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Advances in the Design and Synthesis of Prazosin Derivatives over the Last Ten Years

Andreas Desiniotis[a] and **Natasha Kyprianou**[a,b,*]

[a]Departments of Surgery/Urology and Molecular & Cellular Biochemistry, University of Kentucky College of Medicine, Lexington, KY, USA

[b]Department of Biochemistry, University of Kentucky College of Medicine, Lexington, KY, USA

Abstract

Introduction—Mechanistic, translational and pharmacological studies led to the identification, preferred localization, binding characteristics, structure and functional properties of α1-adrenoceptor (α1-AR) subtypes in the bladder neck, bladder and prostate gland. The evidence gathered on α1-ARs, provided a molecular platform for the development of subtype selective antagonists, resulting in more effective approaches targeting those receptors for the treatment of outlet bladder obstruction and benign prostate hyperplasia.

Areas Covered—This review provides a comprehensive synopsis of advances over the last decade, in the design and optimization of Prazosin, Doxazosin, Terazosin quinazoline-based derivatives as clinically effective α1-AR antagonists. Furthermore, it discusses evidence on the metabolic and growth interference action by these agents, in addition to their smooth-muscle relaxing effects. The new action recognition emerges from compelling data on the inhibitory effect of quinazoline-based antagonists on primary tumor growth and progression to metastasis. In addition to the cellular findings in the prostate, functional validation and therapeutic impact of selected lead pharmaceutically optimized derivatives in the context of impairing vascularity and triggering tumor apoptosis, are also summarized.

Expert Opinion—The expanding knowledge on targeting intracellular signalling pathways driving the cellular response via an α1-AR dependent and independent antagonistic action, must be invested towards the optimization of new agents that while bypassing AR, exhibit improved pharmacological efficacy against human cancer.

Keywords

adrenoceptors; benign prostate hyperplasia; cancer therapy; heart failure; quinazoline based derivatives; Prazosin

2. Functional Regulation of Adrenoceptors

All classes of ARs are classical G-protein-coupled receptors (GPCRs) with seven transmembrane domains, even though they differentially activate Gα subunits; β-ARs couple predominantly to Gs, and α1-ARs to Gq, although both β2- and α1-AR subtypes can also couple to Gi [1]. Within the family of GPCRs, ARs mediate the functional signaling of catecholamines, epinephrine and norepinephrine (Figure 1) [2]. α1-ARs are comprised of

*Corresponding author: Dr. Natasha Kyprianou, Combs Cancer Research Building, Room. 306, University of Kentucky Medical Center, Lexington, KY 40536, USA., Tel. Number: (859) 323-9812; Fax Number: (859) 323-9608. nkypr2@email.uky.edu.

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multiple subtypes that can be classified by both pharmacological and binding studies into at least three subtypes, α1A-AR, α1B-AR, and α1D-AR; specifically, α1-AR subtypes are expressed in different organs of the human body including brain, heart, liver, kidney, prostate, spleen and blood vessels, in which they mediate a wide panel of functional effects such as modulation of neurotransmission, vasoconstriction, cardiac inotropy, chronotropy, and regulation of metabolism [2]. With respect to the multiplicity of α1-AR subtypes, it is of interest that all three subtypes recognize norepinephrine and epinephrine with similar affinity [3]. Functional studies on each AR subtype revealed that the α1A-AR subtypes is responsible for mediating positive inotropic responses in cardiac myocytes of rat right atrium, and it also mediates the contractions of pig uterine artery, rat tail artery, rabbit ear artery, rat renal artery, dog mesenteric artery, rat mesenteric artery, and human umbilical veins, along with contractions of rat corpus cavernosum, human vas deferens, rat vas deferens, human prostate, and human urethra [4]. The α1B-AR subtype in turn mediates contractions of cardiac myocytes of rat right atrium, human prostate (similarly with the α1A-AR subtype), rat spleen, mouse spleen, venules of rat skeletal muscle, pig uterine artery, rat thoracic aorta, rabbit corpus cavernosum, rabbit cutaneous resistance arteries, and canine aorta [4]. Furthermore, the α1D-AR subtype mediates the responses of rat iliac artery, arterioles of rat skeletal muscle, rat carotid artery, rat aorta, rat mesenteric artery, rat pulmonary artery, rabbit aorta, rabbit ventricle myocytes, rat renal artery, and canine mesenteric vein [4].

Stimulation of α1-ARs results in the activation of various effectors including phospholipase C (PLC), phospholipase A_2 (PLA_2), and phospholipase D (PLD), as well as activation of Ca^{2+} channels, Na^{+}-H^{+} and Na^{+}-Ca^{2+} exchange, along with activation or inhibition of K^{+} channels [3]. Predominantly, the primary functional response after activation of all α1-ARs subtypes is a significant increase in intracellular Ca^{2+} [3]. Earlier studies revealed that stimulation of α-ARs and β-ARs in neonatal rat cardiomyocytes rapidly induces mRNA up-regulation of early genes c-fos, c-jun, egr-1, and additionally an increase in the assembly of the contractile protein myosin light chain-2 [5]. Furthermore α1A-ARs agonists induce stimulation of phosphoinositide hydrolysis, transcriptional induction of atrial natriuretic factor (ANF) gene expression, and an increase in myocardial cell size [6]. Significantly enough phenylephrine treatment of rat cardiomyocytes increases Raf-1 and MAPK activities with Rho, a member of the Ras superfamily of GTPases, being implicated in the phenylephrine-induced transcriptional activation of ANF and α1A-AR mediated cardiac myofibrillogenesis [7]. Ras as an important regulator of hypertrophy both in vitro and in vivo activates a kinase cascade involving Raf, the mitogen-activated protein kinase kinase (MEK), the extracellular signal-regulated protein kinase (ERK), and can also activate the c-Jun NH2-terminal kinase (JNK) in cardiomyocytes [8]. α1A-AR mediates its effect on JNK through a pathway requiring Ras and MEK kinase (MEKK). Noradrenaline stimulation of α1A-AR in human vascular smooth muscle cells was able to increase DNA synthesis and ERK activity in a PI3-K-dependent mechanism clearly showing that activation of α1A-AR outside the myocardium stimulates mitogenesis [7]. α1A-AR mediated PI3-K activation was further demonstrated to result in stimulation of the 70-kDa S6 kinase (p70S6K), which appears to play a role in the activation of protein synthesis regulation [9]. Moreover α1A-AR stimulation of adult rat hepatocytes markedly potentiated the proliferative effects of transforming growth factor alpha (TGFα) via mechanistic recruitment of PLC, protein kinase C (PKC), MAPK, PI3-K, and p70S6K [10]. In the same study, α2-AR stimulation had a similar positive effect on proliferation, while β2-AR showed antagonistic effects on TGFα mediated proliferation. Establishing the α1-AR mediated MAPK activation and signaling, it was additionally demonstrated that α1-AR interacts with β-arrestin in coordinating a different signaling networks as β-arrestins are scaffolds for components of the MAPK cascade thus mediating MAPK activation induced by various GPCRs [2]. In dissecting further signaling pathways involving α1-AR mediation, it was revealed that α1B-

AR inhibits interleukin 6 (IL-6) signaling in hepatocytes after treatment with noradrenaline, by induction of MEK1/p42/44 activity resulting in attenuation of IL-6/STAT3 activation [11]. In addition to Gq coupling, α1A-ARs can signal through Gs resulting in elevation of intracellular cAMP levels, and leading to cyclic AMP-response element-binding protein (CREB) phosphorylation in a PKA dependent manner [12]. Regulation of α1A-ARs is shown to occur under a variety of conditions including hypoxia, ischemic reperfusion, catecholamine stimulation, cAMP levels, and growth factors [7].

While prostate growth is controlled primarily by endocrine related molecules, the nervous system plays an important role in its functions, regulating the prostate via noradrenergic and cholinergic innervation [13]. Noradrenergic nerves primarily innervate the prostatic fibromuscular stroma, and in addition to noradrenaline, other neurotransmitters and neuromodulators may cause contractions and regulate the tone of prostatic smooth muscle via the activation of α1-ARs [13]. The prostate gland is a rich source of α1-ARs, and in prostate cancer epithelial cells α1-ARs are directly functionally coupled to Ca^{2+}-permeable diacylglycerol (DAG) – gated cationic channels activating cationic membrane currents by Ca^{2+} influx and causing contractions [14]. Stimulation of α1-ARs promotes proliferation of primary human prostate cancer epithelial cells by inducing store-independent Ca^{2+} entry and subsequent activation of nuclear factor of activated T cells (NFAT) transcription factor [15]. Interestingly, it has been determined that the α1A-AR subtype is dominant in the prostate gland while in two androgen-insensitive, human metastatic cancer cell lines DU145 and PC3 as well as the mouse TRAMP cell lines the major α1-AR subtype found is the α1B-AR [16]. Recently vascular endothelial growth factor (VEGF) expression significantly correlated with activation of α1-ARs. VEGF is a critical inducer for both normal and tumor cell angiogenesis, and its over-expression is associated with progression of and poor prognosis for several tumors, including prostate, breast, as well as hepatocellular carcinoma (HCC) [17]. Norepinephrine induced VEGF expression and HIF-1α protein amount increase via the cAMP-dependent PKA/PI3K/Akt/p70S6K pathway via activation of ARs [17]. In addition, both α1-AR and β-AR are involved in norepinephrine induced VEGF expression and angiogenesis in prostate cancer and HCC cells, whereas only β-AR is required for breast cancer cells [17]. The signal transduction pathways mediated by α1-AR stimulation are summarized in Figure 1. The comparison between hyperplastic and non-hyperplastic prostate tissue revealed that the overall level of α1-AR mRNA does not significantly change, but essential differences are observed in the ratio of the α1-AR subtypes. In both glandular and stromal hyperplasia, there is a significant reduction of the α1B-AR mRNA expression while the α1A-AR is detected in the stroma and not in the glandular epithelium [18]. The α1B-AR is predominantly localized in the epithelium rather than the stroma, whereas the α1D-AR is partially detected in the stroma and is abundant in blood vessels [18]. The α1D-AR subtype is also associated with bladder muscle contraction [19].

3. Therapeutic Targeting of Adrenoceptors

Validation of agents selective for each of the three α1-AR subtypes is ongoing work for over thirty years because of the abundant possible therapeutic applications against different clinical conditions recognized by investigators around the globe in academic settings and big pharmaceutical corporations. In addition to blood pressure reduction, α1-AR antagonists offer the advantage of a favorable effect on plasma lipoproteins and a low incidence of sexual dysfunction [20]. Since the α1A-AR subtype is the predominant receptor involved in human prostate physiology, consequently α1-AR antagonists are effective drugs also for the treatment of benign prostatic hyperplasia (BPH). This is an important consideration given these two conditions occur concomitantly in about 25% of men over the age of 60, and the use of agents to treat both diseases simultaneously is convenient and preferable from the standpoint of patient acceptance, cost, compliance, and safety [21]. BPH as a condition is

governed by the non-malignant proliferation of both epithelial and stromal cells mainly in the periurethral and transition zones of the prostate gland, and its incidence approaches about 90% of men by the age of 80 [19]. Prazosin was the first agent reported to block α-AR signaling, and subsequent agents were developed to maximize blocking efficacy and specificity against different AR subtypes. The nature, intensity and tolerance of the side-effects associated with Prazosin is diverse. **The most frequently observed side effects observed in patients taking quinazoline α1-AR antagonists include vertigo, dizziness, malaise, headache (that can be well-tolerated), and minor gastro-intestinal disorders (nausea, gastralgia, diarrhea or vomiting). There are also less frequently reported side-effects associated with to cardiovascular toxicity such as postural hypotension, syncope, tachycardia, palpitations, fatigue, drowsiness, rash, flushes and oedema.**

3.1 Prazosin and other Quinazoline-based Adrenoceptor Antagonists

As Prazosin (Figure 2) was reported to act as an oral anti-hypertensive agent, its ability to induce peripheral arterioral vasodilatation following direct vascular smooth muscle relaxation and interference with peripheral sympathetic function was established [22]. It was further shown that Prazosin exerts its antihypertensive effect by relaxation of peripheral arterioles as a consequence of post-synaptic α-AR blockade, rather than by direct relaxation of arteriolar vascular muscle, while it had no apparent central action on blood pressure and no effect on neuronal adrenergic function [23]. Prazosin differed from the previously-developed α-AR blockers, phentolamine and phenoxybenzamine, in that they do not block the pre-synaptic α-AR which modulate the release of neurotransmitter, and therefore do not cause as much reflex activation of the sympathetic nervous system [24]. The antihypertensive properties of Prazosin make it straight choice for the treatment of high blood pressure, and in addition it can be used for the treatment of lower urinary tract symptoms (LUTS) associated with BPH, therefore it is a choice for patients who suffer from both problems simultaneously.

The structure of Doxazosin, shown on Figure 2, is a readily absorbed α1-AR antagonist with high bioavailability and long plasma half-life, and this accounts for the prolonged pharmacologic activity of Doxazosin following a single oral dose [25]. Doxazosin has a positive effect on coronary heart disease by decreasing lipids like total cholesterol, total triglycerides, and low density lipoprotein cholesterol, while positive indicators high density lipoprotein and high density lipoprotein/total cholesterol ratio are increased [26]. In BPH, Doxazosin is effective of relieving bladder outflow obstruction through a reduction in prostatic tone mediated via α1-AR blockade [27]. Similar to Doxazosin, Terazosin (Figure 2) and Alfuzosin selectively antagonize the α1-AR mediated contraction of the prostate, prostatic capsule, proximal urethra and bladder base, and urinary symptoms associated with BPH, by reducing the structure tone [28–31].

More than a decade ago we demonstrated that Doxazosin induced smooth muscle cell apoptosis correlated, decreased alpha-smooth muscle actin expression, as an additional mechanism for improving symptoms associated with BPH in patients, while there were no significant changes in the kinetics of proliferation of either prostate epithelial or stromal cells [32]. Moreover, Doxazosin or Terazosin treatment correlated with a significant loss of cell viability in prostate cancer and smooth muscle cells via induction of apoptosis in a dose-dependent manner, whereas it did not induce a significant effect on the rate of cell proliferation [33]. Concurrent inhibition of α1-ARs did not abrogate the apoptotic effect of Doxazosin or Terazosin against human prostate cancer or smooth muscle cells, suggesting that the apoptotic activity of the agent is independent of its α1-AR blockade capacity [33]. Similar results were documented in experimental studies using a mouse model of prostate hyperplasia, in which Doxazosin exhibited a potent apoptotic effect against oncogene

induced glandular prostate growth [34]. It was implicated that quinazoline-driven action is potentially effective against hormone-dependent tissues [35]. It was proposed that these quinazoline-based α1-AR antagonists may potentially have some tyrosine kinase activity that can potentially interfere with the signaling of epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2/neu), and PI-3K pathways, all of which have previously been shown to have repressive effects on TGF-β signaling [35]. Prostate epithelial cells induce TGF-β expression to counterbalance the increased proliferation thus preventing aberrant prostate growth [36]. The mode of action of quinazoline based tyrosine kinase inhibitors (e.g. Gefitinib) that elicit apoptotic and anti-angiogenic effects against many cancer cell types involves preventing the phosphorylation of tyrosine kinase by competing with the ATP-binding site, and it is likely that the intrinsic quinazoline component confers tyrosine kinase inhibitor activity to α1-AR inhibitors [37]. The sensitivity of cells to Terazosin is shown to be independent of p53 and Rb, however Terazosin mediated apoptosis is associated with G1 phase cell cycle arrest, up-regulation of p27/KIP1, up-regulation of Bax and down-regulation of Bcl-2 [38]. Except inducing apoptosis, Doxazosin and Terazosin were additionally shown to inhibit cell adhesion to the extracellular matrix by inducing anoikis (another form of programmed cell death), and prevent cell invasion and migration of prostate cancer epithelial and vascular endothelial cells [37]. It was additionally indicated that Terazosin treatment results in down-regulation of VEGF and consequently inhibition of angiogenesis *in vivo* [39], while analysis of clinical BPH specimens revealed a considerable decrease of VEGF protein levels after Terazosin treatment in comparison to the untreated control [40]. Doxazosin treatment alsoinhibited proliferation of murine and human pituitary tumor cells *in vitro* and *in vivo*, induced G_0-G_1 cell cycle arrest, and increased apoptosis independently of its action against α1-AR [41]. Moreover, Doxazosin treatment reduced EGFR phosphorylation and activity in breast cancer cells along with NFκB signaling [42].

Doxazosin, Terazosin, and Alfuzosin are adrenoceptor antagonists that show equal affinity for all α1-AR subtypes and are therefore categorized as non subtype selective [43]. A fourth adrenoceptor antagonist currently in use is Tamsulosin, which is a sulphonamide chemical structure (Fig. 2), with a higher affinity for the α1A-AR and α1D-AR subtypes, that quickly became known as a subtype selective or super-selective antagonist [19]. Because of its specific interaction with α1A-AR, Tamsulosin is effective in patients with mild to severe LUTS associated with BPH, in patients with diabetes mellitus and in the elderly, does not interfere with concomitant antihypertensive therapy, has not been associated with clinically significant changes in blood pressure [44]. Several clinical trials have established that Tamsulosin has an improved safety profile relative to the quinazoline-based α1-adrenoceptor antagonists [45].

3.2 Recent Advances

Quinazoline bearing compounds are in general typified by Prazosin, and the 2,4-diamino-6,7-dimethoxyquinazoline moiety is considered as analogue of noradrenaline, where a dominant role in the AR recognition process is played by the protonated N1 of the moiety which mimics the amine function of the neurotransmitter, protonated at physiological pH [46]. The different localization of AR subtypes accelerated the possibility of designing drugs that selectively interact with distinct AR subtypes, thus avoiding the occurrence of possible side effects in other organs. Silodosin is the most recently developed, highly selective α1A-AR antagonist, and its selectivity towards α1A-AR blockade was reported to be 38 times higher than Tamsulosin hydrochloride, in Chinese hamster ovary cells expressing three human α1A-AR subtypes, exhibit a high selectivity of Silodosin for the lower urinary tract where α1A-AR is the predominant subtype [47]. Tamsulosin preferentially blocks α1A-AR and α1D-AR, with a 10-fold greater affinity than for α1B-

AR, whereas Silodosin is highly selective for α1A-AR, with a 162-fold greater affinity than α1B-AR and about a 50-fold greater affinity than for α1D-AR [48]. In comparison with Tamsulosin and Prazosin, Silodosin showed favourable α1A-AR selectivity, as determined by the ratio between the dose required to inhibit intra-urethral pressure and that to decrease blood pressure in rat and dog models [47]. Except blocking α1A-AR signaling and inducing smooth muscle relaxation, Silodosin also targets afferent nerves in the bladder, thus acting on bladder overactivity and storage symptoms [49]. In different randomized clinical trials, Silodosin showed significant improvements in the International Prostate Symptom Score (IPSS), maximum urinary flow rate, and favourable blood pressure related tolerability [47,48,50,51].

The use of monoclonal antibodies prevents ligand binding on receptor tyrosine kinases and small molecule tyrosine kinase inhibitors (TKIs) repressing their enzymatic activity of autophosphorylation and downstream intracellular signaling. EGFR is an excellent therapeutic target for cancer treatment that delivered much promise and hope. The most promising small molecule selective EGFR-TKIs are currently Erlotinib (6,7-bis(2-methoxy-ethoxy)-quinazolin-4-yl-(3-ethynylphenyl)amine) (OSI-774) and Gefitinib (4-(3-chloro-4-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy) quinazoline) (ZD1839), both containing the quinazoline nucleus (Figure 3) [52]. Both TKIs showed promising results in preclinical and clinical studies in many human epithelial cancers, including head and neck squamous-cell carcinoma (HNSCC), non small cell lung cancer (NSCLC), colorectal cancer (CRC), breast cancer, pancreatic cancer and brain cancer, where aberrant expression or activity of EGFR has been identified as an important factor of cancer progression [53]. Vandetanib (ZD6474), another orally bioavailable quinazoline substituted with a halogen at the 2- and 4-positions on the phenyl group in phase III clinical trials, is considered to be a dual tyrosine kinase inhibitor targeting EGFR and VEGFR-2 [54].

New quinazoline derivatives were very recently synthesized from 4-chloro-6,7-dimethoxyquinazoline 3, 4-chloro-6,7-methylenedioxyquinazoline, and commercially available anilines, and these molecules were evaluated as potential DNA intercalating agents exhibiting cytotoxic activity via DNA binding [55]. Other compounds also recently synthesized, successfully differentiated the ether linker (methoxy or diethylaminoethoxy) at the C-6 and C-7 positions of the quinazoline core with expected improved water solubility, bioavailability, and cell penetration. These compounds were tested in the androgen-independent prostate cancer cells, PC-3 and the inhibition of various kinase activities; suppression of the basic side chain on the quinazoline core confers an increase of cellular and enzymatic inhibitory activity with high selectivity on EGFR and VEGFR [54]. In addition, replacement of the urea entity by a carbamic acid methyl ester group presented a dual EGFR/VEGFR-2 activity, and it was suggested that this type of compound could bind in the ATP pocket of the receptors with better affinity leading to a more efficient growth inhibition of the tumors [54]. AZD2171 (4-{(4-Fluoro-2-methyl-1H-indol-5-yl)oxy}-6-methoxy-7-{3-(pyrrolidin-1-yl)propoxy}quinazoline) is another orally bioavailable prazosin derivative bearing the quinazoline core that shows strong selectivity and inhibition of VEGF signaling and angiogenesis by targeting VEGFR2 [56]. With its current name Cediranib in new clinical trials, this compound is suggested against a wide array of solid cancers including NSCLC, HCC, RCC, glioblastomas, ovarian, brain, lung, liver, and prostate cancer with the aim of inhibiting angiogenesis and subsequently regressing tumor progression [57–66].

Quinazolines were used as carriers to prepare a series of N-mustard-quinazoline conjugates having a urea or hydrazinecarboxamide linker [67]. These conjugates possess antitumor potential against different human tumor xenografts, and both urea and hydrazinecarboxamide linkers attached to the C-4 position of the 4-aminoquinazolines are

able to lower the reactivity of the N-mustard moiety resulting in a longer half-life in rat plasma; in addition the quinazoline core is proved to be valuable carriers for building DNA-directed alkylating agents [67–69]. Doxazosin induces apoptosis in androgen independent human prostate cancer cells by enhancing Fas-associated death domain (FADD) recruitment and caspase-8 activation, indicating Fas-mediated apoptosis as the underlying mechanism, but also including up-regulation of TGFβ signaling and engaging the inhibitor of NFκBα (IκBα) [70,71]. Microarray-based examination of Doxazosin mediated gene expression in prostate cancer cells revealed the rapid up-regulation of two TGF-β1-modulated genes, IκBα and p21^{WAF-1} via induction of TIEG1 and Smad4 mRNA levels [70], while Doxazosin can also potentially induce increase of Bax protein levels and caspase-8 activation along with caspase-3 activation via FADD recruitment and formation of the death-inducing signaling complex (DISC) [71].

Subsequent structural optimization studies to enhance the apoptotic action of Doxazosin led to the generation of compounds with significantly increased antitumor efficacy. The main modification strategies are illustrated on Figure 4; the aryl carboxamide function of Doxazosin was substituded with aryl sulfonamides to generate intermediate compounds, and then the piperazine moiety of the optimal compounds was replaced by an ethylenediamine linker, while in another strategy the methoxy side chains on the quinazoline ring of the intermediate compounds were replaced [72]. The apoptotic action of Doxazosin was correlated with its efficacy in inhibiting intracellular levels of the survival pathway driven by protein kinase B (PKB)/Akt phosphorylation/activation. Among the new quinazoline compounds, structures with the side chains of tert-butylphenyl, biphenyl, and phenanthren-9-yl-phenyl, represented the optimal compounds, with IC_{50} values in the range of 5-fold less than Doxazosin resulting in apoptosis induction attributable in part, to the inhibition of Akt activation [72]. Structure-activity studies identify that the lead compound, named DZ-50, significantly reduced the ability of prostate cancer epithelial cells to attach to extracellular matrix and migrate through endothelial cells, while *in vivo* studies showed that DZ-50 treatment led to significant suppression of tumor growth as well as prevented prostate cancer initiation by targeting tissue vascularity [73]. Furthermore, prostate tumor cell metastatic lung colonization was inhibited by DZ-50, further evidence confirming that the development of this class of lead quinazoline-based compounds generated agents with higher potency and stronger efficancy than Doxazosin, in suppressing prostate growth at lower concentrations, thus potentially minimizing toxicity [73]. This profound anti-angiogenesis action has also been manifested in human renal tumors: DZ-50 was recently demonstrated to significantly inhibit tumor cell adhesion, migration, and invasion at lower doses than Doxazosin in renal cancer cell lines, by repressing the focal adhesion complex signaling and downstream the Akt survival pathway [74]. Additional novel Prazosin related compounds inducing apoptosis were synthesized by an independent group of investigators where 2-Chloro-*N*-(4-methoxyphenyl)-*N*-methylquinazolin-4-amine was prepared from reaction of 2,4-dichloroquinazoline with *N*-methyl-4-methoxyaniline [75]. This compound inhibited tubulin polymerization in cells over-expressing Pgp1, and exerted antitumor action against in the human MX-1 breast and PC-3 prostate cancer mouse models; moreover the methyl group on the nitrogen linker of the compound was essential its the apoptosis-inducing activity and substitution in the 6- and 7-positions of the quinazoline core structure decreased potency against EGFR [75]. Terazosin exists in four solvent-free forms that can be prepared directly to the forms of dehydrate or methanolate, but also an isomorphic solvent free form can be prepared by desolvation of the methanolate, thus showing improved stability than the commercially available Terazosin monohydrochloride [76].

Other Prazosin derivatives were also designed by transforming the piperazinyl-quinazoline moiety into an amino-methyl-tetrahydroacridine system [77]. The tetrahydroacridine moiety was shown to be the most promising skeleton for α1-AR antagonism and the derivatives

displayed a tendency to selectively target α1B-AR, whereas the pharmacological profile of these compounds at α1A-AR and α1D-AR was significantly negatively affected [77]. In another study, hybrid tetra-amine disulfides were synthesized by combining the structural features of Prazosin, and Benextramine, an irreversible α1/α2-adrenoreceptor antagonist, and their biological profiles were assessed in isolated rat vas deferens (α1A), spleen (α1B), and aorta (α1D), revealing that the disulfide bridge of these molecules was responsible for their binding potential to α1A-AR and α1B-AR but not in α1D-AR; it was postulated that α1A-AR and α1B-AR subtypes but not α1D-AR probably include in their binding pocket a suitable thiol function that would suffer an interchange reaction due to the disulfide moiety of the agents [78]. A critical structural feature, necessary for the α1-AR affinity is a phenyl ring on the nitrogen atom of the piperazine moiety opposite to the protonatable nitrogen atom, thus the phenylpiperazine scaffold is crucial for binding; consequently compounds possessing the positively ionizable nitrogen atom but lacking the integrity of the phenylpiperazine system are inactive [79]. Furthermore, the length of the alkyl chain acting as a spacer between the phenylpiperazine and the terminal moiety has been demonstrated to influence affinity toward a1-AR, and a three or four-carbon atom spacer represents the optimal distance between the two major molecular portions [79]. New compounds were designed and characterized by a flavone system linked through an ethoxy or propoxy spacer to a phenyl- or pyridazinone-piperazine moiety resulting in a nanomolar affinity potential toward α1-AR, whereas affinity was less pronounced for α2-AR [80]. Efforts to enhance the biological action of Prazosin related compounds, aimed at different modifications of the Prazosin structure. Replacing the furoyl moiety of prazosin with the lipoyl fragment of lipoic acid or of its lower homologues or with 1,4-naphthoquinone, new prazosin derivatives were synthesized including both α1-AR antagonist and antioxidant properties, but also anti-proliferative potential against prostate cancer cells [20]. The use of lipoic acid was based on the potential of the molecule to scavenge a number of free radicals in both membrane and aqueous domains and act as a protective anti-oxidant against pathological conditions associated with oxidative stress [20].

The finding that affinity profiles of Prazosin derivatives depends on the type of moiety linking the two nitrogen atoms of the piperazine ring of Prazosin, led to the synthesis of Cystazosin. The structural design of Cystazosin involved replacement of the piperazine ring with a cystamine moiety, which is a structural feature of benextramine, an irreversible α-AR antagonist [81]. Significantly enough, Cystazosin displayed a higher affinity profile for α1D-AR subtype and a significantly lower selectivity for all other α1-AR subtypes when compared with Prazosin [81]. Cyclazosin was another potent molecule synthesized as a Prazosin derivative with imporoved selectivity. Cyclazosin (+)-2-{(4aS,8aR)-4-(2-furoyl)octahydroquinoxalin-1(2H)-yl}-6,7-dimethoxyquinazolin-4-amine-hydrochloride(+)-1} was designed as a cis-octahydroquinoxaline analogue of Prazosin with further insertion of an alkane chain in the octahydroquinoxaline core, and showed very strong selectivity on α1A-ARs [82,83]. Additional Cyclazosin derivatives were generated by introducing structural modifications on its furan ring by integration of selected substituents at position 5 of the furan ring, and replacement of the furan moiety with classical isosteric ring [84]. These derivatives exhibited higher selectivity than Cyclazosin in targeting and binding α1B-AR subtype, while keeping similar selectivity for the α1B-AR over the α1D-AR subtype [84]. Further exploitation of the cyclazosin structure gave rise to two novel analogues , 2-{4-(2,3-dihydro-1,4-benzodioxin-2-ylcarbonyl)-cis-octahydroquinoxalin-1(2H)-yl}-6,7 dimethoxyquinazolin-4-amine (or also called cyclodoxazosin), and 2-{4-(2,3-dihydro-1,4-benzodioxin2-ylcarbonyl)-trans-octahydroquinoxalin-1(2H)-yl}-6,7-dimethoxyquinazolin-4-amine, incorporating a 2,3-dihydro-1,4-benzodioxine-2-carbonyl moiety instead of the 2-furoyl group [85]. These compounds showed enhanced anti-proliferative and apoptotic properties against three different prostate cancer cell lines, while their anti-angiogenic potential was significantly

higher than Doxazosin [85]. Several new octahydroquinazoline derivatives structurally similar to Prazosin were generated using Mannich reaction of 3-(4-chlorophenylamino)-5,5-dimethyl-2-cyclohexenone with different aromatic amines in the presence of formaline [86]. The newly synthesized compounds showed high hypotensive effect through α1-AR blockade similar to Prazosin, without causing reflex tachycardia; interestingly there was prolonged duration of action when tested in adrenaline induced hypertension in anaesthetized rats [86].

Computational methods have also been used for designing pharmacologic targeting of ARs with evolving degrees of success. Development of pharmacophores to study the specific structural requirements for antagonistic activity to the various α1-AR subtypes [87], revealed that the most important structural feature of α1-AR antagonists concerning their affinity is the distance between the basic nitrogen the aromatic ring [87]. Recent computational methods have been applied for the development of specific pharmacophores for each α1-AR. Those pharmacophores were generated using the HypoGen algorithm in Catalyst software with the feature options of H-bond acceptor (HBA), H-bond donor (HBD), hydrophobic (aromatic) (Har), hydrophobic (aliphatic) (Hal) and positive ionisable (PI) [88]. The PI feature represents atoms, with the ability to be protonated and thus become positively charged, Har and Hal features were chosen to allow differentiation between aromatic (π-π) interactions and more generic hydrophobic interactions, and uncertainty values were calculated as the ratio between the maximum and minimum affinity values [88]. Additional docking studies with Prazosin (as control compound), revealed that the α1D-AR pocket is the smallest, the α1A-AR pocket the largest and the α1B-AR pocket in between [88].

A major challenge of successful outcomes of cancer chemotherapy is the emergence of drug resistance due to increased cellular expression of P-glycoprotein (Pgp1) and the multidrug resistance protein (MRP1), which act as efflux pumps for various anticancer drugs [89]. Iodoazidoaryl prazosin (IAAP), a photoactive analog of prazosin, has been previously reported to act as a multidrug resistance reversal agent by binding and inhibiting Pgp1 function [90]. As the synthesis of IAAP following the earlier route [91] proved to be dangerously unreliable, a convergent route involving direct addition of an acylated piperazine to 2-chloroquinazoline intermediate was established [92]. Erlotinib can also inhibit multidrug resistance by reversing ABC subfamily B member 1 (ABCB1; P-glycoprotein) and ABC subfamily G member 2 (ABCG2; breast cancer resistance protein/ mitoxantrone resistance protein) functions in cancer cells through direct inhibition of the drug efflux function of ABCB1 and ABCG2 [93]. Other TKIs like Imatinib, Nilotinib, and Dasatinib were shown to compete labeling of ABCB1 and ABCG2, pointing to interactions at the Prazosin binding site of both proteins [94].

4. Conclusion

The aggressive pursuit of the expression profile, subtype characterization, cellular localization, pharmacological characteristics, structure and function of the α1-AR subtypes, established an ideal molecular platform for the discovery and development of a large number of subtype selective antagonists that impacted clinical care and therapeutic approaches of various conditions, primarily, benign prostate hyperplasia/bladder outlet obstruction and hypertension [46]. The existence of multiple α1-AR subtypes points out the need of developing new molecules, which target only one receptor while not affecting others localized at different sites. Prazosin still represents a valid choice of treatment for pathologies leading to hypertension and its early developed derivatives have shown clinical improvement in the treatment of LUTS symptoms associated with BPH, as well as hypertension. In this review we summarized the recent advances in design and synthesis of Prazosin derivatives and pharmacologic optimization of new compounds. While the

evidence drove patients to embrace the potential use of these agents as potential prevention strategies, their scientific “acceptance” as anti-cancer agents in the pharmacological and clinical arena awaits confirmation.

5. Expert Opinion

Medicinal chemistry attempts to improve the curative properties of the newly synthesized agents and points out the need for compounds that target specifically each α1-AR subtype, while they are also more stable than their parental compounds and can also bear additional properties for activity against other conditions simultaneously, thus leading to monotherapy. In the early 90s when the clinical use of AR antagonists such as Doxazosin, Prazosin and Terazosin reached an exciting peak and the big pharma had secured their place in the clinical area with a great deal of promise, it would be safe to assume that a potential anticancer action was not even philosophically considered. Just over a decade later the scenario has dramatically changed although the acceptance as anti-tumor agents is still challenged. Indeed a new series of compounds that derive from Prazosin, Doxazosin, Terazosin, and Cyclazosin, bearing the quinazoline core, are tested for their efficacy in inducing apoptotic and anti-angiogenic effects predominantly in prostate but also in other cancer models both *in vitro* and *in vivo.* Recently, novel quinazoline compounds were further developed with Erlotinib and Lapatinib as templates. The substitution pattern at the 4-substituted quinazoline pharmacophores was selected in order to confer the electronic environment that would affect the lipophilicity and hence the activity of the target molecules, towards the objective of forming these hybrids was an additional attempt to create a potent antitumor agent with enhanced activity and selectivity toward cancerous cells [95]. Novel AR antagonists harbouring the quinazoline nucleus effectively impair tumor growth and progression to metastasis by targeting vascularity of solid tumors via anoikis induction, as shown by *in vitro* and *in vivo* studies; moreover such novel compounds can potentially prevent the onset of cancer [73,96]. Ongoing efforts by independent groups are directed at molecular docking studies, pharmacophores, and utilization of software aiming at visualizing the binding sites of α1-ARs and other membrane receptors towards designing new agents with higher affinity and selectivity. Identification of the transmebrane receptors and their downstream signalling pathways, targeting of which impairs tumor growth and progression, is a primary task and a most challenging. Since Doxazosin and its derivative new compound DZ-50, significantly inhibit tumor cell adhesion, migration, and invasion, via disruption of focal adhesions, key regulators of the focal adhesion complex, including focal adhesion kinase (FAK), integrin-linked kinase (ILK), and Talin, were assigned roles as regulators determining the cellular response to these drugs [74,96]. Cell-matrix interactions mediated mainly by integrins and the focal adhesion complex, as well as cell-cell interactions mediated by cadherins, provide not only solid structural support, but also mediate survival of tumor cells via anoikis inhibition [97]. The work demonstrating that a subclass of α1-AR antagonists, (the quinazoline-based), disrupts cancer cell survival and induce apoptosis or anoikis, warrants further efforts to enhance our understanding of mechanisms of apoptotic action and identification of critical anti-apoptotic regulators to be functionally interrupted. Structural exploitation of the different chemical components of Prazosin and related derivatives is also required in understanding the acquisition of anti-tumor action and the molecular targets downstream of α1-AR signaling. The knowledge gathered so far must be processed with careful consideration of the multiple signalling pathways navigating the cellular response to α1-adrenoceptor-dependent and independent antagonistic inhibition towards the optimization of existing and newly synthesized compounds with minimized toxicity and improved pharmacological profiles for the treatment of human cancer.

Abbreviations

AR	Adrenoceptor
GPCR	G-protein-coupled receptor
PLC	phospholipase C
PLA_2	phospholipase A_2
PLD	phospholipase D
ANF	atrial natriuretic factor
MEK	mitogen-activated protein kinase
ERK	extracellular signal-regulated protein kinase
JNK	c-Jun NH2-terminal kinase
MEKK	MEK kinase
PI3K	phosphoinositol–3 kinase
p70S6K	70-kDa S6 kinase
TGFα	transforming growth factor alpha
PKC	protein kinase C
IL-6	interleukin 6
CREB	cyclic AMP-response element-binding protein
DAG	diacylglycerol
NFAT	nuclear factor of activated T cells transcription factor
VEGF	vascular endothelial growth factor
HCC	hepatocellular carcinoma
BPH	benign prostatic hyperplasia
LUTS	lower urinary tract symptoms
EGFR	epidermal growth factor receptor
HER2/neu	human epidermal growth factor receptor 2
IPSS	International Prostate Symptom Score
TKI	tyrosine kinase inhibitor
HNSCC	head and neck squamous-cell carcinoma
NSCLC	non small cell lung cancer
CRC	colorectal cancer
IκBα	inhibitor of NFκBα
PKB	protein kinase B
HBA	H-bond acceptor
HBD	H-bond donor
Har	hydrophobic (aromatic)
Hal	hydrophobic (aliphatic)

PI	positive ionisable
Pgp1	P-glycoprotein
MRP1	multidrug resistance protein 1
IAAP	Iodoazidoaryl Prazosin
ABCB1	ABC subfamily B member 1
ABCG2	ABC subfamily G member 2
FADD	Fas-associated death domain
DISC	death-inducing signaling complex
FAK	focal adhesion kinase
ILK	integrin-linked kinase

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Highlights

- α1-ARs are comprised of multiple subtypes that can be classified by both pharmacological and binding studies into at least three subtypes, α1A-AR, α1B-AR, and α1D-AR.
- Prazosin was the first agent reported to block α-AR activation and signaling, and subsequently further agents were developed to maximize blocking efficacy and specificity against different AR subtypes.
- Quinazoline α1-AR antagonistc derivatives Doxazosin, Terazosin, and Tamsulosin selectively antagonize the α1-AR mediated contraction of the prostate, prostatic capsule, proximal urethra and bladder base, and urinary symptoms associated with BPH.
- Tyrosine kinase inhibitors Gefitinib and Erlotinib containing the quinazoline core along with Doxazosin, Terazosin and other derivatives show promising results in preclinical and clinical studies as anti-cancer agents.
- Ongoing efforts are directed at molecular docking studies, pharmacophores, and utilization of software aiming at visualizing and describing the binding sites of α1-ARs and other receptors in the process of designing new agents with better affinity and selectivity.

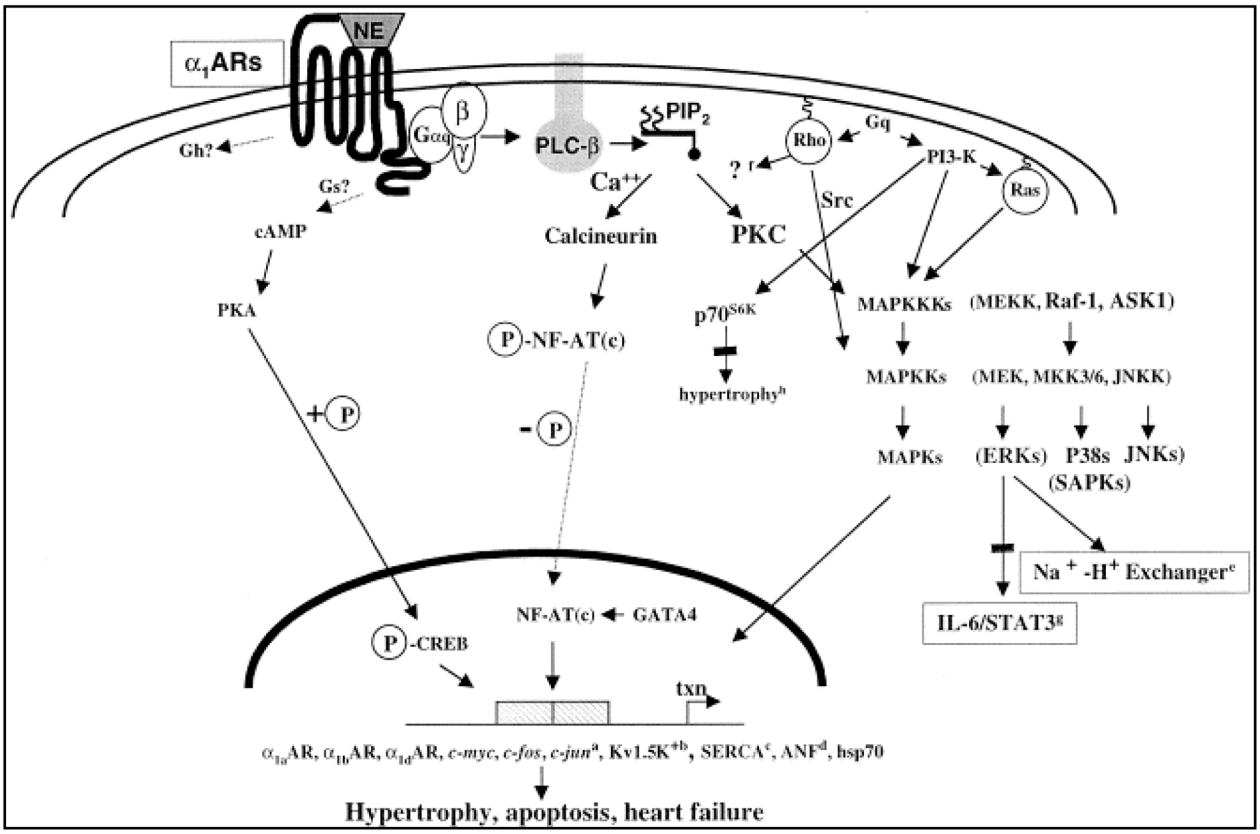

Figure 1.

Signaling pathways downstream of α1-AR activation. Activation of α1-ARs via agonistic binding of norepinephrine or mutations results in activation of Gα subunits and further activation of various effectors including PLC, PLA_2, PLD, leading to induction of different transcription factors leading to heart diseases and possibly cancer [7].

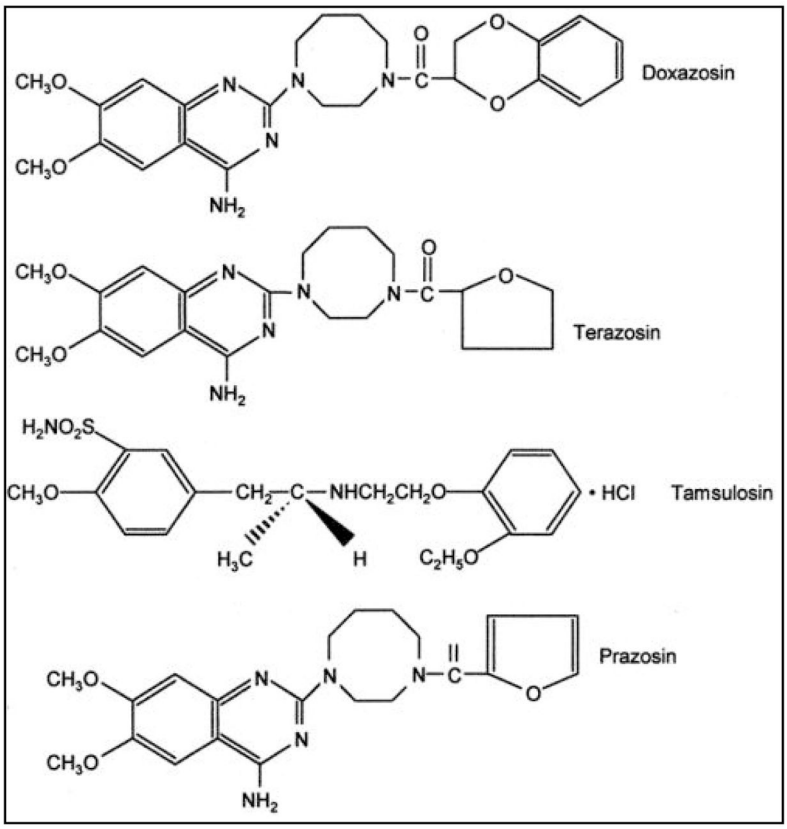

Figure 2.

Chemical structures of Prazosin and quinazoline α1-AR antagonistc derivatives Doxazosin, Terazosin, and Tamsulosin [98]. Those agents selectively antagonize the α1-AR mediated contraction of the prostate, prostatic capsule, proximal urethra and bladder base, and urinary symptoms associated with BPH. Recently, Doxazosin, Terazosin and their derivatives have affiliated as potential anti-cancer agents.

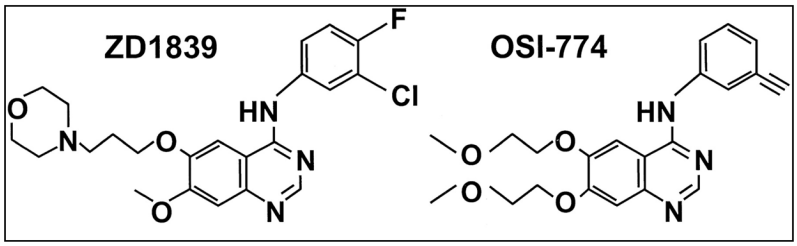

Figure 3.

Chemical structures of the tyrosine kinase inhibitors Gefitinib (ZD1839) and Erlotinib (OSI-774) containing the quinazoline core. Both TKIs show promising results in preclinical and clinical studies in many human epithelial cancers, including HNSCC, NSCLC, CRC, breast cancer, pancreatic cancer and brain cancer, where aberrant expression or activity of EGFR has been identified as an important factor of cancer progression.

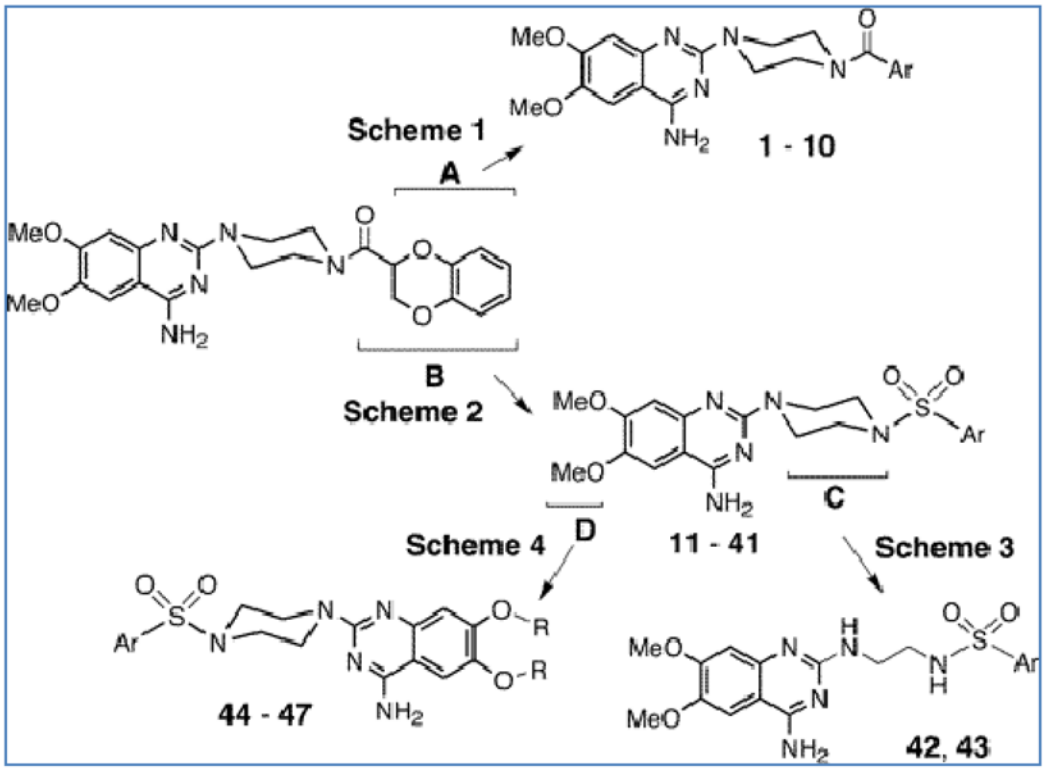

Figure 4.

Strategies for structural modifications of doxazosin. A, B, C, and D indicate four modification strategies that target the 2,3-dihydro-benzo{1,4} dioxane moiety, the terminal acyl function, the piperazine linker, and the methoxy side chain ofthe quinazoline base, respectively leading to the synthesis of new Doxazosin derivatives with different properties [72].