MOLECULAR RECOGNITION AND DRUG DESIGN*

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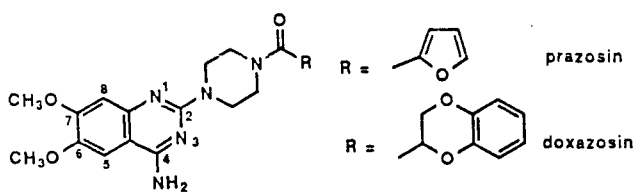
Molecular recognition processes control every aspect of life on our planet. The ability of molecules to recognise, and discriminate between, closely related partners is a key determinant of chemical reactivity, enzyme catalysis, gene regulation and many other fundamental processes. Understanding molecular recognition processes, particularly those which influence the binding of small molecules to proteins, is essential for medicinal chemists, and is a vital component of modern drug discovery. New drugs must be highly discriminating at the molecular level, so that diseases can be controlled without untoward side effects. Drug molecules must be specifically designed to recognise only those particular enzymes or receptors involved in the disease process, and to ignore the multitude of close relatives which subserve normal biological mechanisms. This account summarises our understanding of structure activity relationships for a series of 2,4-diamino-6,7-dimethoxyquinazolines which display high affinity and selectivity for α_1-adrenoceptors. Agents of this mechanistic class, such as prazosin and doxazosin, are now widely available for the treatment of hypertension. In addition, these drugs produce potentially beneficial effects in plasma lipids, which may be important in reducing the risks of heart disease.

1. INTRODUCTION

Molecular recognition processes control every aspect of life on our planet. Thus, the ability of individual molecules to recognise, and discriminate between, closely related partners is a key determinant of chemical reactivity, enzyme catalysis, gene regulation and many other fundamental processes. Understanding molecular recognition processes, particularly those which influence the binding of small molecules to complex proteins, is an essential skill for medicinal chemists, and is a vital component of modern drug discovery. New drugs must be highly discriminating at the molecular level so that diseases can be controlled without untoward side effects. Therefore, drug molecules must be specifically designed to recognise only those particular enzymes or receptors involved in the disease process, and to ignore the multitude of close relatives which subserve normal biological mechanisms. Moreover, the medicinal chemist should also be aware that **in vivo** degradation can offset intrinsic potency and receptor/enzyme selectivity, and interaction of drug molecules with metabolising enzymes must be minimised.



This account summarises our understanding of structure activity relationships for a series of 2,4-diamino-6,7-dimethoxyquinazoline[3] which display high affinity and selectivity for α_1-adrenoceptors[1-6]. Agents of this mechanistic class, such as prazosin[7] and doxazosin[8], are now widely available for the treatment of hypertension. In addition, these drugs produce potentially beneficial effects on plasma lipds, which may be important in reducing the risks of heart disease.[9]

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2. PRAZOSIN, THE PROTOTYPE α_1-ADRENOCEPTOR ANTAGONIST

Prazosin was synthesised in 1965 in our Groton laboratories during a search for novel antihypertensive agents with vasodilator properties. Animal and clinical evaluation showed that prazosin was an effective, safe antihypertensive agent which reduced blood pressure without increasing heart rate. At the time however, it was difficult to rationalise this unique pharmacological profile in terms of a specific mechanism of action. Although prazosin displayed affinity for α-adrenoceptors, the compound was quite distinct from classical α-antagonists, and alternative mechanisms were indirectly implicated. However, in the 1970s it was demonstrated that, in addition to the α_1-adrenoceptors on the blood vessel wall, a second subtype (α_2) was present on the sympathetic nerve endings[10]. It was soon shown that prazosin was a potent, selective antagonist of the α_1-mediated vasoconstrictor actions of noradrenaline but did not interfere with the prejunctional α_2-sites which modulate transmitter release[11, 12]. By contrast, phentolamine was non-selective, whereas yohimbine showed some preference for α_2-adrenoceptors. These studies provided a compelling rationale for the clinical profile observed with prazosin and for the poor antihypertensive efficacy of earlier α-antagonists. The demonstration of absolute discrimination between α_1- and α_2-adrenoceptors by prazosin was an important stimulus in re-awakening interest in the field, not only in our own laboratories. Thus, we initiated a new research programme with the objective of identifying second generation α_1-antagonists with potential advantages over prazosin. However, in order to place our synthetic programme on a rational basis we decided first to define the structural features and molecular recognition processes which under-

wrote the exceptional potency and selectivity demonstrated by prazosin for α_1-adrenoceptors.

3. RECOGNITION OF THE QUINAZOLINE NUCLEUS BY THE α_1-ADRENOCEPTOR

Our approach to defining molecular recognition processes derived from the fact that prazosin (1) is a potent ($pA_2 = 8.37 \pm 0.24$) competitive antagonist of the α_1-mediated responses to noradrenaline (2), and from the subsequent assumption that these molecules compete for common receptor binding sites. Indeed, considerable structural similarity does exist between prazosin and noradrenaline and it might be expected that α_1-antagonist activity could be expressed in less complex analogues. Even so, the high affinity and selectivity displayed by 4-amino-2-dimethylamino-6,7-dimethoxyquinazoline (3) for α_1-adrenoceptors is quite remarkable, and clearly demonstrates that the quinazoline nucleus present in prazosin dominates receptor interactions (Fig. 1).

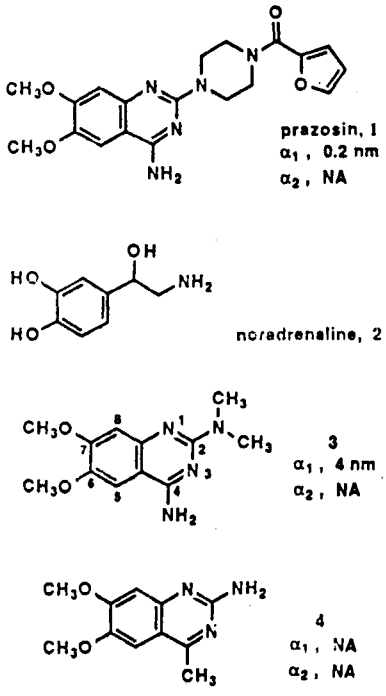


Figure 1. α–Adrenoceptor binding affinity (K_i values) for representative quinazoline derivatives[13]. (NA indicates no activity at 10^{-6}M)

Moreover, the enthalpy of binding for 3 (-11.49 kcal/mole) at α_1-sites is greater than predicted by the Andrews' approach[14] (-9.3 kcal/mole) which confirms a particularly effective receptor fit, and suggests quite specific molecular recognition processes. Elimination of one or both of the 2-amino substituents in 3 reduced α_1-affinity by some 10- and 50-fold respectively whilst removal of the 6,7-dimethoxy groups totally abolished activity. Introduction of any substituents into the quinazoline nucleus which reduced basicity such that protonation was unfavoured at physiological pH (7.4), also obliterated α_1-affinity (e.g.4, pKa = 5.2). This latter observation was not unexpected since noradrenaline is also highly basic (pKa = 9.6) as are the vast majority of other α-agonist/antagonist structures. These initial SAR studies suggested strongly that the protonated 2,4-diamino-6,7-dimethoxyquinazoline nucleus present in prazosin (pKa = 6.8 ± 0.04) and 3 (pKa = 8.1 ± 0.08) might serve as a particularly effective, conformationally-restricted bioisostere for noradrenaline.

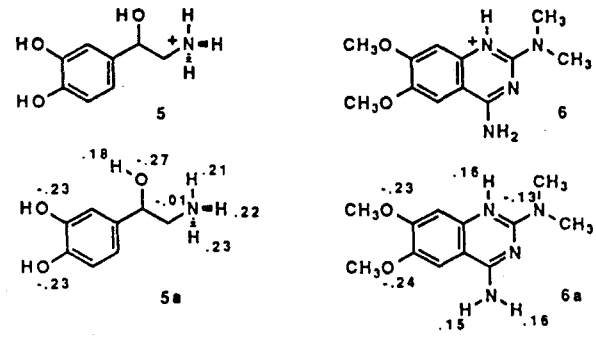


Figure 2. Protonated forms of noradrenaline and 3, charge localised (**5, 6**); delocalised (**5a, 6a**); CNDO/2 charge distribution by Mulliken population analysis (only selected centers shown).

Noradrenaline contains only a single basic centre and the protonated species (**5**) will predominate (ca 95%) at physiological pH. At first glance, four potential protonation sites are available for 3 (*ca* 80% protonated at physiological pH) although molecular orbital calculations show that N-1 is overwhelmingly favoured over the exocyclic nitrogen centres (**6**) Similar conclusions have been reached for quinazoline dihydrofolate reductase inhibitors[15] whilst protonation and quaternisation of 2,4-diaminopyrimidine derivatives also predominate at N-1[16].

These results suggest major electronic differences between the amino function of noradrenaline and the quinazoline 2-nitrogen atom and their ability to participate in the same molecular recognition processes must be questioned. However, formal location of positive charge on single nitrogen centres (**5, 6**) is solely a matter of convenience since molecular orbital calculations indicate considerable dispersion over neighbouring atoms[17, 18]. Thus, for noradrenaline most of the positive charge resides on the three hydrogen atoms attached to the nitrogen (**5a**), and there seems little reason to focus on either the location, or Coulombic interaction, of an essentially neutral nitrogen centre in agonist-receptor recognition. Charge delocalisation is more extensive for the protonated quinazoline (**6a**) and, although both the N-1 H and 4-NH_2 functions could act as focal points in any receptor recognition process, only the fomer will be considered initially. These results suggested that charge-reinforced hydrogen bonding would be important for both agonist and antagonist molecules, providing an anionic site is present on the receptor which is equally accessible to both noradrenaline and the quinazoline series. Computer-simulated superimposition of **5a** and **6a** (Fig.3) shows how these two molecules might compete for the same receptor site which could contain a hydrophobic area to accommodate the aromatic rings from either series, a recognition site for the vicinal oxygen atoms and an anionic centre (A) which accepts a positively charged hydrogen atom from either protonated species.

In order to refine this simple model, we next made two further assumptions:- (a) that the aromatic ring, the quinazoline N-1 H and the counterion were coplanar and (b) that the anion should be capable of binding simultaneously with the benzylic hydroxyl and the ammonium head of noradrenaline. In order to identify potential receptor counterions, the interaction of chloride, phosphate and carboxylate anions with

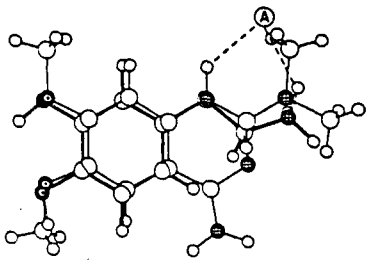


Figure 3. Computer simulated superimposition of **5a** (hollow bonds, benzylic hydroxy function removed for clarity) and **6a** (solid bonds) with respect to common anionic centre A.

noradrenaline was evaluated using molecular mechanics techniques to identify favourable binding positions followed by full relaxation energy minimisation to optimise interaction geometries. Final binding energies (enthalpies of interaction) were calculated by standard INDO methods. Although all three counterions appeared equally well suited for detailed evaluation[19, 20, 21] the carboxylate anion was selected mainly because salt bridges between aspartate and glutamate residues and protonated heterocyclic nucleii have been detected in other enzyme systems[22]. Interestingly, the amino acid sequences of several receptor subtypes have been determined in the last few years, and a common aspartate residue has been proposed as an important recognition centre for the onium heads of various natural transmitters[23, 24].

For noradrenaline, a coplanar cyclic hydrogen bonding arrangement (Fig. 4, **7**) is preferred (binding energy, - 155.93 kcal/mol), a conformation which lies close (<2 kcal/mol) to the global minimum (phenyl ring rotated through 60º) and which would easily be accessible to the natural α_1-transmitter. Similarly, a protonated quinazoline derivative also demonstrated charge-reinforced hydrogen bonding (**8**, binding energy, -72.2 kcal/mol) but closer approach (<2.5Å) of the carboxylate anion was prevented by the piperidine ring[25].

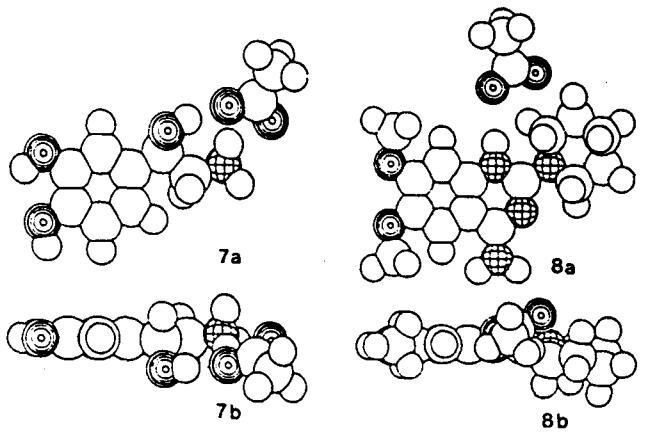


Figure 4. Interaction of noradrenaline (**7**) and a quinazoline derivative (**8**) with a carboxylate counterion. Face-on (a) and side-views (b) illustrated.

Comparison of structures (**7**) and (**8**) indicates that the carboxylate counterions are differently located (*ca.* 4 Å separation) relative to the parent aromatic rings and appear incompatible with the previous concept of fixed recognition sites. However, while initial agonist and antagonist receptor recognition may be similar, the consequences of binding are quite different. Agonists activate the receptor to produce a physiological response whereas antagonists exert "squatters'rights" and need not disturb the active site. Indeed, for both α- and β-receptors, agonist binding is enthalpy-driven, consistent with strong bonding to the receptor in order to overcome an unfavourable decrease in entropy[26]. On the other hand, antagonist interaction is entropy-driven, since an important contribution to binding affinity results from the entropy increase associated with released water molecules[27].

Complex **8** may therefore represent the interaction of the protonated heterocycle with the ground state of the α_1-adrenoceptor, and the high binding affinity reflects a hydrophobic attraction, charge-reinforced hydrogen bonding and a favourable entropy component associated with release of bound water molecules[28]. This drug-receptor complex is also a minimum enthalpy arrangement, given the original constraints, and any conformational reorganisation required for receptor activation would be energetically unfavourable.

When noradrenaline approaches this receptor ground state, the carboxylate counterion forms a hydrogen bond with the benzylic hydroxyl function and initiates a medium-range electrostatic interaction with the ammonium head (Fig. 5, **9** binding energy, -74.54 kcal/mol). Charge-reinforced hydrogen bonding can then be optimised by a 4Å migration of the counterion (**7**, binding energy, -155.93 kcal/mol). Thus, the conformational change in the protein structure usually associated with receptor activation could be promoted by the free energy decrease accompanying transformation of the initial agonist complex (**9**) into the more stable arrangement (**7**). A simple α_1-adrenoceptor model can therefore be proposed which rationalises the different consequences of agonist and antagonist receptor occupancy.

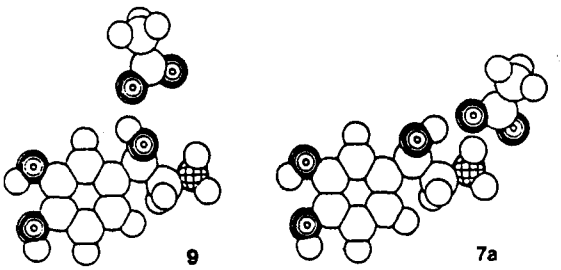
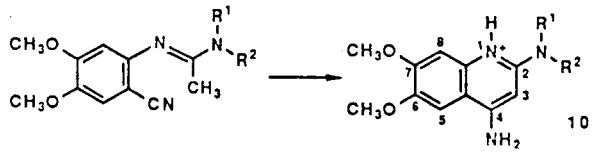


Figure 5. Interaction of noradrenaline with a carboxylate counterion; α_1-adrenoceptor ground state (**9**); activated state (**7a**).

Importantly, for S(+)- noradrenaline, which is 100-fold less potent than the natural transmitter, the counterion complex is less favoured (binding energy, -141.86 kcal/mol) due to repulsive interactions between the hydroxyl proton and the positively charged ammonium head. Moreover, the remarkable α_1-adrenoceptor selectivity of this quinazoline series is consistent with a receptor model containing the hydrophobic binding area and carboxylate counterion in parallel planes. By contrast, initial analysis of α_2-adrenoceptor SARs suggests that these key areas may be orthogonal to one another, and a flat quinazoline nucleus could not accommodate such alternative geometry.

A key feature of the above receptor model was the suggestion that an N-1 protonated quinazoline was exquisitely suited for charge reinforced hydrogen bonding with a carboxylate counterion in the ground state conformation of the α_1-adrenoceptor. In order to substantiate these proposals, we decided to replace the parent nucleus by isosteric heteroaro-

matic systems such as quinoline (**10**) and isoquinoline (**11**). N-1 protonation to provide the required pharmacophore is only possible for **10** and comparison of these isomeric series provides a critical test for previous modelling studies. The 2,4-diaminoquinoline ring system (**10**) was constructed *via* a novel intramolecular cyclisation of an acetamidine derivative under basic or Lewis acid conditions[30].



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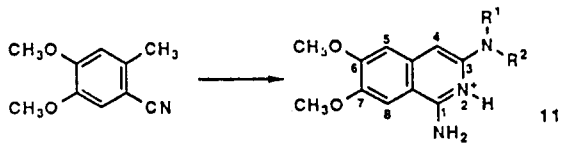
Entry into isoquinoline series (**11**), albeit in moderate yield, was effected by treatment of 2-methyl-4,5-dimethoxybenzonitrile with LDA at -70°C followed by addition of an appropriate cyanamide[31].



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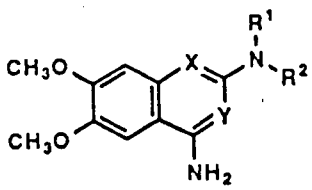
In general, a wide range of 2,4-diaminoquinoline derivatives showed similar or higher, α_1-adrenoceptor affinity to the original quinazoline series whereas the corresponding isoquinolines were weak or inactive[30, 31]. These results are best illustrated by comparison of the data in Table 1. Thus, in the quinoline series, the 2-dimethylamino analogue (**12**) is roughly half as potent as **3** whereas **13** displayed similar activity to prazosin. Thus, these quinoline and quinazoline systems appear to be recognised in a common fashion at the α_1-adrenoceptor with N-1 presumably playing a similar role for either nucleii. Moreover, the enhanced basicity of these 2,4-diaminoquinolines compared to the corresponding quinazolines allows more facile protonation at N-1. Indeed, at physiological pH, **13** will exist mainly (86%) as the N-1 protonated form whereas only 20% protonation of prazosin will occur. Functional assays show that **13** is a highly potent (pA_2 = 9.76 ± 0.26) competitive antagonist of the α_1-mediated vasoconstrictor effects of noradrenaline and is some 20 times more potent than prazosin. Thus, the enhanced basicity of **13** may be more evident in functional, rather than binding, assays since the former requires efficient displacement of the noradrenaline cation.

By contrast, the isoquinoline (**14**) shows no relevant affinity for α_1-adrenoceptors even though substantial protonation (34%) would be expected at physiological pH. However, protonation of **14** will occur on N-2, as confirmed by X-ray analysis of the hydrochloride salt of **15**[31]. Comparison of the positive charge distribution in the protonated forms of **3, 12, 14** shows that electron densities on the dimethoxy, amino and dimethylamino functions are very similar, although, obviously, the ring protonation sites are quite different (Table 2). These results provide strong support for the proposal that N-1 protonation is a fundamental requirement for effective interaction of these heterocyclic nucleii with the α_1-adrenoceptors and that other functionalities may be of secondary importance. For example, an alternative receptor binding mode in which the primary amino function acts as a bioisostere for the benzylic hydroxyl group in noradrenaline appears most unlikely.

The modest α_1-adrenoceptor affinity exhibited by **15** probably results from a hydrophobic interaction involving the 3-substituent since extrapolation of the pKa data in Table 1

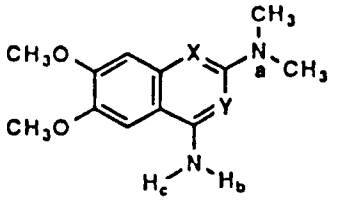
Table 1. Binding[13] and pKa Data for Quinazoline, Quinoline and Isoquinoline Derivatives



No.	X	Y	R_1,R_2	α-receptor binding affinity[a], K_i, (nM)	pKa
3	N	N	$(CH_3)_2$	4.10 ± 0.62	8.1 ± 0.08
prazosin	N	N	$(CH_2CH_2)_2$NCO-2-furyl	0.19 ± 0.02	6.8 ± 0.04
12	N	CH	$(CH_3)_2$	11.37 ± 2.00	9.3 ± 0.09
13	N	CH	$(CH_2CH_2)_2$NCO-2-furyl	0.14 ± 0.07	8.18 ± 0.03
14	CH	N	$(CH_3)_2$	NA	7.1 ± 0.09
15	CH	N	$(CH_2CH_2)_2$NCO-2-furyl	160 ± 29	

[a]apart from prazosin (K_i, 4830 ± 1280 nM for displacement of [^{3}H]clonidine), none of these compounds displayed α_2-adrenoceptor affinity up to 10^{-6}M

Table 2. Calculated Positive Charge Distribution in the Protonated Forms of **3, 12, 14** (CNDO/2 Mulliken population analysis, only selected centres shown).



No	X	Y	O_6	O_7	(X)-H	(Y)-H	H_b,H_c	N_a
3	$^+$NH	N	-0.24	-0.23	0.14		0.16,0.15	-0.13
12	$^+$NH	CH	-0.24	-0.23	0.14	0.04	0.14,0.14	-0.13
14	CH	$^+$NH	-0.23	-0.24	0.03	0.15	0.17,0.17	-0.15

shows that the molecule would not be efficiently protonated at physiological pH. The differences in binding affinity between prazosin and **15** (binding energies, -13.3 and -9.3 kcal/mol) indicate that charge-reinforced hydrogen bonding between the N-1 protonated quinazoline nucleus and an anionic site on the receptor contributes about 4.0 kcal/mol. However, computer-assisted comparison of the X-ray structures of prazosin and **15** shows that the piperazino moieties are displaced from one another, although, obviously the parent heterocyclic nuclei are an exact match. Rotation of the piperazine ring into a coplanar arrangement with the isoquinoline nucleus allows an almost exact fit with prazosin, albeit at a cost of some 1.0 - 1.6 kcal/mol. If this coplanar arrangement of **15** is a prerequisite for recognition at the α_1-adrenoceptor then the binding energy between the N-1 protonated quinazoline nucleus and the carboxylate counterion on the protein can be revised to 2.4 - 3.0 kcal/mol. This value is quite close to a recent estimate (1.8 kcal/mol) for the binding free energy of salt bridge formation between a protonated pteridine nucleus and an aspartate anion in dihydrofolate reductase[32].

In conclusion, these studies provide strong support for the α_1-adrenoceptor model proposed previously and confirm the importance of the N-1 protonated quinazoline and quinoline pharmacophores for effective interaction with the receptor active site. The molecular recognition processes which contribute to the exceptionally high binding affinity of these systems appear to be quite specific and are exquisitely dependent on charged reinforced hydrogen bonding. It is quite remarkable that relatively simple structures such as **3** and **12** can compete most effectively with noradrenaline at the receptor active site, and that a subtle difference in protonation site can have a devastating effect on the biological activity of **14.**

4. THE ROLE OF THE QUINAZOLINE 2-SUBSTITUENT

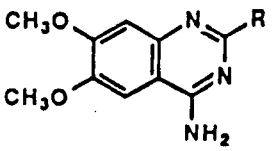
The SAR analysis so far has stressed the important role of the quinazoline nucleus in prazosin in dominating receptor interactions, and it is not immediately obvious whether an extended 2-substituent provides any additional benefits. Inspection of the data in Table 3 indicates a thousand fold increase in binding affinity for prazosin over the unsubstituted 2-amino analogue (**16**) although a more detailed analysis is required to establish "goodness of fit". Thus, while compounds **16** and **17** may be the weakest members of this quinazoline series, the observed enthalpies of binding are some 1.5 - 1.7 kcal/mole higher than expected from Andrews calculations. These simple compounds are therefore exceptionally well-tailored for the α_1-adrenoceptor although the receptor fit can be further optimised with **3.**

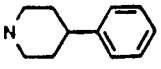
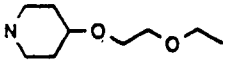
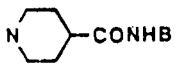
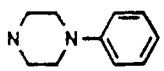
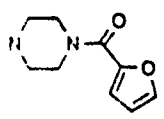
Elaboration of the 2-dimethylamino moiety in **3** has little immediate effect on binding affinity (**18-20**) although 10- and 10- fold improvements are achieved with **21** and prazosin. However, there are now substantial discrepancies between the observed and calculated binding energies and "goodness of fit" of these more elaborate molecules has obviously deteriorated. Moreover, the wide variation of physicochemical properties (CLOG P3 values[33]) of the quinazoline 2-substituents (data not shown) seems to have little influence on molecular recognition processes at the α_1-adrenoceptor. These studies suggest that the quinazoline 2-substituent (R) may occupy a relatively open site on the receptor, and that any improvements in potency derive from the entropy gain as water molecules are forced from the active site, rather than from any specific contact with the protein structure. These observations, coupled with the high binding affinity displayed by **16, 17** and **3,** reinforce the concept that the N-1 protonated quinazoline/quinoline nuclei are particularly effective bioisosteres for noradrenaline which participate in highly efficient molecular recognition processes at the α_1-adrenoceptor. Finally, the selectivity of the compounds in Table 3 for α_1-rather than α_2-adrenoceptors was at least 1,000 and, in most cases, was substantially greater (data not presented[1-6]).

Although binding studies provide a most convenient measure of instrinsic receptor affinity, potential drugs must be able to block the functional effects of noradrenaline. Indeed, all of the compounds in Table 3, which were tested, proved to be potent, competitive antagonists of the α_1-mediated, vasoconstrictor actions of noradrenaline. Moreover, these compounds, like prazosin, did not interfere with the prejunctional α_2-adrenoceptor which modulates transmitter release[1-6].

However, while this quinazoline series obviously demonstrates outstanding potency and selectivity for α_1-adrenoceptors *in vitro*, SARs for antihypertensive activity *in vivo* must also be defined since high receptor affinity affords no protection against metabolic vulnerability, poor oral absorption or

Table 3. Binding affinities[13], binding energies[14], and antihypertensive activities[34] for representative quinazoline derivatives



No.	R	α_1-receptor binding affinity (K_inM)	binding energy (kcal/mole)		% reduction in SHR blood pressure
			obs	calc	
16	NH_2	190	9.21	7.7	5
17	$NHCH_3$	37±15.0	10.18	8.5	-
3	$N(CH_3)_2$	4.1±0.62	11.49	9.3	-
18		6.1±1.2	11.25	11.7	18
19		1.0	12.33	15.2	26
20		1.81±1.45	11.97	13.6	83
21		0.67±0.2	12.57	16.7	100
22		3.4	11.60	15.6	45
prazosin		0.19±0.02	13.32	18.6	70

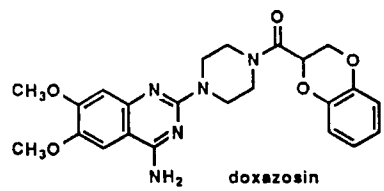
limited pharmacokinetics. The quinazoline derivatives in Table 3 were therefore evaluated in the spontaneous hypertensive rat (SHR) since this model is sensitive to most clinically effective antihypertensive agents, and also allows a fairly rapid compound throughput. It is immediately apparent from the data in Table 3 that, while the quinazoline 2-substituent has some influence on binding affinity, it plays a major role in governing *in vivo* performance. Thus, compound **16** is weakly active, and only a modest improvement is observed with the cyclised derivatives **18, 19**. However, introduction of an appropriate substituent into the piperidine ring (**20, 21**) has a marked impact on antihypertensive efficacy which is maintained with an N-acylpiperazino derivative such as prazosin itself. In addition to absolute reductions in blood pressure, duration of action is also important since once-daily administration of antihypertensive agents is preferred in clinical practice. Thus, more extensive evaluation[4-6]showed that the antihypertensive activities of **21** and prazosin were maintained over the whole test period (4.5h) in SHR whereas the response to **20** was obviously waning. These results demonstrate that the quinazoline 2-substituent plays a key role in influencing antihypertensive activity and duration of action, and that appropriate structural modification would be an important feature in the design of superior analogues.

5. NOVEL, CLINICALLY EFFECTIVE α_1-ADRENOCEPTOR ANTAGONISTS

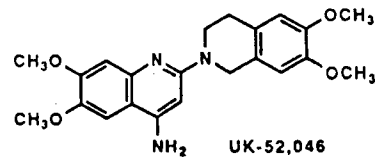
The major objective of the above SAR programme was to identify the structural features which underwrote the exceptional pharmacological profile demonstrated by prazosin both *in vitro* and *in vivo*, and then to apply this understanding to the design of improved analogues. One approach focussed on the design of novel α_1-adrenoceptor antagonists with improved duration of action over prazosin which would be suitable for once-daily administration in man to control elevated blood pressure. Naturally, the 2,4-diamino-6,7-dimethoxyquinazoline nucleus was retained as a key building block and synthetic attention was focussed on elaboration of the 2-piperazino substituent. Thus, replacement of the furan moiety of prazosin with a benzodioxan system, which was known to be compatible with α-adrenoceptor blocking activity, provided doxazosin[35]. This compound proved to be a potent, highly selective α_1-adrenoceptor antagonist with long-lasting antihypertensive properties in rats and dogs. In the latter species, 24hr control of blood pressure was clearly achieved after single

daily doses (0.5mg/kg). Heart rate was barely affected and there were no signs of tolerance after chronic dosing. Pharmacokinetic evaluation in dogs indicated an extended plasma half life when compared to prazosin[36](4.7 vs 1.5 hr) and differences were even more apparent in man[37](22 vs 2-3 hr). This marked improvement for doxazosin appears to derive from a lower plasma clearance rate presumably because the major route of metabolism for these quinazoline derivatives, 6/7-O-demethylation, is much less favoured. Thus, it is interesting to note that structural modification in one area of such a complex molecule can have a profound influence on the molecular recognition processes which control acceptance of the distal methoxy functions by the O-demethylases.

Doxazosin has undergone extensive safety evaluation in animals with no untoward effects, and excellent toleration has also been observed in clinical studies to date. As a result, doxazosin is receiving widespread approval by regulatory authorities for once-daily, first-line treatment of hypertension. In addition to providing effective blood pressure control, doxazosin significantly reduced total cholesterol, LDL-cholesterol and triglycerides while significantly increasing the HDL-cholesterol to total cholesterol ratio. The beneficial effects of doxazosin on blood pressure and lipid profile may favourably affect the risk of coronary heart disease.



doxazosin



UK-52,046

In an alternative approach to identifying novel α_1-adrenoceptor antagonists with clinical utility, SARs in the 2,4-diaminoquinoline series (**10**) were examined in detail[30]. Although most derivatives displayed high α_1-adrenoceptor activity, the binding affinity of UK-52,046 proved to be quite exceptional. Indeed, the IC_{50} (6×10^{-12}) is the lowest we have observed and represents a 30-fold improvement over prazosin. The receptor binding energy for UK-52,046 (-15.37 kcals/mole) is quite close to the Andrews value (-16.2 kcal/mole) and may reflect preference for a highly protonated (95%, pKa = 8.76), essentially coplanar system with limited degrees of freedom.

Pharmacological profiling of UK-52,046 in animals showed that the compound was effective in controlling cardiac arrhythmias provoked by adrenaline, ischaemia or reperfusion[37, 38]. These observations suggest an important role for α_1-adrenoceptors in the genesis of various types of arrhythmias. Preliminary studies in volunteers show that the α_1-antagonist effects of UK-52,046 persist for up to 12h after a single intravenous dose (0.5 μg/kg) without marked effects on blood pressure or heart rate[39]. The potential for UK-52,046 to provide a novel mechanistic approach to the limited anti-arrhythmic therapies currently available, remains to be defined.

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$$\% \text{ reduction in hypertension} = \frac{\text{fall in blood pressure}}{\text{control blood pressure} - 130} \times 100$$

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