**RELATIONSHIP BETWEEN CHEMICAL STRUCTURE,
BINDING AFFINITY AND SELECTIVITY TOWARDS
 α_1 -ADRENOCEPTORS IN THE GROUP OF SUBSTITUTED
N-PHENYLPIPERAZINES. PART 2*. COMPOUNDS
CONTAINING ETHANE-1,2-DIYL
CONNECTING CHAIN**

¹Malík, I. – ¹Sedlářová, E. – ¹Andriamainty, F. –
¹Gališínová, J. – ²Csöllei, J.

¹Department of Pharmaceutical Chemistry, Faculty of Pharmacy,
Comenius University, Bratislava, Slovak Republic

²Institute of Chemical Drugs, Faculty of Pharmacy,
University of Veterinary and Pharmaceutical Sciences, Brno, Czech Republic

The *N*-phenylpiperazine structures exhibit very extensive multiple receptor activities including the influencing of α_1 -adrenoceptors (α_1 -AR). Their antagonistic activity towards α_1 -AR is intensively applied in the therapy of cardiovascular system diseases – e. g. hypertension as well as in the treatment of benign prostatic hyperplasia. The limited ratio of selective effect on the specific subtypes of the α_1 -AR by certain drugs used in the practice (azosine-type structures) leads to multiple side effects which includes postural hypotension, syncope or first dose phenomena. The existence of multiple α_1 -AR subtypes holds promise for the discovery, projection and development of more specific selective drug molecules targeting only one α_1 -adrenoceptor subtype and making them free from side effects. Towards this aim wide-ranging modifications have been reported in the literature on the „basic“ structure of the *N*-phenylpiperazine-based molecules. The present paper deals with the affinity features of (substituted) *N*-phenylpiperazines towards α_1 -ARs in which the structure is a connecting chain formed by (unsubstituted) ethane-1,2-diyl moiety bonded through certain atom or group (S, O, NH, NHCO-fragment, respectively) at the lipophilic part of the molecule.

Key words: *N*-phenylpiperazines – α_1 -adrenoceptors – affinity – selectivity

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INTRODUCTION

Structure and function of α_1 -adrenergic receptors

The α_1 -adrenergic receptors (α_1 -ARs) belong to the seven transmembrane-domain receptor super family and play a primary role in the regulation of several physiological processes, particularly in the cardiovascular system (see Figure).

To date, three different α_1 -AR subtypes, namely, α_{1A} - (α_{1a} -), α_{1B} - (α_{1b} -), and α_{1D} - (α_{1d} -) AR, have been cloned and characterized – they are three subtypes of human high sensitivity α_{1H} -adrenoceptors where upper/lower case letters indicate pharmacologically defined and cloned subtypes, respectively [1-4]. Because of the initial confusion in nomenclature, the α_{1C} designation has been dropped. In addition to these three subtypes, the existence of an additional α_1 -AR (low sensitivity α_{1L}) has been postulated [5] but a discrete protein with α_{1L} -adrenoceptor characteristics has to be cloned yet. Recent evidence, however, suggests that this subtype represents the low-affinity state (functional phenotype) of the α_{1A} -AR, and not a distinct receptor [6]. In addition to the wild-type α_{1A} -AR isolated originally, three carboxyl terminal splice variants of the human α_{1A} -AR have been cloned and characterized, i.e. the α_{1A-1} (wild-type), α_{1A-2} , α_{1A-3} and α_{1A-4} ; each of them has identical ligand binding and signalling characteristics [7,8]. The α_{1A} -ARs are abundantly expressed in human liver, heart, cerebellum, cerebral cortex and prostate [9-11]. α_{1B} -AR messenger ribonucleic acid (mRNA) is present at high levels in human spleen and kidney; α_{1D} -AR mRNA is abundant in human aorta [12]. In the heart, all three α_1 -AR subtypes have been identified at the mRNA level, but only α_{1A} and α_{1B} appear to be translated and functional [13]. A large body of evidence indicates that α_{1A} -ARs are very important in the hypertrophic growth response *in vitro* [14,15]. An important possible role for the α_1 -ARs in the heart is as an alternate source of inotropic reserve in pathophysiological conditions in which the β -adrenergic system is desensitised.

Stimulation of the α_1 -ARs results in the activation of various effectors, including phospholipase C (PLC), phospholipase D (PLD) and phospholipase A₂ (PLA₂), as well as in the activation of Ca²⁺ channels and the Na⁺/H⁺ exchangers, modulation of K⁺ channels [13], and an activation of other signalling pathways, such as that involving activation of mitogen-activated protein kinases or leading to transcriptional activation of early and late response genes. All three α_1 -AR subtypes can activate phosphoinositide turnover and the calcium signalling. Indeed, although the Ca²⁺ influx [16,17] response was initially thought to be specific for the α_{1A} -AR, it was later found to be mediated also by the other subtypes. Both voltage-dependent and voltage--independent Ca²⁺ channels have been implicated in these responses.

Figure. Model of agonist and antagonist binding to α_1 -adrenergic receptors. The binding pocket of α_1 -adrenoceptors is depicted from an extracellular viewpoint, transmembrane domains 1 – 7 are numbered. Amino acids involved in agonist binding and receptor activation are depicted in blue, residues which mediate antagonist binding are shown in red [1]

All α_1 -AR RNA and proteins are expressed on peripheral arteries from humans [18], and α_1 -blockers have been used for many years in the treatment of an arterial hypertension. Data from isolated vessels have shown that there is considerable diversity in the vascular tree regarding the α_1 -subtypes that regulate smooth muscle cells contractions. Although there is little evidence supporting a role for α_{1B} -ARs as mediators of the vascular contraction, α_{1A} -ARs have been shown to regulate both renal and caudal arteries. The α_{1A} -AR subtype is the predominant receptor, causing a vasoconstriction in many vascular beds, including following arteries: mammary, mesenteric, splenic, hepatic, omental, renal, pulmonary and epicardial coronary. It is also the predominant subtype in the *vena cava* and the saphenous and pulmonary veins. The α_{1A} -AR regulates arterial blood pressure in prostate and urinary tissues, mediating contraction of the tissues, and is a target for the treatment of benign prostatic hyperplasia. Together with the α_{1B} -AR subtype it promotes cardiac growth and structure. The α_{1B} -AR subtype enables contraction of heart, vascular, prostate and spleen tissues (the most abundant type in the heart) whereas the α_{1D} -AR subtype is the predominant receptor causing vasoconstriction in the aorta. There is evidence to support the idea that the α_{1B} -ARs mediate behaviours such as reaction to novelty and exploration and they are involved in the behavioural sensitisation and in vulnerability to an addiction. The α_{1D} -ARs have been implicated in the contraction of the aorta, femoral, iliac and superior mesenteric arteries [19-21].

A recent paper has reviewed the current research on the discovery and evaluation of a variety of chemically diverse structures as selective antagonists of the α -ARs and α_1 -AR subtypes [22].

Azosines, classical antagonists of the α_1 -ARs containing (substituted) *N*-phenylpiperazine moiety in the basic part of the molecule

The different agents, antagonists of the α_1 -ARs, can be separated into nine claimed classes with *N*-aryl and *N*-heteroaryl piperazine derivatives representing particularly important categories. These structures are one of the most studied classes of molecules with an affinity towards the α_1 -ARs. The introduction of prazosin, the first highly selective α_1 -AR antagonist, is the classic example of improved therapeutic efficacy as a result of subtype selectivity. Prazosin (compound **I**) and also related long acting quinazoline derivatives with incorporated piperazin-1,4-diyl moiety – terazosin (**II**) and doxazosin (**III**) are considered as the most effective and clinically useful class of selective α_1 -AR antagonists, approved for using in the treatment of symptomatic benign prostatic hyperplasia [23], since they have high index of α_1/α_2 adrenoceptor affinity [24]. Together with tiodazosin (**IV**) and bunazosin (**V**) they are employed clinically, as they are vasodilators with strong action in the arteriolar vascular bed. Further, they have many advantages like dictating both resistance and capacitance of blood vessels, favourable hemodynamic effects, virtual absence of reflux tachycardia and maintenance of renal blood flow and glomerular filtration rate with intact auto regulation of noradrenaline due to non-blockade of presynaptic α_2 -ARs. They also have favourable effects on the lipid profile, carbohydrate metabolism and insulin resistance. These drugs are also useful in the treatment of Congestive Heart Disease (CHD), variant or Prinzmetal's angina or Raynaud's disease [25]. Most antagonists, including the prototype of the α_1 -adrenoceptor selective antagonist prazosin, show little or no selectivity between three known α_1 -adrenoceptor subtypes, consistent with the structural homology of these subtypes in the transmembrane domains. On the other hand, it is speculated that orthostatic hypotension caused by present α_1 -blockers is a result of its subtype non-selective nature so there is a need to develop more specific analogues with the specific affinities to the receptor subtypes to remove their side effects [25,26]. Towards this aim wide-ranging modifications have been reported on the basic azosine-like structure.

The present paper is the continuance of the structure – α_1 -adrenoceptor affinity (α_1 -adrenoceptor antagonistic activity) study of *N*-phenylpiperazine compounds and is especially focused on the (substituted) phenylpiperazine structures containing (unsubstituted) ethane-1,2-diyl connecting chain which is branched through certain atoms or groups (S, O, NH, NHCO-fragment, respectively) at variable substituted lipophilic moiety.

N-Phenylpiperazine structures, antagonists of the α_1 -ARs, containing unsubstituted ethane-1,2-diyl connecting chain

The pharmacophoric model [27] that suggests the three-dimensional structural properties for an ideal α_1 -AR antagonist include: (1) A positively ionizable group, corresponding to the more basic nitrogen atom of the aryl piperazine ring. (2) An *ortho*- or *meta*-substituted phenyl ring, both of which constitute the arylpiperazine system and satisfy three of certain features of the pharmacophoric hypothesis. (3) A polar group that provides a hydrogen bond acceptor feature, filling one of the portions of the pharmacophore that is required at the edge of the molecule opposite the arylpiperazine moiety. (4) A hydrophobic moiety.

The pharmacophoric model also suggests that the hydrophobic region accommodating the substituted phenyl can contain constituents that are larger than a methoxy group. Moreover, affinity and selectivity depend on the length of the (substituted) polymethylene chain that connects the „classical“ lipophilic and arylpiperazine moieties [27].

The target set (VI) was evaluated for the α_1 -AR antagonistic activities. The result showed that three structures from the analyzed group, namely (VI-1), (VI-3) and (VI-5), displayed high α_1 -AR antagonistic pA_2 of 8.56, 8.56 and 9.12, respectively. All three compounds have similar or better α_1 -AR antagonistic activities than prazosin [28].

- (VI-1): Ar=pyridin-4-yl, R¹=R²=2,4-dimethyl;
 (VI-2): Ar=2-furyl, R¹=5-Cl, R²=2-OCH₃;
 (VI-3): Ar=2-furyl, R¹=H, R²=3-OCH₃;
 (VI-4): Ar=2-furyl, R¹=H, R²=4-OCH₃;
 (VI-5): Ar=2-furyl, R¹=H, R²=2-OCH₃;
 (VI-6): Ar=pyridin-4-yl, R¹=H, R²=2-OCH₃;
 (VI-7): Ar=pyridin-4-yl, R¹=H, R²=4-OCH₃;
 (VI-8): Ar=pyridin-3-yl, R¹=5-Cl, R²=2-OCH₃

The detailed selective profile of studied compounds of series (VI) from the point of binding towards concrete subtype of α -AR has not been performed yet. The modification of connecting hydrocarbon chain (its elongation to propane-1,3-diyl string) and lipophilic part of the molecule (VI), an incorporation of imidazo[2,1-f]theophylline fragment, led to the structures (VII) and (VIII) for which only *in vivo* binding studies for agonistic/antagonistic affinity towards serotonergic 5-HT_{1A}, 5-HT_{2A} and dopaminergic D₂ receptors and not for α_1 -ARs have been performed until now [29].

R¹=H, CH₃, C₆H₅, R²=H, 2-OCH₃, 3-Cl

Arylpiperazine derivatives bearing a flavone moiety (IX) should exhibited interesting α_1 -AR antagonistic activities. The flavone compounds had phenyl rings (phenyl of the arylpiperazine and the flavone moiety) and OR-groups (R=arylpiperazinylalkyl substituent) which could act as the hydrophobic regions and hydrogen bond acceptors of the α_1 -AR antagonists, the N¹ atom at the arylpiperazine corresponded to the positively ionisable group [30].

(IX)

$R^1 = \text{H}, 2\text{-CH}_3, 4\text{-CH}_3, R^2 = \text{H}, \text{Cl}, n = 2\text{-}4$

As the experiments reviewed, two carbon atoms which connected the flavone moieties and an arylpiperazine nucleus formed the best polymethylene chain for the activities for all the target structures. With the lengthening of the carbon chain, no remarkable variation was exhibited in the α_1 -AR antagonistic activity [30]. Compounds with a chlorine atom at the flavone nucleus had a relatively higher antagonist activity towards the α_1 -ARs, so it was suggested that a chlorine atom at the aromatic portion could lead to the increase of the α_1 -AR antagonistic activity. Moreover, *ortho*-substituted derivatives were more potent than the *para*-substituted ones. Furthermore, the target molecules (IX) were more effective than the negative controls including the flavones and the synthetic intermediates. It demonstrated that the arylpiperazine and polymethylene chain between flavone and arylpiperazine moieties were necessary pharmacophores of the designed substances [30].

The importance of the substituents attached at a pyridazinone ring was further studied by synthesizing a series of derivatives (X) having arylpiperazinylalkyl chains at different positions of the ring. Most of the synthesized compounds showed high potency on all the assays and some selectivity for the α_{1A} - and α_{1D} -AR subtypes [31].

Structures from the set (XI), characterized by *N*-phenylpiperazinylalkylamino moiety linked to the substituted pyridazinone, were evaluated for the binding affinities towards the α_{1A} -, α_{1B} - and α_{1D} -AR cloned subtypes as well as towards the 5-HT_{1A} receptors. This study indicated that substitutions in the positions 5 and/or 6 of the pyridazinone ring as well as in the positions 2' and 5' of the phenyl ring together with the length of the linker were responsible for modulating the ligand α_1 -AR-binding affinities and α_{1A} -AR/5-HT_{1A} selectivities [32].

(X)

R=H, OCH₃, Cl

(XI)

R=C₆H₅, CH₃, R¹=H, COCH₃, COC₂H₅, COCH(CH₃)₂,
R²=OCH₃, F, Cl, R³=H, Cl, n=1-3

Some compounds belonging to a class of arylpiperazine-quinazolinone-2-carboxylate and their 2-methyl analogues (**XII**) have been prepared through the variation of alkylamido linker between a quinazolinone and an arylpiperazine in the connection with a modification of the substituent at the phenylpiperazine moiety [33]. The fitting of the proposed molecules to the previously built pharmacophore model [34] was done to prioritize the synthesized compounds and to correlate the chemical structure of the studied substances to their pharmacological data. Structures (**XII-1**), (**XII-2**) and also (**XII-3**) were evaluated for their *in vivo* hypotensive activity on the blood pressure of normotensive cats. Substances were tested for their α_1 -adrenoceptor antagonistic activity on isolated thoracic rat aorta revealing superior activity to prazosin as a reference standard [33].

Some structural features have been demonstrated to markedly affect the affinity of the α_1 -AR antagonists and their hypotensive activity. In particular, the addition of *ortho*-methoxyphenyl on piperazine-1,4-diyl ring, propanamido spacer and methyl at 2-position of quinazolinone led to the best α_1 -adrenoceptor affinity profile and the highest hypotensive activity as can be demonstrated by compound (**XII-3**). In addition, the results of the functional bioassay revealed that (**XII-3**) was the most active α_1 -AR antagonist among the tested arylpiperazine-quinazolinone derivatives [33].

(XII)

(XII-1): $R^1 = \text{COOC}_2\text{H}_5$, $R^2 = \text{OCH}_3$;

(XII-2): $R^1 = \text{CH}_3$, $R^2 = \text{H}$;

(XII-3): $R^1 = \text{CH}_3$, $R^2 = \text{OCH}_3$

Sixteen compounds from the series (XIII) were evaluated for their α_1 -AR antagonistic activity. The results showed that two substances with $R^1 = 2\text{-OCH}_3$, $R^2 = \text{NH}_2$, $n = 3$, labelled as (XIII-1), and with $R^1 = 4\text{-OCH}_3$, $R^2 = \text{NH}_2$, $n = 2$, labelled as (XIII-2), displayed high α_1 -AR antagonistic pA_2 of 9.80, and 8.87, respectively. Both of them exhibited better or similar α_1 -AR antagonistic activity compared with prazosin. Compound (XIII-1) in particular, without substitution of 4-amine in a quinazoline ring, showed the highest bioactivity. The corresponding substance with piperidino substitution in 4-position of quinazoline ring indicated lower pA_2 in two orders of magnitude [35].

(XIII)

$R^1 = 2\text{- or } 3\text{- or } 4\text{-OCH}_3$, 5-chloro-2-methoxy, $R^2 = \text{NH}_2$, piperidin-1-yl
 $n = 2, 3$

A series of new structures containing a benzimidazole, benzothiazole or benzoxazole nucleus (XIV) linked to an arylpiperazine moiety by different thioalkyl chains was prepared by Siracusa et al. [36]. Compounds were tested in radioligand binding experiments to evaluate their affinity for 5-HT_{1A} and 5-HT_{2A} serotonergic, α_1 -adrenergic, dopaminergic D_1 and D_2 receptor subtypes. The lower selectivity ratio, defined as $K_i(\alpha_1)/K_i(5\text{-HT}_{1A})$, indicated that studied ligands were more selective towards 5-HT_{1A} receptor subtype compared to that of α_1 -ARs [36,37].

(XIV)

X=NH, S, O, NCH₃, R¹=2-methoxyphenyl, 2-nitrophenyl
pyridin-1-yl, R²=H, Cl, n=0-4

Substitution of R² at the phenyl ring of sixteen synthesized aryloxyalkylamine-type molecules (XV) still had profound impact on the α_1 -AR antagonistic activity. The affinities of selected molecules labelled as (XV-1): R¹ = H, R² = 4-Cl; (XV-2): R¹ = H, R² = 2,4-dichloro; (XV-3): R¹ = 5-Cl, R² = 4-Cl; (XV-4): R¹ = 5-Cl, R² = 2,4-dichloro, decreased obviously, which suggested that electron-withdrawing group may be harmful to activity in the α_1 -AR blocking [38]. The earlier SAR of another structures and their analogues published in [39] indicated that mono halogen (such as chloro and bromo) substitution of R² could remain potent. On the other hand, the derivatives with electron-donating groups (methyl and methoxy) showed an improved affinity on the α_1 -ARs, especially compound (XV-5): R¹ = H, R² = 2-OCH₃, which was the most potent among them [38].

(XV)

R¹=H, 5-Cl, R²=2-CH₃, 3-CH₃, 4-CH₃, 2,6-dimethyl,
2,3-dimethyl, 2-OCH₃, 4-Cl, 2,4-dichloro

CONCLUSION

The *N*-phenylpiperazine compounds represent very wide and rapidly developed group of pharmacologically active drugs. Multireceptor activity is their typical feature; the review was written with the respect to substances with binding affinity (and selectivity) towards particular subtypes of α_1 -adrenergic receptors. Main interest was focused on the *N*-phenylpiperazines with unsubstituted ethane-1,2-diyl connecting chain

which is linked through O-, S-, NH- or NHCO-moiety to diversely modified lipophilic part of the molecule. Further detailed information about the binding and affinity profiles of the *N*-phenylpiperazines with unsubstituted propane-1,3-yl connecting string will be published in other chemical and pharmaceutical journals.

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PharmDr. Ivan Malík, PhD.
Faculty of Pharmacy
Comenius University
Odbojárov 10
832 32 Bratislava
Slovak Republic
malik@fpharm.uniba.sk

**VZŤAH MEDZI CHEMICKOU ŠTRUKTÚROU, VÄZBOVOU AFINITOU
A SELEKTIVITOU K α_1 -ADRENERGNÝM RECEPTOROM
V SKUPINE SUBSTITUOVANÝCH N-FENYLPIPERAZÍNŮV.
ČASŤ 2. ZLÚČENINY OBSAHUJÚCE
ETÁN-1,2-DIYLOVÝ SPOJOVACÍ REŤAZEC**

¹Malík, I. – ¹Sedlárová, E. – ¹Andriamainty, F. – ¹Gališínová, J. – ²Csöllei, J.

¹Katedra farmaceutickej chémie, Farmaceutická fakulta, Univerzita Komenského, Bratislava

²Ústav chemických liečiv, Farmaceutická fakulta, Veterinárna a farmaceutická univerzita,
Brno, Česká republika

N-Fenylpiperazíny vykazujú veľmi širokú multireceptorovú aktivitu vrátane ovplyvnenia α_1 -adrenergných receptorov (α_1 -AR). Ich antagonistické pôsobenie proti α_1 -AR je intenzívne využívané v terapii ochorení kardiovaskulárneho systému – pri hypertenzii rovnako ako pri liečbe benígnej hyperplázie prostaty. Obmedzené selektívne pôsobenie v praxi používaných liečiv azosínového typu na špecifické podtypy α_1 -AR sprevádzajú rôzne vedľajšie účinky, medzi ktoré patrí posturálna hypotenzia, synkopa alebo tzv. efekt prvej dávky (angl. *first dose phenomena*). Existencia viacerých podtypov α_1 -AR je výzvou pre projekciu a vyvíjanie nových selektívnejších molekúl ovplyvňujúcich konkrétny α_1 -adrenoreceptorový podtyp bez vedľajších prejavov. V literatúre sú charakterizované široké možnosti modifikácie „základnej“ N-fenylpiperazínovej štruktúry. V predloženej publikácii sa pozornosť venuje afinitným charakteristikám (substituovaných) N-fenylpiperazínov pri pôsobení na α_1 -AR. V ich štruktúre je zastúpený (nesubstituovaný) etán-1,2-diylový spojovací reťazec, ktorý je viazaný cez určitý atóm, resp. skupinu (O, S, NH, NHCO-zoskupenie) na lipofilnú časť molekuly.

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