Contents by Research Area:

- Hypertension
- Thrombosis and Hemostasis
- Atherosclerosis
- Myocardial Infarction
- Ischemia/Reperfusion Injury
- Arrhythmias
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Cardiovascular Research

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Introduction

Cardiovascular disease is the leading cause of death globally, accounting for about 30% of deaths worldwide. The term refers to a collection of diseases which affect the heart and blood vessels. These conditions can be genetic in nature or triggered by infection, but the major influences on the development of cardiovascular disease are environmental factors including a high saturated fat intake and a sedentary lifestyle.

One of the most common cardiovascular diseases is atherosclerosis – a condition which is characterized by the build-up of fatty deposits within arterial walls and which can trigger heart attack or stroke through the formation of a blood clot. Damage to the heart muscle caused by a heart attack can alter the contractility of the heart, leading to irregular heartbeats (arrhythmias). A reduced ability of the heart to pump blood around the body can eventually lead to the development of heart failure. Due to the close association of cardiovascular disorders, early treatment of these disorders is preferable.

Surgical interventions such as coronary artery bypass and artificial pacemakers are available to treat patients with cardiovascular disease, though the treatments themselves may worsen the overall function of the heart. For many patients, pharmacological intervention is therefore preferable to invasive surgery, particularly for the treatment of early atherosclerosis and high blood pressure. For example, a major breakthrough in the treatment of cardiovascular disease was the development of statins for the treatment of raised cholesterol. However, therapy for other diseases such as heart failure and advanced atherosclerosis is lacking and demands further research.

Our latest cardiovascular research guide aims to discuss current and future therapeutic targets in seven major cardiovascular diseases, all of which are the focus of significant preclinical research. Tocris provides a wide range of pharmacological tools for these targets, a selection of which are highlighted in our ‘Key Products’ boxes within each section. A full product listing can be found on page 20.

Key Cardiovascular Research Products

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Hypertension

Hypertension is defined as a chronic elevation in blood pressure with a systolic pressure over 140 mmHg and a diastolic pressure over 90 mmHg. The majority of hypertension is primary — that is, an increase in blood pressure with no underlying cause — yet pathologies that affect the kidney or endocrine system may also trigger hypertension. This is known as secondary hypertension. The exact mechanism of primary hypertension is yet to be elucidated, though dysfunctions in mechanisms that regulate vascular tone, both directly and indirectly, have been identified as having a major influence on hypertension.

In hypertension, increased arterial pressure is detected by specialized mechanoreceptors called baroreceptors, present in the aortic arch and the carotid sinuses. Baroreceptors are innervated by nerves that synapse in the nucleus tractus solitarius (NTS), an area within the medulla oblongata that regulates blood pressure through the modulation of parasympathetic and sympathetic transmission. In the event of a rise in blood pressure, the baroreceptor firing rate increases; this stimulates the activation of sympathetic neurons that originate in the NTS and synapse in the outer arterial wall, or adventitia. Activation of these sympathetic neurons induces vasoconstriction through the release of noradrenaline and subsequent activation of Gα, and the downstream IP3 signal transduction pathway. As a result, drugs that target α adrenergic receptors modulate blood pressure. The precise effect on vascular tone is dependent on the α adrenergic receptor subtype; α1 adrenergic receptors stimulate the release of noradrenaline from sympathetic nerve terminals, whilst α2 adrenergic receptors inhibit the release of noradrenaline, acting as a feedback mechanism to modulate its release from sympathetic nerve terminals.

In addition to sympathetic mechanisms, targeting the renin-angiotensin-aldosterone system (RAAS) is a proven and effective strategy in hypertension. The activation of the RAAS in response to a fall in blood pressure leads to the release of renin from the juxtaglomerular apparatus in the kidney (Figure 1). Renin cleaves angiotensinogen, which undergoes further cleavage to produce the highly potent vasoconstrictor, angiotensin II. Angiotensin II binding to the membrane-bound GPCR, angiotensin II receptor 1 (AT1), induces vasoconstriction directly through the potentiation of noradrenaline release from sympathetic nerve terminals within blood vessel walls.

The downstream effects of AT1 receptor activation are counterbalanced in part by the activation of AT2 receptors. Due to the potent vasoconstrictor properties of AT1 receptor activation, drugs which act as antagonists at this receptor, such as valsartan (Cat. No. 4216) and losartan (Cat. No. 3798), are effective antihypertensives through their indirect vasodilator activity. Inhibition of angiotensin-converting enzyme (ACE) blocks production of angiotensin II and therefore exhibits antihypertensive effects.

Angiotensin II also acts indirectly by stimulating the secretion of vasopressin (AVP) from the pituitary gland and increasing the release of aldosterone from the adrenal cortex. Both AVP and aldosterone augment water reabsorption in the kidney, thereby increasing blood volume and therefore blood pressure.

Figure 1 | The renin-angiotensin-aldosterone system

Activation of the RAAS in response to a fall in blood pressure stimulates the release of renin from the kidney. This leads to the production of the potent vasoconstrictor, angiotensin II. Angiotensin II also induces aldosterone release from the adrenal cortex, triggering increased water reabsorption. Together these mechanisms counter the decrease in blood pressure. Abbreviations: ACE — angiotensin-converting enzyme; ARB — angiotensin II receptor blocker
Aldosterone receptor antagonists including spironolactone (Cat. No. 2968) and eplerenone (Cat. No. 2397) also exert antihypertensive effects due to their inhibitory actions on water reabsorption. The resultant reduction in circulating blood volume in turn lowers blood pressure. Other diuretics such as furosemide (Cat. No. 3109) and bumetanide (Cat. No. 3108) also lower circulating blood volume and therefore blood pressure, though they act through the inhibition of the Na⁺/K⁺/2Cl⁻ cotransporter (NKCC). The NKCC is an integral membrane pump which drives calcium ion and magnesium ion reabsorption in the renal medulla, resulting in water reabsorption from the loop of Henlé.

In addition to indirect control of vascular tone by the sympathetic nervous system and RAAS, direct control mechanisms within the blood vessel wall are also a valid therapeutic target in hypertension. Key regulators of blood pressure within the vasculature include nitric oxide (NO), endothelin 1 (ET-1) and prostacyclin (PGI₂) (Figure 2). Other major vasodilators including acetylcholine and bradykinin also directly alter vascular tone by inducing the production of endothelial nitric oxide.

Endothelin receptors can be divided into two classes – endothelin A (ETₐₐ) receptors and endothelin B (ETₐₐ) receptors. ETₐₐ receptors are highly expressed in the endothelium whereas ET₁ receptors are absent, yet both receptor subtypes are present on the underlying vascular smooth muscle cells. Activation of ET₁ receptors by ET-1 leads to vasoconstriction whilst the effects of ET₂ receptor activation are cell type-specific; endothelial cell ET₂ receptor (ET₂₁) activation leads to vasodilation through the production of NO and PGI₂, yet smooth muscle cell ET₂ receptor (ET₂₂) activation causes vasoconstriction.

A further therapeutic target in hypertension is NO since its bioavailability is often impaired in hypertensive patients; this is a hallmark of endothelial dysfunction. NO is a key endogenous vasodilator that is secreted in response to endothelial membrane receptor stimulation by agonists such as acetylcholine, bradykinin and 5-HT, as well as shear stress. Activation of endothelial cell membrane receptors by agonist stimulation or shear stress results in an increase in intracellular calcium ion concentration. This increased calcium ion availability activates calmodulin (CaM), a calcium binding protein. The Ca²⁺-calmodulin complex is vital in removing the caveolin-mediated inhibition of endothelial nitric oxide synthase (eNOS), enabling eNOS enzyme activity. The principal reaction of eNOS is to convert L-arginine to L-citrulline, generating nitric oxide as a by-product. NO production and release from endothelial cells triggers an increase in cyclic GMP.
concentration in the underlying smooth muscle cells through the activation of soluble guanylyl cyclase (sGC), which in turn lowers the intracellular calcium ion concentration, prompting smooth muscle cell relaxation and resulting in vasodilation.

Due to the integral involvement of calcium ions in the control of vascular tone, drugs which prevent the influx of calcium ions through calcium channels following cellular depolarization also directly induce vasodilation. Commonly used calcium channel blockers for the treatment of hypertension include nifedipine (Cat. No. 1075) and diltiazem (Cat. No. 0685). Inhibiting the sensitivity of downstream mediators involved in vasodilation, such as the Rho-associated protein kinase p160ROCK, to calcium ions also prompts vasodilation. An example of a compound that produces vasodilation through this alternate mechanism is Y-27632 (Cat. No. 1254).

Other vasodilators secreted by endothelial cells that reduce intracellular calcium within underlying smooth muscle cells include prostacyclin, which acts on IP prostanoid (IP) receptors, and C-natriuretic peptide (CNP) through its actions on natriuretic peptide receptors (NPR). Compounds that target these receptors, directly modulate the vasodilatory properties of these endogenous mediators. The activity of these endogenous vasodilators can also be altered by targeting second messenger signaling molecules, namely cAMP and cGMP. Examples of compounds that increase cytoplasmic cAMP levels include the β adrenergic receptor agonist formoterol (Cat. No. 1448), whilst cGMP levels can be therapeutically increased by the activation of sGC, using compounds such as BAY 41-2272 (Cat. No. 4430) and A 350619 (Cat. No. 2753).

Vasodilation is also achieved by selectively increasing the membrane permeability to K+ ions, leading to cellular hyperpolarization and subsequent relaxation. Activators of ATP-sensitive potassium channels (K₆; K₆₅), such as cromakalim (Cat. No. 1377) and nicorandil (Cat. No. 2147), possess potent vasodilator activity as a result of this mechanism, though the NO donor activity of nicorandil in addition to its K₆ channel activating properties further increases its potency as a vasodilator.

Despite the considerable advances in identifying relevant therapeutic targets involved in hypertension, the side effect profiles resulting from the ubiquitous expression of many of these targets limits their long term use. Rather than directly lowering circulating blood pressure, future perspectives for the treatment of hypertension tend to focus upon ameliorating endothelial dysfunction – through mechanisms such as increasing nitric oxide bioavailability – in order to reduce the target organ damage associated with hypertension and improve prognosis. Since endothelial dysfunction can be triggered by free radical-mediated damage, several clinical trials studied the effects of vitamin E administration in hypertensive patients. These studies reported little or no beneficial effects of the antioxidant, yet there is emerging data of an antihypertensive effect of statins, independent of their lipid-lowering activity. Further potential therapeutic targets in hypertension include increasing L-arginine levels, and preventing the neutral endopeptidase-mediated proteolysis of natriuretic peptides, though additional research focus is required in order to develop novel, effective treatments for hypertension.
Thrombosis and Hemostasis

Thrombosis is a crucial hemostatic process for preventing excessive blood loss following injury, yet aberrant thrombosis can trigger pathological conditions including myocardial infarction and stroke. Therefore the initiation of thrombosis is tightly controlled under physiological conditions.

Platelets are a central component of thrombosis and exhibit a rapid, exponential activation in the event of tissue damage. Produced in the bone marrow, platelets are anucleate cell fragments of megakaryocytes. Despite having no nucleus, platelets possess two different types of granules within the cytoplasm – alpha granules and dense granules – and also express a number of different receptors on their plasma membranes (Figure 3). Both alpha and dense granules contain a variety of bioactive mediators including ADP, calcium and 5-HT as well as growth factors such as platelet-derived growth factor (PDGF), insulin-like growth factor-1 (IGF-1) and transforming growth factor (TGF) β1. Upon activation, platelets undergo degranulation; this releases granule contents into the surrounding environment and promotes the activation and aggregation of neighboring platelets.

Receptors present on the platelet plasma membrane include the purinergic receptors P2X1, P2Y1 and P2Y12; the 5-HT receptor 5-HT2A; the thromboxane A2 (TXA2) receptor TP; and the thrombin receptors (protease-activated receptors) PAR1 and PAR4, as well as the von Willebrand factor (vWF) receptor GPIb/V/IX.

Figure 3 | Platelet signaling and activation

Agonists
- 5-HT (5-HT2A receptors)
- ADP (P2X1, P2Y1, P2Y12 receptors)
- Collagen (GPVI glycoprotein)
- Thrombin (PAR1, PAR4 receptors)
- Thromboxane A2 (TP receptors)

Agonist stimulation of platelets triggers activation of glycoprotein Ib/V/IX; generation of arachidonic acid from membrane phospholipids by the actions of cytosolic phospholipase A2 (cPLA2); and mobilization of intracellular calcium. This in turn triggers the release of granules containing platelet-activating mediators that subsequently act on neighboring platelets, amplifying platelet activation and aggregation.
PAR<sub>4</sub>. Platelet signaling may also be activated by exposure to collagen via the glycoprotein receptor, GPVI. Key downstream mediators of these receptors include the plasma membrane phospholipid phosphatidylinositol 4,5-bisphosphate (PIP<sub>2</sub>), which is cleaved by phospholipase C to form inositol triphosphate (IP<sub>3</sub>) and diacylglycerol (DAG). IP<sub>3</sub> receptor (InsP<sub>3R</sub>) activation triggers the efflux of calcium ions from intracellular calcium stores such as the endoplasmic reticulum, leading to a rise in intracellular calcium (Figure 3).

The mobilization of calcium causes the exocytosis of cytoplasmic granules and the activation of platelet aggregation-inducing glycoproteins such as GPIIb/IIIa. GPIIb/IIIa functions as a cell surface receptor for fibrinogen and promotes the activation of platelets. The pivotal involvement of GPIIb/IIIa in platelet aggregation renders it a useful therapeutic target for anticoagulant therapy. GPIIb/IIIa inhibitors, such as abciximab and echistatin (Cat. No. 3202), are currently used as prophylactic therapy during angioplasty to prevent thrombus formation. Inhibitors of P2Y<sub>12</sub> – for example, clopidogrel (Cat. No. 2490) and ticlodipine (Cat. No. 3931) – also indirectly prevent platelet aggregation by blocking the activation of GPIIb/IIIa.

In addition to GPIIb/IIIa, the integrin receptor complex GPIb/V/IX is also integral in thrombosis. Interaction of the GPIb/V/IX complex with von Willebrand factor (vWF) on exposed collagen at the site of vascular damage promotes platelet adhesion. This is achieved through GPIIb/IIIa-mediated phosphorylation of intracellular signaling proteins, including pp60<sup>src</sup>, PLC<sub>γ</sub>, and the Fc receptor γ-chain (FcγRIIa), which initiates and augments the adhesion of platelets with the extracellular matrix and also with neighboring platelets. Phosphorylation of FcγRIIa by GPIIb/IIIa functions as a cell surface receptor for fibrinogen and promotes the activation of platelets. The pivotal involvement of GPIIb/IIIa in platelet aggregation renders it a useful therapeutic target for anticoagulant therapy. GPIIb/IIIa inhibitors, such as abciximab and echistatin (Cat. No. 3202), are currently used as prophylactic therapy during angioplasty to prevent thrombus formation. Inhibitors of P2Y<sub>12</sub> – for example, clopidogrel (Cat. No. 2490) and ticlodipine (Cat. No. 3931) – also indirectly prevent platelet aggregation by blocking the activation of GPIIb/IIIa.

Agonist stimulation of platelets also initiates the production of arachidonic acid (Cat. No. 2756) from membrane phospholipids, a reaction which is catalyzed by cytosolic phospholipase A<sub>2</sub> (cPLA<sub>2</sub>). Arachidonic acid can be utilized by both cyclooxygenases (COX) to form prostaglandin H<sub>2</sub> (PGH<sub>2</sub>), and also by lipoxygenases (LOX) to form the lipid mediator hydroperoxy-eicosatetraenoic acid (HPETE). PGH<sub>2</sub> is further metabolized to form prothrombotic eicosanoids including TXA<sub>2</sub>. Inhibition of the PGH<sub>2</sub> synthesis pathway using COX inhibitors such as aspirin (Cat. No. 4092), celecoxib (Cat. No. 3786) and diclofenac (Cat. No. 4454), and the TXA<sub>2</sub> synthase inhibitor, dipyridamole (Cat. No. 0691), is an effective therapeutic strategy for preventing thrombosis. PLA<sub>2</sub> inhibitors including AACOCF<sub>3</sub> (Cat. No. 1462) also exhibit antithrombotic effects by inhibiting the activity of the arachidonic acid pathway.

Box 3: Thrombosis and Hemostasis Key Products

A full list of targets and related products are listed on pages 20-30
Atherosclerosis

Atherosclerosis is a disease of the arterial system that is characterized by the accumulation of fatty deposits within arterial walls (Figure 5). These fatty deposits, known as ‘atherosclerotic plaques’, also contain cellular debris and in advanced plaques, calcium deposits (in the form of hydroxyapatite) are often present. The plaque contents are highly thrombogenic and so are separated from the circulating blood by a fibrous cap, composed mainly of vascular smooth muscle cells and extracellular matrix proteins such as collagen, which are synthesized by these cells (Figure 4).

The exact cause of atherosclerosis remains unknown, but the initial process – termed ‘atherogenesis’ – involves the transmigration of monocytes/macrophages across the endothelium into the intima, where they scavenge oxidized lipid (ox-LDL), forming lipid-laden ‘foam cells’. Expression of adhesion molecules by endothelial cells promotes this transmigration. Foam cells undergo apoptosis, forming a lipid-rich core within the developing plaque. The formation of a plaque within the arterial wall triggers an inflammatory response, propagated by the secretion of growth factors and chemokines by resident plaque cells.

Circulating macrophages, recruited to the atherosclerotic plaque through chemotaxis, are a major source of matrix metalloproteinases (MMPs). These zinc-dependent enzymes degrade the fibrous cap, predisposing the plaque to rupture; they may also degrade the elastic laminae between layers of the arterial wall, facilitating the migration of smooth muscle cells from the tunica media to the fibrous cap, thus helping strengthen it.

A thick smooth muscle-cell rich fibrous cap with a small lipid core is characteristic of a ‘stable’ plaque, that is, one which is less likely to rupture. Plaques with a thin fibrous cap and a large, necrotic lipid core are termed ‘unstable’ or ‘vulnerable’ plaques and are more susceptible to rupture. Any defect in the fibrous cap exposes the thrombogenic plaque contents to the circulating blood, triggering thrombosis. Ninety percent of these plaque ruptures are clinically silent, yet the remaining proportion trigger myocardial infarction or stroke, and can be fatal.

In addition to the recruitment of macrophages within an atherosclerotic plaque, other immune mediators are also involved in atherosclerosis. These include various chemokines, cytokines, and growth factors that mediate the recruitment and activation of immune cells and promote the recruitment of macrophages and T lymphocytes to the atherosclerotic plaques. The presence of these immune cells contributes to the propagation of inflammation, further promoting plaque progression and destabilization.

The development of atherosclerosis within a blood vessel wall starts as a fatty streak, composed of a small cluster of lipid-laden macrophages, which progresses over time to form a lipid pool within the vessel wall. Cell debris from apoptotic foam cells within the lipid pool forms a necrotic core. The fibrous cap separates the lipid pool from the blood, but rupture of this cap exposes the thrombogenic plaque contents to circulating blood, triggering thrombus formation.
Lipid accumulation and inflammatory cell invasion (depicted in yellow) within an arterial wall (pink) causes vessel narrowing and stenosis. A thin fibrous cap (arrows) separates the plaque contents from the circulating blood. Rupture of the fibrous cap exposes these thrombogenic contents to the blood, triggering thrombosis.

Figure 5 | Section through a coronary artery with an atherosclerotic plaque

Lipid accumulation and inflammatory cell invasion (depicted in yellow) within an arterial wall (pink) causes vessel narrowing and stenosis. A thin fibrous cap (arrows) separates the plaque contents from the circulating blood. Rupture of the fibrous cap exposes these thrombogenic contents to the blood, triggering thrombosis.

Box 4: Atherosclerosis Key Products
A full list of targets and related products are listed on pages 20-30

Torcetrapib (4184)
Inhibitor of cholesteryl ester transfer protein (CETP)

Zileuton (3308)
Orally active 5-LOX inhibitor

Simvastatin (1965)
HMG-CoA reductase inhibitor

Celecoxib (3786)
Selective COX-2 inhibitor

Echistatin α1 isoform (3202)
Potent, irreversible αvβ3 integrin antagonist

Marimastat (2631)
Broad spectrum MMP inhibitor

SB 657510 (3571)
Selective urotensin-II receptor antagonist

Tyr-Cys-Asn-Gly-Lys-Thr-Cys-Asp-Cys-Pro-Arg-Asn-Pro-His-Lys-Gly-Pro-Ala-Thr

Additional targets with therapeutic potential in atherosclerosis include phospholipases and urotensin II, since the presence of both may trigger foam cell formation, furthering the progression of atherosclerosis.
Myocardial Infarction

Myocardial infarction (MI) – more commonly referred to as a heart attack – is an acute event caused by the interruption of blood supply to regions of the heart, leading to myocardial necrosis. Infarction of a substantial area of the myocardium can disrupt normal conductance of the heart, leading to cardiac arrest.

MI is immediately preceded by the presence of an occlusive thrombus within a coronary artery, blocking blood flow to the downstream tissue (Figure 6). The most common cause of an occlusive thrombus within a coronary artery is the rupture of an atherosclerotic plaque (see pages 8-9 for further details on Atherosclerosis). However, the occlusion of a coronary artery may also result from coronary embolism. This can occur in patients following stent placement, angioplasty, and coronary artery bypass grafting.

One of the few warning symptoms for MI is the occurrence of angina pectoris – a severe, cardiac-induced chest pain which may also radiate down the left arm. Angina is caused by a lack of oxygen to the myocardium due to coronary artery obstruction or spasm, and can be classified as either ‘unstable’ or ‘stable’ angina. Patients with stable angina experience ‘predictable’ chest pain during exertion which resolves following rest or the administration of the NO donor, nitroglycerin. There is little damage to the myocardium during stable angina. However, an episode of unstable angina – that is, chest pain which occurs at rest or in patients with no history of stable angina – may induce myocardial necrosis, albeit at a reduced level to that observed during acute MI. The most common blood biomarkers used to diagnose acute MI or unstable angina are cardiac troponins T (cTnT) and I (cTnI), two components of cardiac muscle whose serum levels rise as a result of myocardial necrosis.

Immediate pharmacological treatment of angina is achieved by the administration of nitroglycerin, but longer term therapy involves either increasing blood supply to the heart using vasodilators such as calcium channel blockers, long-acting nitrates and nicorandil (Cat. No. 2147), or by reducing metabolic demand of the heart through decreasing heart rate by administering β-blockers or ivabradine. A further pharmacological

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Figure 6 | Myocardial infarction

When an atherosclerotic plaque ruptures, blood flow is greatly impeded and thrombosis may occur. Consequently, the artery is occluded and the supply of oxygen to the heart is restricted. Ischemia results, and if it is sustained the heart muscle tissue may become damaged and die. The likelihood of plaque rupture is influenced by a number of factors, including elevated blood pressure and degree of inflammation. This damaged tissue does not function fully; acute myocardial ischemia results in ionic and metabolic disturbances that affect the membrane and action potentials of myocytes. Arrhythmias and heart failure may occur as a result of the slower conduction of electrical impulses.
Mechanism for preventing angina is to increase ATP production whilst maintaining the same oxygen consumption. One of the first antianginal agents, perhexiline, exerts these effects by inhibiting the mitochondrial enzyme, carnitine palmitoyl-transferase-1 (CPT1). Newer antiangiinal agents such as ranolazine (Cat. No. 3118) and etomoxir (Cat. No. 4539) also alter fatty acid oxidation, increasing metabolic efficiency and preventing the occurrence of angina.

In addition to vasodilators, pharmacological treatment of acute MI also includes antiplatelet and fibrinolytic agents such as recombinant human tPA, uPA and streptokinase in combination with heparin (Cat. No. 2812) in order to break down the occluding thrombus and restore blood supply to the downstream myocardium. Angioplasty is the preferred method of restoring vessel patency, however, as it carries a lower risk of reocclusion and stroke. Reducing cardiac output by targeting the RAAS is also a useful therapeutic strategy following MI, particularly in patients at risk of developing heart failure (see pages 16–17 for further information on heart failure). Adenosine receptor activation is also an effective therapeutic strategy for reducing myocardial injury following MI. All four adenosine receptor subtypes – A1, A2A, A2B and A3 – have been shown to be cardioprotective in the ischemic heart.

Research continues to identify novel targets for the treatment of MI. One such target is the cathepsin family, a group of enzymes which degrade myofibrillar proteins during MI and promote ventricular remodeling. The beneficial effects of cathepsin inhibition may be two-fold – in addition to reducing ventricular remodeling following MI, cathepsin inhibition may also prevent atherosclerotic plaque rupture, the principal trigger of MI. A further target in reducing ventricular remodeling and preventing MI-induced heart failure is PI 3-kinase, though its ubiquitous expression limits its use as a therapeutic target.

More recent therapy for the treatment of myocardial infarction centers around the use of stem cells to repair damaged myocardium. Following an infarction, damaged myocardium cannot regenerate and so is replaced by non-contractile scar tissue. This alters both the contractility and the conductance of the myocardium and may subsequently lead to the development of an arrhythmia or heart failure. The injection of multipotent cardiac stem cells to the infarcted area of the heart following a myocardial infarction has shown promise in facilitating regeneration of damaged myocardium, but their availability is limited. As a result, research efforts are currently focused on producing cardiomyocytes by differentiating more readily available stem cell populations, such as undifferentiated skeletal myoblasts or bone marrow-derived adult stem cells. Inducing cardiomyogenic function in these stem cell populations has been achieved using a range of methods. These include cardiac preconditioning, whereby stem cells are differentiated in media previously used to culture primary cardiomyocytes; and also by using small molecule inhibitors such as cardiogenol C (Cat. No. 3851) and XAV 939 (Cat. No. 3748) which modulate stem cell signaling pathways including the Wnt/β-catenin pathway.

Facilitating the repair and regeneration of damaged myocardium following infarction, together with preventing aberrant remodeling, represent promising future therapeutic avenues within the field of myocardial infarction research.

**Box 5: Myocardial Infarction Key Products**

A full list of targets and related products are listed on pages 20–30
Ischemia/Reperfusion Injury

Myocardial ischemia, also known as cardiac ischemia, is defined as the deprivation of oxygen and nutrients to the heart. This phenomenon occurs during a myocardial infarction, when an occlusive thrombus within a coronary artery prevents blood supply to the myocardium, but can occur during cardiac surgery as a result of pharmacological intervention to temporarily stop the heart. Reperfusion restores blood supply to ischemic tissue, but this is paradoxically associated with further tissue damage.

Under ischemic conditions, the lack of oxygenated blood supply to the myocardium means that the energy demands of the heart cannot be met. Numerous metabolic changes result from cardiac ischemia, and if it is prolonged, ischemia may result in irreversible injury. Hypoxic ischemic conditions and the rapid decline in oxygen availability blocks ATP production by oxidative phosphorylation, leading to reduced contractility of the heart. A prolonged reduction in contractility can itself induce ventricular dysfunction.

During anaerobic metabolism, glucose, glycogen and glutamate are broken down and lactate, alanine, succinate and hydrogen ions build up. A build-up of hydrogen ions lowers the pH of the intracellular and extracellular environment. The acidic environment inside and outside cardiomyocytes gradually affects ion homeostasis, leading to increases in intracellular Na⁺ concentration. Increased Na⁺ concentration prompts a resultant

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A rise in intracellular Ca²⁺ concentration ([Ca²⁺]) is evident in ischemia and early reperfusion. This increase has been shown to precede irreversible cardiac injury. Decrease in ATP production, as a result of ischemia, lowers the intracellular pH. This change results in the increased activity of Na⁺/H⁺ and Na⁺/Ca²⁺ exchangers, thus increasing [Ca²⁺]. ATP, generated by glycolysis, is used by F₁F₀-ATPase to create a mitochondrial membrane potential (Δψₘ). This is utilized by the mitochondrial calcium uniporter; an increase in mitochondrial Ca²⁺ concentration, combined with ROS activity and a normalized pH, prompts the opening of the mitochondrial pore during reperfusion. Abbreviations: ANT – adenine nucleoside translocator; ATP – adenosine triphosphate; Cyp D – Cyclophilin D; MCU – mitochondrial calcium uniporter; MPTP – mitochondrial permeability transition pore; ROS – reactive oxygen species; VDAC – voltage-dependent anion channel.
increase in Ca\(^{2+}\) ions in a phenomenon known as ‘Ca\(^{2+}\) overloading’. Apoptosis and necrosis of cardiomyocytes induced by Ca\(^{2+}\) overloading can cause irreparable damage to the heart.

The reperfusion of an ischemic myocardium following a period of ischemia is also a focus of research. Restoration of blood supply to the ischemic zone triggers tissue damage via the release of intracellular enzymes, sarcolemmal rupture, Ca\(^{2+}\) influx and cardiomyocyte hypercontracture. Rupture of the sarcolemmal membranes leads to the movement of Na\(^{+}\) ions through gap junctions between adjacent cells and the induction of reverse Na\(^{+}\)/Ca\(^{2+}\) exchange, propagating the damage to neighbouring myocytes. This process of initial ischemia-related damage followed by further damage induced by reperfusion is known as ischemia/reperfusion (I/R) injury.

The cell death that underlies I/R injury is characterized by features typical of apoptosis, autophagy and necrosis. A key regulator of both apoptotic and necrotic cell death is the mitochondrial permeability transition pore (MPTP) (Figure 7). Low pH, induced during ischemia, inhibits MPTP opening; only upon reperfusion does pH return to normal. Elevated matrix Ca\(^{2+}\) concentrations and reactive oxygen species (ROS) are the primary activators of the MPTP during I/R. Inhibition of ion exchangers that influence cytosolic Ca\(^{2+}\) levels, such as the Na\(^{+}\)/H\(^{+}\) exchanger (NHE) and Na\(^{+}\)/Ca\(^{2+}\) exchanger (NCX), have been shown to reduce I/R injury. One such inhibitor – zoniporide (Cat. No. 2727) – selectively inhibits NHE1 and provides cardioprotection from ischemic injury \textit{in vivo}. In addition to agents targeting the NHE and NCX, inhibitors of MPTP, such as cyclosporin A (Cat. No. 1101), help protect against reperfusion injury.

A further cardioprotective strategy currently under investigation for I/R injury is ischemic preconditioning. This method aims to reduce the damage associated with I/R injury by subjecting the vascular system to brief, sublethal periods of ischemia. An advantage of this method is that the same protective effects can be obtained even when inducing ischemia in a tissue distinct from the heart, such as the upper or lower limbs; this is known as remote preconditioning. The cardioprotective tissue response to ischemic preconditioning is thought to involve a number of biological targets, including adenosine receptors. Activation of these receptors prior to ischemia or during reperfusion has been shown to confer cardioprotection; for example, the subtype-selective A\(_3\) agonist, IB-MECA (Cat. No. 1066) exhibits cardioprotective properties in a rat model.

Newer cardioprotective targets include GSK-3β, a multifunctional kinase that has also been linked to protection against I/R damage; the mitochondrial calcium uniporter (MCU), which has been linked to the cardioprotective response to ischemic preconditioning; and the sarco/endoplasmic reticulum Ca\(^{2+}\)-ATPase (SERCA). Enhancement of SERCA activity has been shown to reduce infarct size and preserve cardiac function in a rodent model of transient myocardial ischemia. Administration of interventional drugs at the initiation of reperfusion is limited since they must be introduced within 10 minutes of reperfusion starting, yet therapeutic targeting of intracellular processes invoked during both ischemia and reperfusion remain a promising strategy for the prevention and/or limitation of both the occurrence and the extent of I/R injury.

**Box 6: Ischemia/Reperfusion Injury Key Products**

A full list of targets and related products are listed on pages 20-30.
Arrhythmias

An arrhythmia (also known as cardiac dysrhythmia) is defined as an irregular heartbeat, and results from abnormal electrical activity in the heart. There are various different types of arrhythmia, often resulting in a heartbeat that is too fast (tachycardia) or too slow (bradycardia). Atrial and ventricular fibrillation, which are the most common cardiac arrhythmias, account for 10-20% of all deaths among adults in the Western world. The incidence of atrial fibrillation increases with age; it not only affects cardiac function, but also increases the risk of stroke and may worsen heart failure.

A normal heartbeat is driven by various stages of membrane depolarization and repolarization in single heart cells, propagating from the sinoatrial (SA) node to the atrium and the ventricle. There are two types of action potentials: the fast response action potential, which occurs in cardiac muscle and Purkinje fibers; and the slow response, evident in the SA and atrioventricular (AV) nodes. Action potentials enable rapid changes in heart rate. Contraction of the cardiac muscle occurs in response to depolarization. By generating action potentials and setting off a wave of depolarization, the SA node thus acts as a pacemaker, setting the rate of contraction of the heart. Dysfunction of the SA node may therefore result in an irregular heartbeat. The mechanism of normal cardiac action potential generation in cardiac muscle cells is depicted in Figure 8. The effective refractory period (ERP) is a mechanism that helps protect the heart from arrhythmias, by preventing the generation of new action potentials during the propagation of an existing one. Antiarrhythmics such as quinidine (Cat. No. 4108) can be used to prolong the ERP, preventing premature activation. However, quinidine also prolongs the QT interval (Figure 9) and can induce Torsades de pointes (TdP; a type of ventricular tachycardia that can be transient or lead to lethal ventricular fibrillation).

In addition to SA node dysfunction, arrhythmias can also occur as a result of abnormalities in the electrophysiology of heart cells or in cell-to-cell (impulse) propagation, which takes place through gap junctions. These enable conduction of a wave of depolarization between cells. Ion channels are responsible for the conduction of coordinated electrical impulses, and

Figure 8 | Action potentials in cardiac muscle cells

Phase 0: Rapid depolarization occurs. Fast Na⁺ channels open, generating an inward current that overcomes the outward current.
Phase 1: Early repolarization occurs. The fast Na⁺ channels are inactivated, and there follows an efflux of K⁺ ions.
Phase 2: The 'plateau' phase. This is the longest phase, and marks the entry of Ca²⁺ ions into the myocardial cell via L-type Ca²⁺ channels. Reduced outward K⁺ current continues.
Phase 3: Rapid repolarization occurs. The membrane potential is restored to its resting value (~ -90 mV for cardiac muscle cells; ~ -60 mV for SA node cells).

Abbreviation: ERP – effective refractory period
Arrhythmias – continued

Arrhythmias can be detected by electrocardiography (ECG or EKG), which measures the electrical activity of the heart. A normal ECG trace will have a consistent, regular form, representing the different intervals involved in cardiac rhythm. This includes the QT interval, during which the left and right ventricles depolarize and repolarize. During ventricular fibrillation, a type of arrhythmia, the heart does not contract in an ordered fashion; the absence of normal heart rhythm is apparent when comparing ECG traces.

consequently dysregulation of their activity has been linked to the development of arrhythmias. For example, mutations in genes encoding the Kv11.1 (hERG) potassium channel, the sodium NaV1.5 channel, and the calcium CaV1.2 channel have been linked to long QT syndrome (LQTS). In LQTS, the QT interval is extended and repolarization is delayed; this increases

the risk of Torsades de pointes. Cardiac ion channel blockade represents the traditional action of antiarrhythmic drugs. Directly or indirectly altering ion channel conductance changes the characteristics of cardiac action potentials and decreases atrial fibrillation.

In addition to ionic imbalances, arrhythmogenic stimuli in the heart include: metabolic substances (e.g. phospholipids and eicosanoids), thrombosis, atheromas and coronary artery spasm (angina). Arrhythmias can also result from myocardial ischemia.

Antiarrhythmic drug therapy aims to restore normal cardiac rhythm and conduction, and to prevent more serious arrhythmias from occurring. Vaughan Williams created one of the most widely used classification schemes for antiarrhythmic drugs. The scheme divides antiarrhythmic drugs into five classes (I-V), each of which concerns a different target. Class I compounds are sodium channel blockers; class II are beta-blockers; class III contains agents that target potassium channels; and class IV agents block calcium channels. Class V includes drugs that act via an unknown mechanism. Within these classes exist further subclasses, which exhibit slightly different properties at different points of the cardiac action potential, and which may affect the overall duration of the action potential. For specific types of arrhythmia, different agents may also be used: for example, adenosine (Cat. No. 3624) and verapamil (Cat. No. 0654) may be used to treat supraventricular tachycardia. The main advances in arrhythmic therapy have been made in the use of electronic devices, such as artificial pacemakers, and direct current cardioversion.

Figure 9 | ECG traces of arrhythmia

<table>
<thead>
<tr>
<th>Normal heart rhythm</th>
<th>Ventricular fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>P wave</td>
<td></td>
</tr>
<tr>
<td>QT interval</td>
<td></td>
</tr>
</tbody>
</table>

Box 7: Arrhythmia Key Products

A full list of targets and related products are listed on pages 20-30

- **CGP 20712 (1024)**
  - Highly potent and selective β₁ antagonist

- **ICI 118,551 (0821)**
  - Very selective β₂ antagonist

- **Flecainide (1470)**
  - Cardiac Na⁺ channel blocker. Antiarrhythmic

- **E-4031 (1808)**
  - Kᵥ11.1 (hERG) channel blocker; inhibits rapid delayed rectifier K⁺ current (Iᵦᵣ)

- **DPO-1 (2533)**
  - Blocker of Kᵥ1.5 channel and Iᵦᵣ current

- **(S)-(-)-Bay K 8644 (1546)**
  - Ca²⁺-channel activator (L-type)

- **JNJ 303 (3899)**
  - Potent and selective Iᵦᵣ blocker
Cardiac function. Cardiac dysfunction, either systolic or diastolic, triggers a decrease in stroke volume and a resultant decrease in cardiac output. In healthy individuals the body responds to decreases in cardiac output by initiating the renin-angiotensin-aldosterone system to promote fluid retention, and also by activating the sympathetic nervous system to cause peripheral vasoconstriction. Under normal circumstances this counteracts the imbalance in stroke volume, restoring cardiac output to normal levels.

In patients with heart failure the increase in blood volume, together with the heightened peripheral resistance and elevated levels of circulating catecholamines, causes an increased load on the already weakened ventricles with each contraction, and the stroke volume does not return to normal levels. Repeated cycles of this process further weaken the ventricle walls, prompting ventricular hypertrophy and a decreased force of contraction (Figure 10).

Surgical intervention is available for patients with heart failure – current options include the implantation of a left ventricular assist device – but these are invasive and are not suitable for all patients. Pharmacological intervention is common and there are a range of drugs available to target the different stages of the heart failure mechanism. However, none of these current therapeutic options are able to reverse the pathology of heart failure and act only to slow the progression of the disease.

Heart Failure

Heart failure, also known as congestive heart failure or CHF, is an inability of the heart to pump sufficient blood around the body. Heart failure typically occurs secondary to an existing pathology that alters cardiac function. Examples of syndromes that can precede heart failure include myocardial infarction, arrhythmia or infection. These can also cause dilated cardiomyopathy, a condition which accounts for around one third of all cases of heart failure.

The pathogenesis of heart failure is cyclical and progressive; endogenous mechanisms, which are activated during heart failure in an attempt to counteract the symptoms, actually worsen cardiac function. Cardiac dysfunction, either systolic or diastolic, triggers a decrease in stroke volume and a resultant decrease in cardiac output. In healthy individuals the body responds to decreases in cardiac output by initiating the renin-angiotensin-aldosterone system to promote fluid retention, and also by activating the sympathetic nervous system to cause peripheral vasoconstriction. Under normal circumstances this counteracts the imbalance in stroke volume, restoring cardiac output to normal levels.

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Figure 10 | The mechanism of heart failure

Abbreviations: ACE – angiotensin-converting enzyme; ARBs – angiotensin II receptor blockers; AVP – arginine vasopressin; RAAS – renin-angiotensin-aldosterone system.
The two most common pharmacological therapies for heart failure are to increase intracellular calcium concentration within myocytes by activating second messenger signaling pathways, and also to block or counteract the neurohormonal compensatory reflexes through the inhibition of the RAAS. Pharmacological agents which trigger a rise in intracellular calcium include the positive inotrope digoxin (Cat. No. 4583), an Na+/K+ ATPase blocker; β adrenergic receptor agonists; and phosphodiesterase inhibitors.

However, indirectly targeting the signaling pathways involved in cardiac contractility also induces mechanism-related adverse effects. More recent therapy using small molecule drugs – such as the cardiac myosin activator, omecamtiv mescaril – looks to be a promising and more effective strategy for improving contractility in patients with heart failure.

Blocking the neurohormonal reflexes in the failing heart is a more efficacious therapeutic strategy for heart failure compared to increasing contractility, and is achieved using ACE inhibitors such as perindopril (Cat. No. 4302), or ARBs including valsartan (Cat. No. 4216).

The administration of diuretics reduces symptoms associated with heart failure, such as peripheral edema, but it does not reverse or halt the disease pathology. Examples of diuretics used in the treatment of heart failure include furosemide (Cat. No. 3109), an NKCC co-transporter inhibitor, and spironolactone (Cat. No. 2968), an aldosterone receptor antagonist.

### Box 8: Heart Failure Key Products

A full list of targets and related products are listed on pages 20-30

<table>
<thead>
<tr>
<th>Compound</th>
<th>Description</th>
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<tr>
<td>Eplerenone</td>
<td>Selective mineralocorticoid receptor antagonist</td>
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<tr>
<td>SIN-1 (0756)</td>
<td>Water-soluble NO donor</td>
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<tr>
<td>Ouabain (1076)</td>
<td>Na’/K’ ATPase inhibitor</td>
</tr>
<tr>
<td>AS 605240 (3578)</td>
<td>Potent and selective PI 3-kinase γ (PI3Kγ) inhibitor</td>
</tr>
<tr>
<td>Losartan (3798)</td>
<td>Selective, nonpeptide AT1 antagonist</td>
</tr>
</tbody>
</table>

Vasodilators such as nicorandil (Cat. No. 2147), SIN-1 (Cat. No. 0756) and hydralazine are also used in the treatment of heart failure since they induce peripheral vasodilation, thereby reducing ventricular afterload.

In addition to the existing compounds, future therapeutic targets include the collagenase enzymes MMP-2 and MMP-9. The expression of these metalloproteinases is increased in heart failure whilst the expression of their endogenous inhibitors, tissue inhibitors of metalloproteinases (TIMPs), has been shown to be downregulated in the same tissue. In support of this, experimental inhibition of MMP-9 reduces ventricular dilatation in a model of heart failure.

A further therapeutic target in heart failure, central to disease progression, is the activity of G protein-coupled receptor kinases (GRKs), in particular the cardiomyocyte-expressed GRK2. GRK2 activation during heart failure leads to the desensitization of β adrenergic receptors (βARs) and therefore reduces contractility and depresses cardiac function. Circulating levels of GRK2 and GRK5 are upregulated in the early stages of heart failure, whilst both cardiac isoforms of βARs – β1ARs and β2ARs – have been shown to be downregulated, or non-functional. Cardiomyocyte-specific overexpression of GRK2 triggered βAR uncoupling and led to a reduction in contractility, whereas the expression of an inactive form of GRK2 in either cardiac or adrenal tissue caused an increase in contractility in response to adrenergic stimulation. Therefore, cardiomyocyte- or adrenal-specific inhibition of GRK2 may represent a new therapeutic target for heart failure.
# List of Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACE</td>
<td>Angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ACh</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>ANT</td>
<td>Adenine nucleotide translocase</td>
</tr>
<tr>
<td>ARB</td>
<td>Angiotensin II receptor blocker</td>
</tr>
<tr>
<td>AV</td>
<td>Atrioventricular</td>
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<tr>
<td>AVP</td>
<td>Arginine Vasopressin</td>
</tr>
<tr>
<td>βAR</td>
<td>β-androgen receptor</td>
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<tr>
<td>BP</td>
<td>Blood pressure</td>
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<tr>
<td>CaM</td>
<td>Calmodulin</td>
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<tr>
<td>cAMP</td>
<td>Cyclic adenine monophosphate</td>
</tr>
<tr>
<td>cGMP</td>
<td>Cyclic guanosine monophosphate</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>CK</td>
<td>Creatine kinase</td>
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<tr>
<td>COX</td>
<td>Cyclooxygenase</td>
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<tr>
<td>cPLA2</td>
<td>Cytosolic phospholipase A2</td>
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<tr>
<td>CPT1</td>
<td>Carnitine palmitoyltransferase 1</td>
</tr>
<tr>
<td>cTnI</td>
<td>Cardiac troponin I</td>
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<tr>
<td>cTnT</td>
<td>Cardiac troponin T</td>
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<td>DAG</td>
<td>Diacylglycerol</td>
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<tr>
<td>DNA-PK</td>
<td>DNA protein kinase</td>
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<tr>
<td>ECG/EKG</td>
<td>Electrocardiography/Elektrokardiogramm</td>
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<tr>
<td>eNOS</td>
<td>Endothelial nitric oxide synthase</td>
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<tr>
<td>ERP</td>
<td>Effective refractory period</td>
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<tr>
<td>ET</td>
<td>Endothelin</td>
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<td>FcRγ</td>
<td>Fc receptor γ-chain</td>
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<td>GPVI</td>
<td>Glycoprotein VI</td>
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<td>GRK</td>
<td>G protein-coupled receptor kinase</td>
</tr>
<tr>
<td>GSK-3β</td>
<td>Glycogen synthase kinase-3β</td>
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<tr>
<td>GTP</td>
<td>Guanosine triphosphate</td>
</tr>
<tr>
<td>hERG</td>
<td>Human ether-à-go-go-related gene</td>
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<tr>
<td>HPETE</td>
<td>Hydroperoxyeicosatetraenoic acid</td>
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<tr>
<td>IGF-1</td>
<td>Insulin-like growth factor-1</td>
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<td>IL</td>
<td>Interleukin</td>
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<td>InsP3R</td>
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<td>IPR</td>
<td>I prostanoid receptor</td>
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<tr>
<td>ITAM</td>
<td>Immunoreceptor tyrosine-based activation motif</td>
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<tr>
<td>KᵥATP</td>
<td>ATP-sensitive potassium channel</td>
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<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>Kᵅᵣ</td>
<td>Inward rectifying potassium channel</td>
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<td>Kᵥ</td>
<td>Voltage-gated potassium channel</td>
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<td>LOX</td>
<td>Lipoxigenase</td>
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<td>LQTS</td>
<td>Long QT syndrome</td>
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<td>MCU</td>
<td>Mitochondrial calcium uniporter</td>
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<td>MLCK</td>
<td>Myosin light chain kinase</td>
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<tr>
<td>MMP</td>
<td>Matrix metalloproteinase</td>
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<tr>
<td>MPTP</td>
<td>Mitochondrial permeability transition pore</td>
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<tr>
<td>mTOR</td>
<td>Mammalian target of rapamycin</td>
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<tr>
<td>NA</td>
<td>Noradrenalin</td>
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<tr>
<td>NCX</td>
<td>Na⁺/Ca²⁺ exchanger</td>
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<tr>
<td>NHE</td>
<td>Na⁺/H⁺ exchanger</td>
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<tr>
<td>NKCC</td>
<td>Na⁺/K⁺/2Cl⁻ cotransporter</td>
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<tr>
<td>NO</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>NTS</td>
<td>Nucleus tractus solitarius</td>
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<td>ox-LDL</td>
<td>Oxidized low-density lipoprotein</td>
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<td>PAR</td>
<td>Protease-activated receptor</td>
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<td>PBR</td>
<td>Peripheral benzodiazepine receptor</td>
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<tr>
<td>PDGF</td>
<td>Platelet-derived growth factor</td>
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<td>PGH₂</td>
<td>Prostaglandin H₂</td>
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<td>PGI₂</td>
<td>Prostacyclin</td>
</tr>
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<td>Protein kinase G</td>
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</tr>
<tr>
<td>PMN</td>
<td>Polymorphonuclear leukocyte</td>
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<tr>
<td>RAAS</td>
<td>Renin-angiotensin-aldosterone system</td>
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<tr>
<td>ROS</td>
<td>Reactive oxygen species</td>
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<tr>
<td>SA</td>
<td>Sinoatrial</td>
</tr>
<tr>
<td>SERCA</td>
<td>Sarco/endoplasmic reticulum Ca²⁺-ATPase</td>
</tr>
<tr>
<td>sGc</td>
<td>Soluble guanylyl cyclase</td>
</tr>
<tr>
<td>TGF-BRI</td>
<td>Transforming growth factor-B type I receptor</td>
</tr>
<tr>
<td>TIMP</td>
<td>Tissue inhibitor of metalloproteinase</td>
</tr>
<tr>
<td>IPA</td>
<td>Tissue plasminogen activator</td>
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<td>TXA₂</td>
<td>Thromboxane A₂</td>
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<td>uPA</td>
<td>Urokinase plasminogen activator</td>
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<td>VDAC</td>
<td>Voltage-dependent anion channel</td>
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<tr>
<td>vWF</td>
<td>von Willebrand factor</td>
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</table>
Related literature from Tocris that you may be interested in:

**Regulation of Vascular Reactivity by G-protein-coupled Receptors**
J. Maguire and A. Davenport, University of Cambridge
Cardiovascular disease remains one of the major causes of morbidity and mortality in the Western world and therefore this therapeutic area continues to be of great interest to researchers. This poster highlights the key GPCRs regulating vascular reactivity.

**Apoptosis – Regulation and Intervention**
D. Crighton *et al*. Beatson Institute for Cancer Research
Apoptosis is an orchestrated cell death mechanism that brings about removal of cells without inflammation and stress. The key signaling pathways associated with the regulation of apoptosis are summarized in this poster.

**7-TM Receptor Signaling**
T. Kenakin, GlaxoSmithKline Research and Development
R. Lefkowitz and J. Violin, Duke University Medical Center
M. Bouvier and G. Oligny-Longpré, Université de Montréal
Seven-transmembrane (7-TM) receptors are now recognized as complex processors of information that can bind to molecules and cytosolic interactants on the cell membrane. The 7-TM poster highlights the multiple behaviors of 7-TMs including G-protein-dependent and -independent signaling as well as the concept of collateral efficacy.

**G-protein-coupled Receptors & Signaling Networks**
M. Marinissen, Universidad Autonoma de Madrid
J. Gutkind, National Institutes of Health
This poster reviews G-protein-coupled receptors (GPCRs), their physiological roles and the cellular responses they mediate. The network of intracellular signaling pathways involved in GPCR function are also explored.

**P2X and P2Y Receptors**
K. Jacobson, National Institutes of Health
P2X and P2Y receptors are widely distributed in the body. In particular, P2X$_1$, P2Y$_1$, and P2Y$_12$ have been isolated in platelets. This review covers the subtypes and structures of P2 receptor families and the pharmacological probes used to study them.

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## Cardiovascular Research Compounds from Tocris

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<th>Class</th>
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<th>Unit Size</th>
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### Cardiovascular Research Compounds – continued

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<td>2098</td>
<td>Apoptosis Activator 2</td>
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<td>Gambogic acid</td>
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### Cardiovascular Research Compounds – continued

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<td>KF 38789 Selective inhibitor of P-selectin-mediated cell adhesion</td>
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<td>AY 9944 Inhibitor of hedgehog (Hh) signaling; inhibits Δ 7-dehydrocholesterol reductase</td>
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<td>Cyclic GMP</td>
<td>1089</td>
<td>B-Bromo-cGMP cGMP analog; activates PKG</td>
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<td>SSR 69071</td>
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<td>Endothelin 1 (human, porcine)</td>
<td>Potent vasoconstrictor peptide</td>
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<td>Sarafotoxin S6a</td>
<td>Endothelin receptor agonist</td>
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<td><strong>Fatty Acid Oxidation</strong></td>
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<td>(a)-Propionylcarnitine</td>
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<td></td>
<td>1484</td>
<td>Oleylthanolamide</td>
<td>GPR55 agonist; also PPARα agonist</td>
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<td></td>
<td>50mg</td>
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<td></td>
<td>3118</td>
<td>Ranolazine</td>
<td>Antianginal; activates pyruvate dehydrogenase</td>
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<td>GRK2i</td>
<td>GRK2 inhibitory polypeptide; Gβγ antagonist</td>
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<td>Picropodophyllotoxin</td>
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<td>BAY-X 1005</td>
<td>Orally active 5-lipoxygenase activating protein (FLAP) inhibitor</td>
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<td>Inhibitor of 5-lipoxygenase-activating protein (FLAP)</td>
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<td></td>
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<td>PD 146176</td>
<td>Selective 15-lipoxygenase inhibitor</td>
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<td>5-, 12-, 15-Lipoxygenase inhibitor</td>
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### Matrix Metalloproteinases

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<td>Marimastat</td>
<td>Broad spectrum MMP inhibitor</td>
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### Mitochondrial Calcium Uniporter

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<td>3603</td>
<td>Kaempferol</td>
<td>Mitochondrial Ca(^{2+}) uniporter (MCU) activator; proapoptotic</td>
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<td>MCU inhibitor; also inhibits Na(^+)/Ca(^{2+}) exchange</td>
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<td></td>
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### Mitochondrial Permeability Transition Pore

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<td>Cyclosporin A</td>
<td>Calcineurin inhibitor</td>
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<td>Oligomycin A</td>
<td>Inhibitor of mitochondrial ATPase</td>
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<td>2906</td>
<td>TRO 19622</td>
<td>Binds voltage-dependent anion channel (VDAC)</td>
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### Muscarinic Receptors (mACHRs)

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<td>AF-DX 116</td>
<td>Selective M(_2) antagonist</td>
<td>10 mg</td>
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<td>4-DAMP</td>
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<td>Potent, selective M(_4) antagonist</td>
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### Na\(^+\)/Ca\(^{2+}\) Exchanger

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<td>Bepridil</td>
<td>Nonselective calcium channel blocker</td>
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<td>CGP 37157</td>
<td>Antagonist of mitochondrial Na(^+)/Ca(^{2+}) exchange</td>
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<td></td>
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<td>50 mg</td>
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<td>Na(^+)/Ca(^{2+}) exchange inhibitor (reverse mode)</td>
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### Na\(^+\)/H\(^+\) Exchanger

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### Na\(^+\)/K\(^+\) ATPase

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<th>Cat. No.</th>
<th>Product Name</th>
<th>Primary Action</th>
<th>Unit Size</th>
<th>Euro</th>
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<tbody>
<tr>
<td>4583</td>
<td>Digoxin</td>
<td>Na(^+)/K(^+) ATPase inhibitor</td>
<td>50 mg</td>
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<tr>
<td>1076</td>
<td>Ouabain</td>
<td>Na(^+)/K(^+) ATPase inhibitor</td>
<td>100 mg</td>
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### Natriuretic Peptide Receptors

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<tr>
<td>1912</td>
<td>Atrial natriuretic factor (1-28) (rat)</td>
<td>Endogenous peptide regulating blood pressure</td>
<td>1 mg</td>
<td>285</td>
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<tr>
<td>1906</td>
<td>Atrial natriuretic factor (1-28) (human, porcine)</td>
<td>Endogenous peptide regulating blood pressure</td>
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<td>3520</td>
<td>C-type natriuretic factor peptide (1-22) (human, rat, swine)</td>
<td>Endogenous peptide agonist at NPR2</td>
<td>500 μg</td>
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<td>Class</td>
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<td><strong>Nitric Oxide</strong></td>
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<td><strong>Donors</strong></td>
<td>2147</td>
<td>Nicorandil</td>
<td>K_{a6} (K_{ATP}) channel opener and NO donor</td>
<td>50 mg</td>
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<td>0756</td>
<td>SIN-1</td>
<td>Water-soluble NO donor</td>
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<td></td>
<td>0603</td>
<td>SNOG</td>
<td>NO carrier, breaks down to release NO</td>
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<td></td>
<td>1135</td>
<td>Spermine NONOate</td>
<td>Slow NO releasing agent</td>
<td>10 mg</td>
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<td><strong>Inhibitors</strong></td>
<td>0546</td>
<td>L-NIO</td>
<td>Potent eNOS inhibitor</td>
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<tr>
<td><strong>Other</strong></td>
<td>0598</td>
<td>SNAP</td>
<td>A stable analog of endogenous S-nitroso compounds</td>
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<td><strong>Substrates</strong></td>
<td>0722</td>
<td>N'-Acetyl-N-acetoxy-4-chlorobenzenesulfonamide</td>
<td>Nitroxyl precursor</td>
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<td>0663</td>
<td>L-Arginine</td>
<td>Endogenous substrate for NOS</td>
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<td><strong>NKCC Cotransporter</strong></td>
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<td><strong>Inhibitors</strong></td>
<td>3108</td>
<td>Bumetanide</td>
<td>Na^{+}/2Cl^{-}/K^{+} (NKCC) cotransporter inhibitor</td>
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<td>3109</td>
<td>Furosemide</td>
<td>Na^{+}/2Cl^{-}/K^{+} (NKCC) cotransporter inhibitor; also antagonizes GABA_{A}</td>
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<td><strong>Oxidative Phosphorylation</strong></td>
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<td><strong>Inhibitors</strong></td>
<td>0452</td>
<td>CCCP</td>
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<td>3612</td>
<td>Enterostatin</td>
<td>Binds to β-subunit of F_{1}-ATPase; anorexigenic peptide</td>
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<td>0453</td>
<td>FCCP</td>
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<td>3616</td>
<td>Rotenone</td>
<td>Inhibits complex I of the mitochondrial electron transport chain</td>
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<td><strong>Inhibitors</strong></td>
<td>4274</td>
<td>AP 24534</td>
<td>Potent multi-kinase and pan-BCR-ABL inhibitor</td>
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<td>1222</td>
<td>DMPQ</td>
<td>Potent, selective inhibitor of PDGFRβ</td>
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<td>3785</td>
<td>PD 166285</td>
<td>Potent Src inhibitor; also inhibits FGFR1, PDGFRβ and Wee1</td>
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<td>3304</td>
<td>SU 16f</td>
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<td>3335</td>
<td>SU 6668</td>
<td>PDGFR, VEGFR and FGFR inhibitor</td>
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<td>3768</td>
<td>Sunitinib</td>
<td>Potent VEGFR, PDGFRβ and KIT inhibitor</td>
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<td><strong>Inhibitors</strong></td>
<td>0691</td>
<td>Dipyridamole</td>
<td>PDE inhibitor; coronary vasodilator</td>
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<td>3053</td>
<td>Mesopram</td>
<td>Orally active PDE4 inhibitor</td>
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<td>1349</td>
<td>(R)-(-)-Rolipram</td>
<td>PDE4 inhibitor; more active enantiomer of rolipram (Cat. No. 0905)</td>
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<td>Sildenafil</td>
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<td>1676</td>
<td>T 0156</td>
<td>Highly potent, selective PDE5 inhibitor</td>
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<td>Zardaverine</td>
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# Cardiovascular Research Compounds – continued

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<td>D609</td>
<td>Selective PC-PLC inhibitor</td>
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<td>m-3M3FBS</td>
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<td>740 Y-P</td>
<td>Cell-permeable PI 3-kinase activator</td>
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<td><strong>Inhibitors</strong></td>
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<td>AS 605240</td>
<td>Potent and selective PI 3-kinase γ (PI3Kγ) inhibitor</td>
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<td>BAG 956</td>
<td>Dual PI 3-kinase and PDK1 inhibitor</td>
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<td>Cromakalim</td>
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<td>Levcromakalim</td>
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<td>(Cat. No. 1377)</td>
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<td>Minoxidil</td>
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<td>Kᵥ₇.2 and Kᵥ₇.4 channel opener</td>
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<td>Nicorandil</td>
<td>Kᵥ₆ (K₆ATP) channel opener and NO donor</td>
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<td>NS 3623</td>
<td>Kᵥ₁₁.1 (hERG) channel activator; antiarrhythmic</td>
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<td>P1075</td>
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<td><strong>Blockers</strong></td>
<td>2533</td>
<td>DPO-1</td>
<td>Blocker of Kᵥ₁.5 channels; prevents atrial arrhythmia</td>
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<td>Kᵥ₁₁.1 (hERG) channel blocker; class III antiarrhythmic agent</td>
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<td>Gilbenclamide</td>
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<td>Potent and selective Iₖᵥ₆ blocker</td>
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<td>Nateglinide</td>
<td>Kᵥ₆ (K₆ATP) blocker; displays high affinity for SUR1/Kᵥ₆.2 channels</td>
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<td>Terfenadine</td>
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<td>5-Azacytidine</td>
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<td>XAV 939</td>
<td>Inhibits Wnt signaling; promotes cardiomyogenesis</td>
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<td>Zebularine</td>
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### TGF-β Receptors

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Prices are correct for 2016. For a full product list please visit www.tocris.com
Further Reading

Please refer to the list of recommended papers for more information.

Hypertension


Atherosclerosis


Thrombosis and Hemostasis


Myocardial Infarction


Arrhythmia

Grant (2009) Cardiac ion channels. *Circ.Arrhythm.Electrophysiol.* **2** 185


Myocardial I/R Injury


Heart Failure

