ADRENOCEPTOR PHARMACOLOGY

Emma Robinson and Alan Hudson
Psychopharmacology Unit
Department of Pharmacology
School of Medical Sciences
University of Bristol, University Walk
BS8 1TD, UK

Dr Alan Hudson is Head of Preclinical Research for the Psychopharmacology Unit, Emma Robinson is a Teaching Assistant in the Department of Pharmacology

Introduction

Adrenoceptors are membrane bound receptors located throughout the body on neuronal and non-neuronal tissues where they mediate a diverse range of responses to the endogenous catecholamines noradrenaline and adrenaline. The adrenoceptor family was first divided into two subtypes, the α- and β-adrenoceptors as determined by pharmacological studies in isolated tissue.[1] A quarter of a century later, the α-adrenoceptors were further subdivided based on their anatomical location, with α-adrenoceptors located on peripheral sympathetic nerve terminals designated α_2-adrenoceptors and those located post-synaptically designated α_1-adrenoceptors.[2] This anatomical classification rapidly gave way to the identification of pharmacological differences between the α-adrenoceptors, notably the ability of yohimbine and rauwolscine to act as α_2-adrenoceptor antagonists. Subsequent studies using pharmacological and molecular biological techniques have further subdivided the α-adrenoceptor family; three subtypes within each group have now been cloned and pharmacologically characterised. The α_1-adrenoceptor subtypes have been classified as the α_{1A}, α_{1B} and α_{1D}-adrenoceptor and the α_2-adrenoceptors have been classified as the α_{2A} (α_{2D} species variation of the human α_{2A}), α_{2B} and α_{2C}-adrenoceptor.

β-Adrenoceptors are also heterogeneous in nature and were again initially subdivided into β_1- and β_2-adrenoceptors, on the basis of the relative potencies of a series of catecholamines in *in vitro* and *in vivo* systems.[3] Subsequently the β-adrenoceptors have been classified using functional studies, receptor binding and genetic techniques. The β-adrenoceptor family is subdivided into three distinct subtypes, the β_1- and β_2-adrenoceptors and the atypical β_3-adrenoceptor.[4] There is an additional β-adrenoceptor subtype which has been identified in cardiac tissue and is a putative, atypical subtype classified as the β_4-adrenoceptor.[5]

α_1-Adrenoceptors

α_1-Adrenoceptor subtypes

Subdivision of the α_1-adrenoceptors has been facilitated by both pharmacological and molecular biological techniques.[6] The initial classification of the α_1-adrenoceptors as α_{1A} and α_{1B}-subtypes was determined from differences in the binding characteristics of the competitive antagonist WB 4101 and the site-directed alkylating agent chloroethylclonidine (CEC). From radioligand binding studies it was determined that the α_{1A}-subtype has a high affinity for WB 4101 and is CEC-insensitive, whilst

Table 1. α_1-Adrenoceptor characteristics

Receptor type	α_{1A}-Adrenoceptor	α_{1B}-Adrenoceptor	α_{1D}-Adrenoceptor
Selective agonists	**oxymetazoline, A61603**	none	none
Non-subtype selective agonists	**cirazoline**, **M-6434**, methoxamine, phenylephrine,	**cirazoline, M-6434**, methoxamine, phenylephrine,	**cirazoline, M-6434,** methoxamine, phenylephrine,
Selective antagonists	**RS 17053, WB 4101, (S)-(+)-niguldipine**, 5-methylurapidil, SNAP5089, Rec152739, SB216469, Ro700004, KMD3213	CEC (irreversible)	**BMY 7378**, SKF105854, CEC (irreversible)
Non-subtype selective antagonists	**corynanthine, prazosin**	**corynanthine, prazosin**	**corynanthine, prazosin**
Transduction mechanism	activates $G_{p/q}$, ↑ PI turnover, ↑$[Ca^{2+}]_{i.c.}$, activates voltage-gated Ca^{2+} channels		
Physiological function	smooth muscle contraction, myocardial contraction	smooth muscle contraction	smooth muscle contraction

(bold text denotes compounds available from Tocris)

the α_{1B}-subtype exhibits a low affinity for WB 4101 but is sensitive to CEC (Table 1). These characteristics were also shown in a variety of tissue preparations confirming the presence of functional receptor subtypes.[7] In addition, three different cDNAs which coded for α_1-subtypes were isolated. These have since been characterised and are believed to code for three functional α_1-adrenoceptors: the α_{1A} and α_{1B}-subtypes as described above and a third subtype, the α_{1D} which has a low affinity for oxymetazoline in contrast to the α_{1A}-subtype, and is only partially sensitive to CEC, thus making it pharmacologically distinct from the α_{1B} receptor.[8] The putative α_{1L}-adrenoceptor shows similar characteristics to the α_{1A}- and α_{1D}-adrenoceptor but exhibits a low affinity for prazosin and, as yet the gene has not been identified.[9] Compounds displaying a high affinity for the α_1-adrenoceptor subtype compared to other receptors include the agonists cirazoline and M-6434 and antagonists such as prazosin and HEAT. These two α_1-selective antagonists are also used as radioligands for investigating the binding characteristics of α_1-adrenoceptors. However, following the initial characterisation of the α_1-adrenoceptor subtypes subtype selective agonists and antagonists are now being developed which include the α_{1A}-selective agonists A61603[10] and oxymetazoline,[4] and the α_{1A}-selective antagonist RS17053.[11] The α_{1B}-adrenoceptor subtype has a higher affinity for CEC than the α_{1A}-subtype but CEC also exhibits a similar affinity for the α_{1D}-subtype. However, antagonists selective for the α_{1D}-subtype such as BMY7378 and SKF105854 are now available.[12, 13]

Signal transduction mechanism

The α_1-adrenoceptors mediate their response via G-protein coupled receptors through a G_p/G_q mechanism. All the subtypes are coupled to phospholipase C and activation of the receptor results in the production of IP_3 and DAG. The production of these second messengers results in an activation of both voltage dependent and independent Ca^{2+} channels as well as stimulation of protein kinase C, phospholipase A_2 and D, arachidonic acid release and cyclic AMP formation.[14, 15]

Location and function

The α_1-adrenoceptors are located in the central and peripheral nervous system. In the CNS they are predominantly located post-synaptically where they mediate an excitatory role. Following cloning of the α_1-adrenoceptor subtypes, mRNA studies have shown α_1-adrenoceptor mRNA in the hippocampus and cortex.[16] Peripheral α_1-adrenoceptors are located on both vascular and non-vascular smooth muscle where activation of the receptor results in contraction.[17] On vascular smooth muscle the α_1-adrenoceptors are located intrasynaptically where they mediate the response to endogenous neurotransmitter release. They are also located on the heart where they mediate a positive inotropic effect and on the liver where they activate glycogen phosphorylation. With the availability of subtype selective compounds the α_{1A}-subtype has been shown to be responsible for the contraction of vas deferens smooth muscle. Vasoconstriction in some blood vessels has been shown to be α_{1B}-mediated[18] and contraction of the rat aorta is α_{1D}-mediated.[16, 19]

α_2-Adrenoceptors

α_2-Adrenoceptor subtypes

The α_2-adrenoceptors are located on both pre and post synaptic neurones where they mediate an inhibitory role in the central and peripheral nervous system.[20] The heterogeneous nature of the α_2-adrenoceptor was first determined from the different pharmacological profiles of the receptor between species and subsequent studies have revealed the presence of different subtypes within the same tissue. Thus, on the basis of radioligand binding profiles, amino acid sequence and chromosomal location, four distinct subtypes of the α_2-adrenoceptor have been characterised.[21] These α_2-adrenoceptor subtypes, α_{2A}, α_{2B}, α_{2C} and α_{2D} are found in a variety of species and tissues and have been characterised using tissue and cell lines expressing only one subtype. The α_{2D}-subtype exhibits a distinct pharmacological profile but, from the sequence homology is believed to be a species variation of the α_{2A}-subtype and is not recognised as separate.[22] Although selective compounds are now being developed to differentiate between the α_2-adrenoceptor subtypes there is no ligand available that is highly selective in functional studies for the α_2-adrenoceptor subtypes. Characterisation is based on the affinity of a range of compounds which exhibit different affinities for the subtypes (Table 2). Oxymetazoline displays a higher affinity for the $\alpha_{2A/D}$-subtype whilst prazosin exhibits a higher affinity for the α_{2B}-subtype. The α_{2C}-subtype has a high affinity for prazosin and low affinity for oxymetazoline, characteristic of the α_{2B}-adrenoceptor subtype but the affinity for yohimbine is characteristic of the α_{2A}-subtype. The antagonist MK

Table 2. α_2-Adrenoceptor characteristics

Receptor type (previous name)	α_{2A}-Adrenoceptor (α_{2A}, α_{2D}, α_2-C10, RG20)	α_{2B}-Adrenoceptor (α_2-C2, RNG)	α_{2C}-Adrenoceptor (α_2-C4)
Selective agonists	**oxymetazoline** (partial agonist), **guanfacine**	none	none
Non-subtype selective agonists	**UK 14,304** **Clonidine**	**UK 14,304** **Clonidine**	**UK 14,304** **Clonidine**
Selective antagonists	**BRL 44408**, BRL 48962	**ARC 239**, **imiloxan**	**rauwolscine**, MK 912
Non-subtype selective antagonists	**RS 79948, yohimbine**, RS 15385, RX821002, SKF 86466, MK-912, **rauwolscine**, **prazosin**	**RS 79948, yohimbine**, RS 15385, RX821002, SKF 86466, MK-912, **rauwolscine**, **prazosin**	**RS 79948, yohimbine**, RS 15385, RX821002, SKF 86466, MK-912, **rauwolscine**, **prazosin**
Transduction mechanism	activates $G_{i/o}$,inhibits adenylyl cyclase, ↓cAMP, inhibits voltage-gated Ca^{2+} channels, activates Ca^{2+}-dependent K^+ channels		
Physiological function	hypotension, sedation, analgesia, anaesthesia, inhibition of neurotransmitter release	vasoconstriction	not determined

(bold text denotes compounds available from Tocris)

912 has been shown to have a partial selectivity for the α_{2C}-adrenoceptor subtype in binding studies.[23] Although these ligands can be used for radioligand binding studies to determine the receptor subtype present in a tissue, the selectivity is not sufficient for characterisation of the function of receptor subtypes *in vivo*. Subtype selective compounds which have been developed include the antagonists BRL 4408 and BRL 48962,[24] selective for the α_{2A}-subtype, ARC 239 and imiloxan,[25, 26] selective for the α_{2B}-subtype and rauwolscine which shows a 10-20 fold selectivity for the α_{2C}-subtype.[27] Highly selective α_2-adrenoceptor compounds such as the agonists UK 14, 304 and *p*-aminoclonidine, and antagonists RX821002 and RS79948 exhibit a high affinity for the α_2-adrenoceptor compared to other receptors such as the α_1-adrenoceptor.

Signal transduction mechanism

The α_2-adrenoceptors are part of the large family of G-protein coupled receptors and mediate their functions through a variety of G-proteins including G_i/G_o. All the subtypes have been shown to be negatively coupled to adenylate cyclase and mediate an inhibitory effect through the inhibition of cyclic AMP production. In addition there is now evidence linking the α_2-adrenoceptor to stimulation of Ca^{2+} influx and also activation of K^+ channels, phospholipase A_2 and Na^+/H^+ exchange.[28]

Location and function

α_2-Adrenoceptors are found in both the central and peripheral nervous system, and located both pre and post synaptically.[20] Functional studies to determine the role of the different receptors based on anatomical location has been achieved by the use of selective agonists and antagonists and also by the use of lesioning experiments whereby the pre-synaptic nerve terminals are destroyed with for example the toxin DSP-4.[29] In the CNS these receptors play an important role in regulating neurotransmitter release through autoreceptors located on noradrenergic nerve terminals and heteroreceptors located on other neurotransmitter terminals. Their importance in regulating the release of both noradrenaline and serotonin has resulted in the investigation and development of α_2-antagonists such as idazoxan for use in the treatment of depression. They also mediate central cardiovascular responses and α_2-agonists such as clonidine cause hypotension and bradycardia. Furthermore, the sedative properties of α_2-agonists, mediated by somatodendritic autoreceptors on the locus coeruleus, have resulted in the development of α_2-adrenoceptor agonists such as dexmedetomidine as veterinary sedatives and anaesthetics. The α_2-agonists also have the advantage of being analgesic, a response mediated by α_2-adrenoceptors in the spinal cord. Other central effects of α_2-adrenoceptors include the regulation of blood pressure, hypothermia, pupil diameter and a role in cognitive function. Peripheral functions include contraction of vascular smooth muscle, inhibition of lypolysis through α_2-adrenoceptors located on fat cells and hyperpolarisation of sympathetic ganglia.

β-Adrenoceptor

β-Adrenoceptor subtypes

The β-adrenoceptors were first subdivided into β_1- and β_2-adrenoceptors following comparison of the rank order of potency of various adrenergic agonists.[3] The β_1-adrenoceptor is predominant in the heart and on adipose tissue and displays equal affinity for adrenaline and noradrenaline. In contrast, the β_2-adrenoceptor is predominant on vascular, uterine and airway smooth muscle and exhibits a higher selectivity for noradrenaline than adrenaline.[30] Following the identification of these two β-adrenoceptor subtypes, compounds selective for the subtypes have been developed (Table 3). These include the selective β_1-adrenoceptor agonist xamoterol,[31] and the selective β_2-adrenoceptor agonists salmeterol, salbutamol, clenbuterol[32] and procaterol.[33] Selective antagonists for the β_1-adrenoceptor include CGP20712A, atenolol, bisoprolol and betaxolol[34, 35] whilst ICI118551 is a selective β_2-adrenoceptor antagonist.[36] ICI118551 is also available as a radioligand for direct labelling of β_2-adrenoceptors.[37]

The classification of β-adrenoceptors is not limited to β_1- and β_2-adrenoceptors. Characterisation of β-adrenoceptor mediated responses resulted in evidence for a further atypical subtype which is insensitive to typical β-adrenoceptor antagonists.[38, 39] This subtype has since been classified as the β_3-adrenoceptor. Selective agonists for the β_3-adrenoceptor include BRL37344[40] and ZD7114[41] while, SR59230A is a selective antagonist.[42] Pharmacological evidence also suggests the presence of another atypical β-

Table 3. β-Adrenoceptor characteristics

Receptor type	β_1-Adrenoceptor	β_2-Adrenoceptor	β_3-Adrenoceptor	β_4-Adrenoceptor
Selective agonists	**xamoterol**, denopamine	**clenbuterol**, **procaterol**, **salbutamol**, salmeterol, formoterol, terbutaline, fenoterol	**BRL 37344**, **ZD 7114**, **CGP12177**, CL316243	none
Selective antagonists	**betaxolol, bisoprolol**, **atenolol practolol**, CGP20712A	**ICI-118,551**	SR59230A	none (bupranolol >CGP20712A)
Radioligands	[^{125}I]-iodocyanopindolol, [^{3}H]-CGP12177	**[^{3}H]-ICI-118,551**	[^{125}I]-iodocyanopindolol, [^{3}H]-CGP12177	[^{3}H]-CGP12177
Transduction mechanism	↑ adenylyl cyclase (via G_s)	↑ adenylyl cyclase (via G_s) or ↑ /↓ adenylyl cyclase	↑ adenylyl cyclase ↓ adenylyl cyclase	↑cAMP levels, stimulation of cAMP-dependent protein kinase (via G_s)
Physiological function	↑heart rate and force	smooth muscle relaxation e.g. bronchodilation	lipolysis, cardioinhibition	↑ heart rate and force

(bold text denotes compounds available from Tocris)

adrenoceptor subtype, the β_4-adrenoceptor which is localised in cardiac tissue.[5] Although there are no selective compounds for this subtype, the β_4-adrenoceptor has a low affinity for adrenaline and noradrenaline but is blocked by the β-adrenoceptor antagonists bupranolol and CGP20712A.[43,44]

Signal transduction mechanism

The β-adrenoceptors, like the α-adrenoceptors, are coupled to G-proteins and subsequent intracellular second messenger systems.[45] The β_1-adrenoceptor is positively coupled to adenylate cyclase via activation of G_s G-proteins as are the β_2- and β_3- adrenoceptors. However, activation of the β_2- and β_3- adrenoceptors results in stimulation or stimulation and inhibition of adenylate cyclase. Activation of the β_4-adrenoceptor results in increased cAMP and stimulation of cAMP-dependent protein kinase. There is also evidence to suggest β-adrenoceptors are linked via a stimulatory G-protein to voltage-gated Ca^{2+} channels.[46]

Location and function

The β_1- and β_2-adrenoceptors have distinct patterns of distribution in the CNS determined using *in situ* hybridisation studies.[47] β_1-Adrenoceptors are found in high density in the striatum and a selective decrease in the number of these receptors has been observed in Huntington's chorea.[48] Activation of β_1-adrenoceptors increases the force and rate of the heart whilst β_2-adrenoceptor activation results in vasodilatation and bronchodilation. Therefore drugs acting on β-adrenoceptors located on cardiac muscle, airway muscle and fat cells are of particular interest for their use in the treatment of cardiovascular disease, asthma and obesity. The atypical β_3-adrenoceptor is expressed predominantly in adipose tissue where it is proposed to be involved in regulating noradrenaline induced changes in energy metabolism and thermogenesis. Therefore, β_3-adrenoceptor agonists are likely to be of benefit in the treatment of obesity.[5]

Clinical Application and Future Directions

Many adrenergic compounds are currently in widespread clinical use, and are used to treat a range of disorders. The inhalation of β_2-adrenoceptor selective compounds has long been established as an effective therapy for the treatment of asthma and other bronchospastic conditions; salbutamol and salmeterol are examples of such drugs in current clinical use. Beta blockers are used in the treatment of angina pectoris and cardiac arrhythmias; they are used both as a treatment for acute congestive heart failure (e.g. dobutamine), and for long-term management of patients who survive myocardial infarction. In addition, β-adrenoceptor antagonists such as betaxolol and bisoprolol have been utilised as effective antihypertensives for several decades. Beta-blockers have also been used for management of the alcohol withdrawal syndrome, anxiety disorders, migraine prophylaxis, hyperthyroidism and tremor, and can also be applied topically to treat ocular hypertension and glaucoma. Conversely, the actions which result from β-adrenoceptor blockade can also be disadvantageous; heart failure, heart-block and bronchospasm being unwanted and serious side-effects. α-Adrenoceptor ligands can provide an effective therapy for hypertension; α_1-adrenoceptor antagonists such as indoramin and prazosin are widely employed as antihypertensive agents, as is the α_2-adrenoceptor agonist clonidine. The sedative effects of clonidine and other α_2-adrenoceptor agonists make them useful as adjuncts to general anaesthetics; xylazine and medetomidine are commonly used as such in veterinary medicine. α_1-adrenoceptor antagonists such as prazosin and alfuzosin are also thought to be effective in the management of benign prostatic hypertrophy although the cardiovascular side-effects associated with the blockade of vascular α_1-adrenoceptors can be problematic.

As is apparent, adrenergic ligands have a diverse range of clinical applications. In addition to the established therapeutic uses for these drugs, there is an interest in potential new applications which include the use of α_2 adrenergic compounds as analgesics and the use of selective β_3-adrenoceptor agonists as anti-obesity agents. There is also a need for improvement of the therapeutic profiles of the adrenergic compounds in common clinical use to minimise the side-effects often seen, and these may well follow on from the continuing development of more subtype selective adrenergic compounds and a clearer understanding of the functional roles of the individual subtypes within the two adrenoceptor families.

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Adrenergics Available from Tocris

α_1-Adrenoceptor Selective Compounds

Agonists

1052	A 61603	α_{1A} agonist
0888	Cirazoline	Selective α_1 agonist
0461	M-6434	α_1 agonist
1142	Oxymetazoline	α_{1A} agonist

Antagonists

1006	BMY 7378	Selective α_{1D} antagonist, 5-HT_{1A} partial agonist
1143	Corynanthine	α_1 antagonist
0535	HEAT	Highly selective α_1 antagonist
0545	Ifenprodil	α_1 antagonist. Also NMDA antagonist
0661	2-[[4-(2-Methoxyphenyl)piperazin-1-yl] methyl]-6-methyl-2,3-dihydroimidazo [1,2-c]-quinazolin-5(6H)-one	Potent, selective α_1 antagonist and σ_2 ligand
0597	Naftopidil	α_1 antagonist
1124	(R)-(-)-Niguldipine	Less active enantiomer of (1123)
1123	(S)-(+)-Niguldipine	α_1 antagonist, L-type Ca^{2+} channel blocker
0627	2-[(4-Phenylpiperazin-1-yl)methyl]-2,3-dihydroimidazo[1,2c]quinazolin-5(6H)-one	Potent, selective α_1 antagonist
0623	Prazosin	α_1 antagonist. MT_3 antagonist
0985	RS 17053	α_{1A} antagonist
0946	WB 4101	α_{1A} antagonist

General

0451	3-[2-[4-(2-Chlorophenyl)piperazin-1-yl] ethyl]-pyrimido[5,4-b]indole-2,4-dione	α_1 ligand and σ_2 ligand
0580	3-[2-[4-(2-Methoxyphenyl)piperazin-1-yl] ethyl]-1,5-dimethylpyrimido[5,4-b]indole-2,4-dione	α_1 ligand
0581	3-[2-[4-(2-Methoxyphenyl)piperazin-1-yl] ethyl]-pyrimido[5,4-b]indole-2,4-dione	α_1 ligand

α_2-Adrenoceptor Selective Compounds

Agonists

0690	Clonidine	α_2 agonist. Also imidazoline I_1 ligand
0885	Guanabenz	α_2 agonist. Also I_2 selective ligand
1030	Guanfacine	α_{2A} agonist
1142	Oxymetazoline	α_{2A} partial agonist
0790	Rilmenidine	α_2 agonist. Also imidazoline I_1 ligand
0425	UK 14,304	α_2 agonist

Antagonists

0928	ARC 239	α_{2B} antagonist
1133	BRL 44408	Selective α_{2B} antagonist
0986	Imiloxan	Highly selective α_{2B} antagonist
0891	Rauwolscine	α_2 antagonist
0987	RS 79948	Potent, selective α_2 antagonist
0631	Spiroxatrine	Potent α_2 ligand
1127	Yohimbine	α_2-selective antagonist

General

0842	Agmatine	α_2 ligand. Also imidazoline ligand

General α-Adrenoceptor Compounds

0474	Dihydroergocristine	Partial α agonist. Non selective
0475	Dihydroergotamine	Partial α agonist. Non selective
0604	Nicergoline	α antagonist

β_1-Adrenoceptor Selective Compounds

0387	(±)-Atenolol	β_1 antagonist
0392	R(+)-Atenolol	Inactive isomer
0393	S(-)-Atenolol	Active isomer
0906	Betaxolol	Selective β_1 antagonist
0914	Bisoprolol	β_1 antagonist

β_1-Adrenoceptor Selective Compounds continued

0831	Practolol	β_1 antagonist
0649	(S)-Timolol	β_1 antagonist
0950	Xamoterol	β_1 selective partial agonist

β_2-Adrenoceptor Selective Compounds

0688	Clenbuterol	β_2 agonist
0821	ICI-118,551	Very selective β_2 antagonist
R821	[^{3}H]-ICI-118,551 ☢	Radiolabelled form of (0821)
1102	Procaterol	Potent β_2 agonist
0634	Salbutamol	β agonist (β_2>β_1)

β_3-Adrenoceptor Selective Compounds

0948	BRL 37344	β_3 agonist
1134	CGP 12177	β_3 partial agonist. β_1/β_2 antagonist
0929	ICI 215,001	β_3 agonist
0930	ZD 7114	β_3 agonist
0994	Pindolol	β_3 partial agonist. Also 5-HT$_{1A/1B}$ antagonist
1060	(S)-(-)-Pindolol	More active enantiomer

General β-Adrenoceptor Compounds

0435	Cimaterol	β agonist
0848	N-Desisopropylpropranolol	Propranolol metabolite
0515	Dobutamine	β_1 and β_2 agonist. Also α_1 agonist
0832	ICI-89406	β antagonist
0850	1-Naphthoxyacetic acid	Propranolol metabolite
0849	1-Naphthoxylactic acid	Propranolol metabolite
0829	Pronethanol	β antagonist
0624	Propranolol	β antagonist
0835	R-(+)-Propranolol	Less active enantiomer
0834	S-(-)-Propranolol	More active enantiomer
0851	Propranolol glycol	Propranolol metabolite
0952	Sotalol	β antagonist

Adrenergic Uptake Inhibitors

0935	Maprotiline	Noradrenaline re-uptake inhibitor
1025	Nisoxetine	Noradrenaline re-uptake inhibitor

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Tocris Cookson Ltd.
Northpoint Fourth Way
Avonmouth BS11 8TA UK
Tel: + 44 (0)117 982 6551
Fax: + 44 (0)117 982 6552
customerservice@tocris.co.uk

www.tocris.com
technicalsupport@tocris.co.uk

Tocris Cookson Inc.
16144 Westwoods Business Park
Ellisville MO 63021 USA
Tel: (800) 421-3701
Fax: (800) 483-1993
customerservice@tocrisusa.com