agents the quinazoline-based alpha1-antagonists, may have promising therapeutic effects not only in the long-term management of BPH, but also in prostate cancer, potentially resulting in decreased morbidity. The elucidation of the molecular pathway(s) with which these quinazoline-based drugs induce apoptosis in androgen independent prostate cancer cells (with minimal effect against normal cells) would clearly be beneficial, since it would provide an additional basis for the design of novel, more effective regimens with an established safety and tolerance profile for the effective management of prostatic diseases.

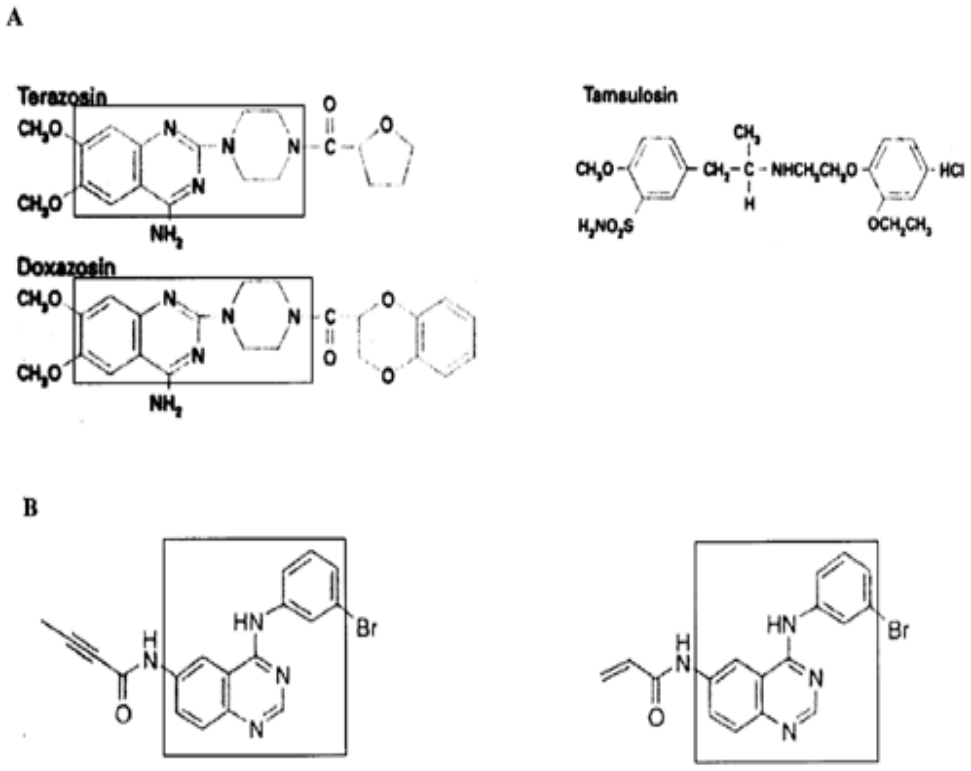
Induction of prostate apoptosis by alpha1-adrenoceptor antagonists: mechanistic significance of the quinazoline component

Table 1 Effects of the quinazoline based α_1-adrenoceptor antagonists on prostate cell growth

	Biological effect	References
Clinical specimens		
Benign prostatic hyperplasia (BPH)	Apoptosis, increased TGF-β secretion, no effect on cell proliferation	Kyprianou *et al*, 1998 Chon *et al*, 1999 Glassman *et al*, 2000
Prostate cancer	Apoptosis, reduced microvascular density, no effect on cell proliferation	Keledjian *et al*, 2001
In vitro		
Prostate cancer cell lines, PC-3, DU-145	Apoptosis induction in androgen-dependent and independent cells	Kyprianou and Benning, 2000 Kyprianou, *et al*, 2000 Cai *et al*, 2000
Prostate smooth muscle cells	Differentiation	Smith *et al*, 1999
LNCaP prostate cancer cells	Significant reduction in PSA	Benning and Kyprianou, 2001
Animal models		
Mouse prostate reconstitutional model (BPH)	Apoptosis, increased TGF-β protein expression, no effect on cell proliferation	Yang *et al*, 1997
PC-3 prostate cancer xenograft	Apoptosis, reduced tumorigenicity	Kyprianou and Benning, 2000

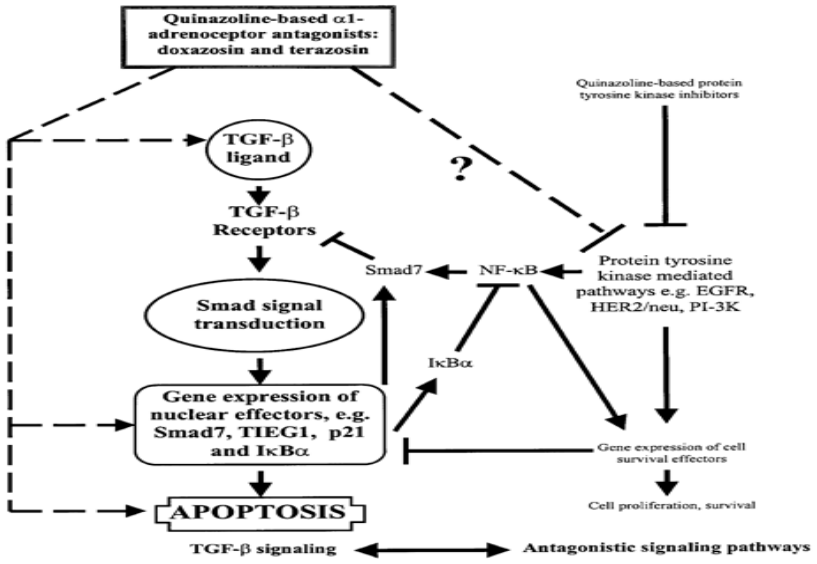
Effects of the quinazoline based alpha1-adrenoceptor antagonists on prostate cell growth

Figure 1



Chemical structures of alpha1-adrenoceptor antagonists and quinazoline-based tyrosine-kinase inhibitors. The quinazoline nucleus is shared by the two quinazoline derived alpha1-adrenoceptor antagonists doxazosin and terazosin (A) and the TKI (B) (see boxed areas), but not by the sulphonamide-based alpha1-adrenoceptor antagonist tamsulosin (A). The two quinazoline derived chemicals, a butynamide-substituted 4-aniloquinazoline (B, left panel) and an acrylamide-substituted 4-aniloquinazoline (right panel) are clinically designed as EGFR specific tyrosine kinase inhibitors.84

Figure 2



A model outlining the potential action of quinazoline-based alpha1-adrenoceptor antagonists, on apoptosis signaling pathways in prostate cancer cells. TGF-beta signaling involves formation of the receptor complex, Smad activation, nuclear translocation and gene transcription that subsequently leads to apoptosis. Cell survival or mitogenic pathways initiated by activated protein tyrosine kinases (PTK) can repress this pathway at different levels and may inhibit TGF-beta signaling. Since strong evidence suggests that quinazoline-based drugs can prevent PTK activation, doxazosin (as a quinazoline-based alpha1-adrenoceptor antagonist) could potentially uncouple these pathways to facilitate apoptotic signaling by TGF-beta.

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