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Cardiovascular Research

Product Guide | Edition 2

Wild Garlic
Allium ursinum
A source of Allicin

Contents by Research Area:

- Hypertension
- Thrombosis and Hemostasis
- Atherosclerosis
- Myocardial Infarction
- Ischemia/Reperfusion Injury
- Arrhythmias
- Heart Failure

Cardiovascular Research

Contents

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

Hypertension

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.

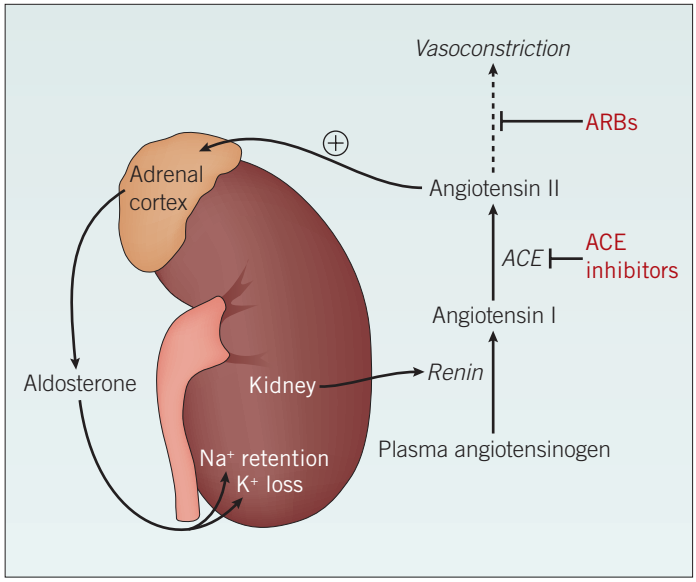
In hypertension, increased arterial pressure is detected by specialized mechanoreceptors called baroreceptors, present in the aortic arch and the carotid sinuses. Baroreceptors are innervated by nerves that synapse in the nucleus tractus solitarius (NTS), an area within the medulla oblongata that regulates 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 G_q and the downstream IP_3 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; α_1 adrenergic receptors stimulate the release of noradrenaline from sympathetic nerve terminals, whilst α_2 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 (AT_1), induces vasoconstriction directly through the potentiation of noradrenaline release from sympathetic nerve terminals within blood vessel walls.

The downstream effects of AT_1 receptor activation are counterbalanced in part by the activation of AT_2 receptors. Due to the potent vasoconstrictor properties of AT_1 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

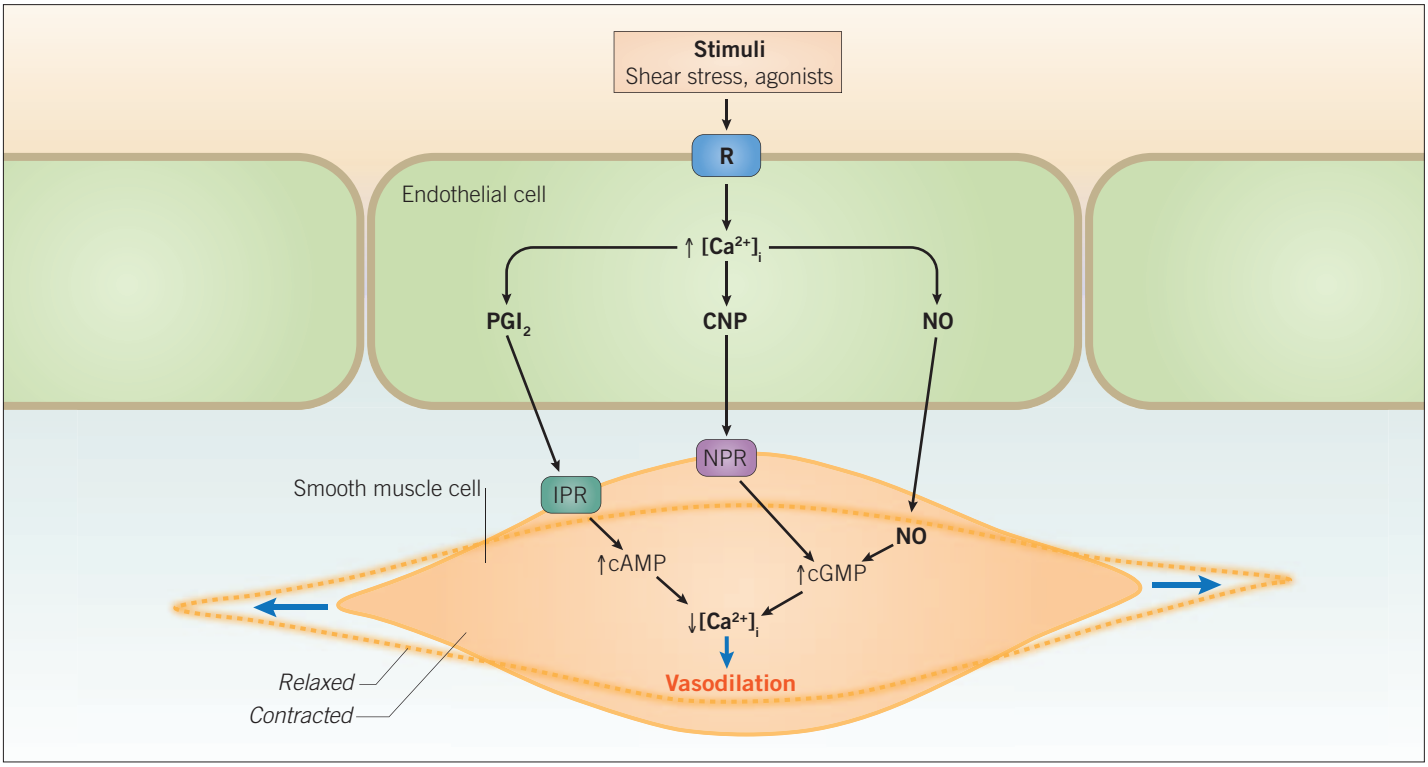
Aldosterone receptor antagonists including spironolactone (Cat. No. 2968) and eplerenone (Cat. No. 2397) also exert antihypertensive effects due to their inhibitory actions on water reabsorption. The resultant reduction in circulating blood volume in turn lowers blood pressure. Other diuretics such as 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 (PGI_2) (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 (ET_A) receptors and endothelin B (ET_B) receptors. ET_B receptors are highly expressed in the endothelium whereas ET_A receptors are absent, yet both receptor subtypes are present on the underlying vascular smooth muscle cells. Activation of ET_A receptors by ET-1 leads to vasoconstriction whilst the effects of ET_B receptor activation are cell type-specific; endothelial cell ET_B receptor (ET_{B1}) activation leads to vasodilation through the production of NO and PGI_2, yet smooth muscle cell ET_B receptor (ET_{B2}) 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 Ca^{2+}-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

Figure 2 | Nitric oxide-mediated vasodilation

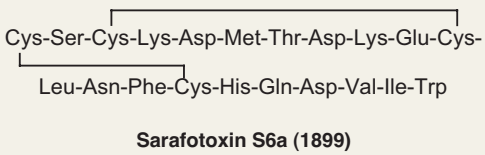


Endothelial cell surface receptor activation by vasodilatory stimuli triggers a rise in intracellular Ca^{2+} ($[Ca^{2+}]_i$). Downstream intracellular signaling pathways lead to the generation of vasodilatory mediators including PGI_2, CNP and NO. By binding to their respective receptors on the underlying vascular smooth muscle cell membranes, these mediators prompt a decrease in intracellular calcium within vascular smooth muscle cells through the actions of second messengers including cAMP and cGMP. Decreased intracellular calcium triggers vascular smooth muscle cell relaxation, and subsequent vasodilation. Abbreviations: cAMP – cyclic adenosine monophosphate; cGMP – cyclic guanosine monophosphate; CNP – C natriuretic peptide; IPR – I prostanoid receptor; NO – nitric oxide; NPR – natriuretic peptide receptor; PGI_2 – prostacyclin; R – receptor.

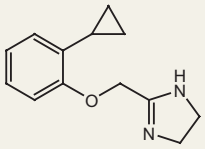
Hypertension – continued

Box 1: Vasoconstrictor Key Products

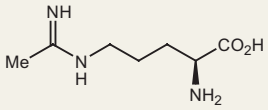
A full list of targets and related products are listed on pages 20-30



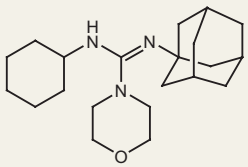
Sarafotoxin S6a (1899)
Potent endothelin receptor agonist; vasoconstrictor



Cirazoline (0888)
Selective α_1 agonist



L-NIO (0546)
Potent eNOS inhibitor



PNU 37883 (2095)
Vascular $K_{ir}6$ (K_{ATP}) channel blocker

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).

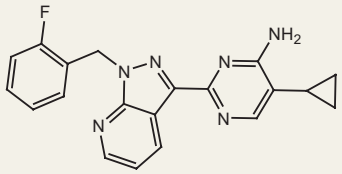
Other vasodilators secreted by endothelial cells that reduce intracellular calcium within underlying smooth muscle cells include prostacyclin, which acts on I prostanoid (IP) receptors, and C-natriuretic peptide (CNP) through its actions on natriuretic peptide receptors (NPR). Compounds that target these 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 ($K_{ir}6$; K_{ATP}), 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 $K_{ir}6$ channel activating properties further increases its potency as a vasodilator.

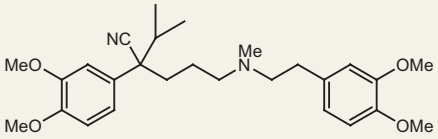
Despite the considerable advances in identifying relevant therapeutic targets involved in hypertension, the side effect profiles resulting from the ubiquitous expression of many of these targets limits their long term use. Rather than directly lowering circulating blood pressure, future perspectives 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.

Box 2: Vasodilator Key Products

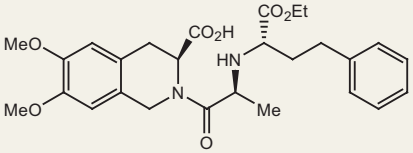
A full list of targets and related products are listed on pages 20-30



BAY 41-2272 (4430)
Soluble guanylyl cyclase (sGC) activator



Verapamil (0654)
Ca^{2+} channel blocker (L-type)



Moexepril (2691)
Angiotensin-converting enzyme (ACE) inhibitor

Thrombosis and Hemostasis

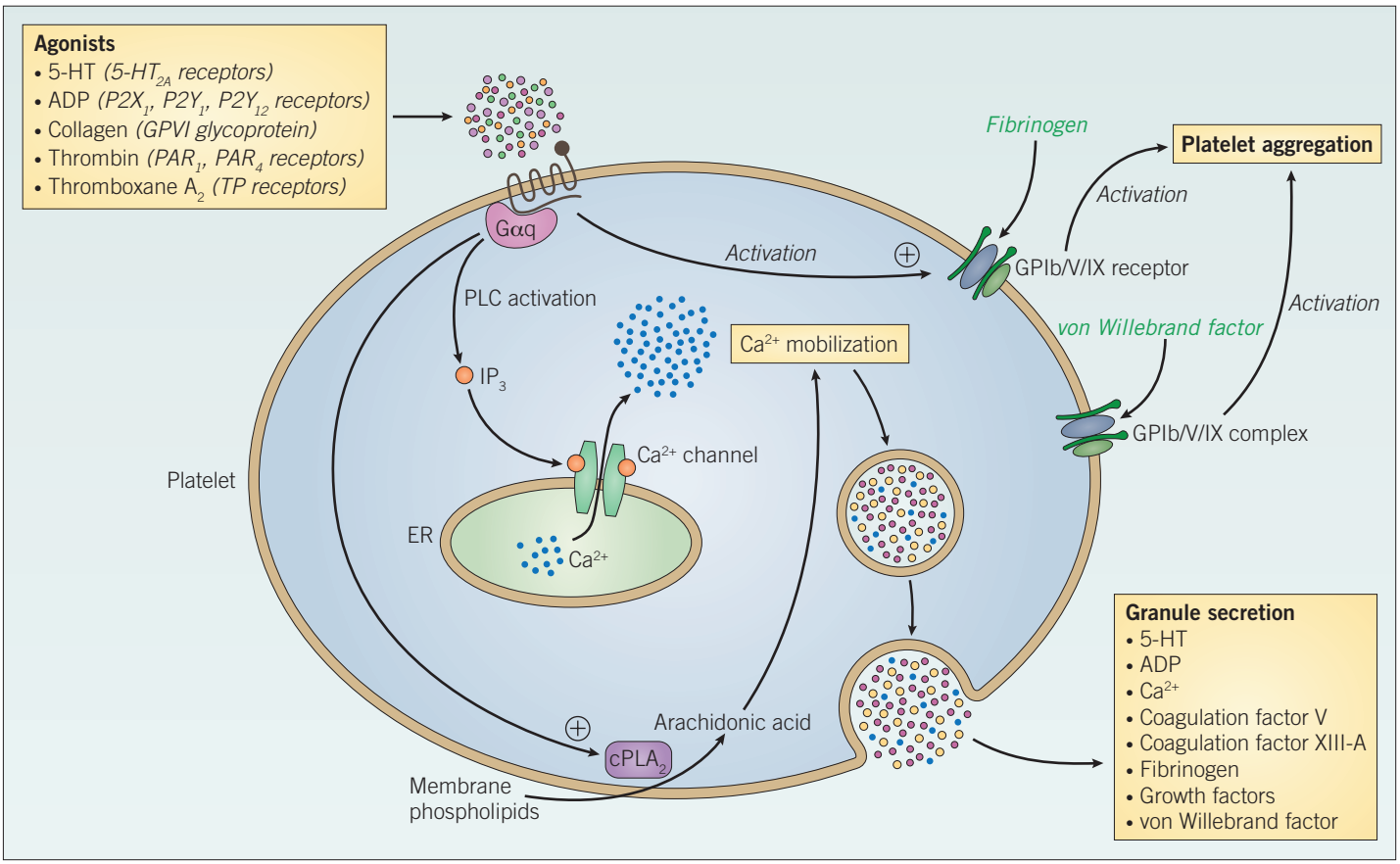
Thrombosis and Hemostasis

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 $P2X_1$, $P2Y_1$ and $P2Y_{12}$; the 5-HT receptor $5\text{-}HT_{2A}$; the thromboxane A_2 (TXA_2) receptor TP; and the thrombin receptors (protease-activated receptors) PAR_1 and

Figure 3 | Platelet signaling and activation



Agonist stimulation of platelets triggers activation of glycoprotein Ib/V/IX; generation of arachidonic acid from membrane phospholipids by the actions of cytosolic phospholipase A_2 ($cPLA_2$); 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.

Thrombosis and Hemostasis – continued

PAR_4. 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_2), which is cleaved by phospholipase C to form inositol triphosphate (IP_3) and diacylglycerol (DAG). IP_3 receptor (InsP3R) 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).

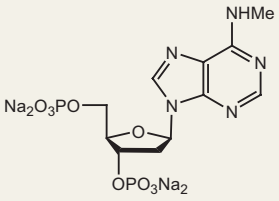
The mobilization of calcium causes the exocytosis of cytoplasmic granules and the activation of platelet aggregation-inducing glycoproteins such as GPIIb/IIIa. GPIIb/IIIa functions as a cell surface receptor for fibrinogen and promotes the activation of platelets. The pivotal involvement of GPIIb/IIIa 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 $P2Y_{12}$ – 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 GPIb/V/IX-mediated phosphorylation of intracellular signaling proteins, including $pp60^{Src}$, PLC_γ and the Fc receptor γ-chain (FcRγ), which initiates and augments the adhesion of platelets with the extracellular matrix and also with neighboring platelets. Phosphorylation of FcRγ by GPIb/V/IX induces FcRγ-GPIb/V/IX functional coupling; this promotes platelet activation through immunoreceptor tyrosine-based activation motif (ITAM)-driven signaling.

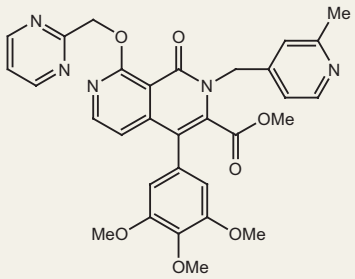
Agonist stimulation of platelets also initiates the production of arachidonic acid (Cat. No. 2756) from membrane phospholipids, a reaction which is catalyzed by cytosolic phospholipase A_2 ($cPLA_2$). Arachidonic acid can be utilized by both cyclooxygenases (COX) to form prostaglandin H_2 (PGH_2), and also by lipoxygenases (LOX) to form the lipid mediator hydroperoxyeicosatetraenoic acid (HPETE). PGH_2 is further metabolized to form prothrombotic eicosanoids including TXA_2. Inhibition of the PGH_2 synthesis pathway using COX inhibitors such as aspirin (Cat. No. 4092), celecoxib (Cat. No. 3786) and diclofenac (Cat. No. 4454), and the TXA_2 synthase inhibitor, dipyridamole (Cat. No. 0691), is an effective therapeutic strategy for preventing thrombosis. PLA_2 inhibitors including $AACOCF_3$ (Cat. No. 1462) also exhibit antithrombotic effects by inhibiting the activity of the arachidonic acid pathway.

Box 3: Thrombosis and Hemostasis Key Products

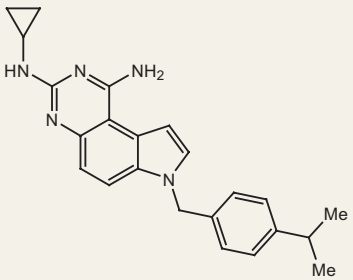
A full list of targets and related products are listed on pages 20-30



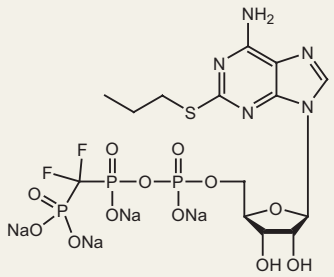
MRS 2179 (0900)
Selective $P2Y_1$ antagonist



T 0156 (1676)
Highly potent, selective PDE5 inhibitor



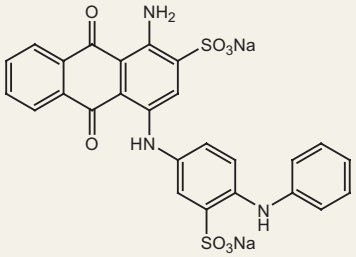
SCH 79797 (1592)
Potent, selective non-peptide PAR_1 antagonist



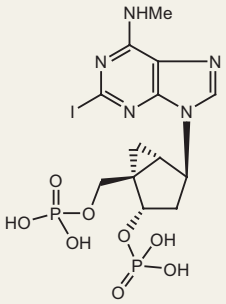
AR-C 66096 (3321)
Potent and selective $P2Y_{12}$ antagonist

Thr-Phe-Leu-Leu-Arg-NH_2

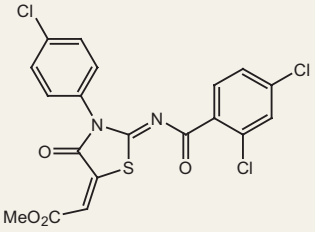
TFLLR-NH_2 (1464)
PAR_1-activating peptide



PSB 0739 (3983)
Highly potent $P2Y_{12}$ receptor antagonist



MRS 2500 (2159)
Extremely potent and selective $P2Y_1$ antagonist



FR 171113 (3643)
PAR_1 antagonist

Atherosclerosis

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).

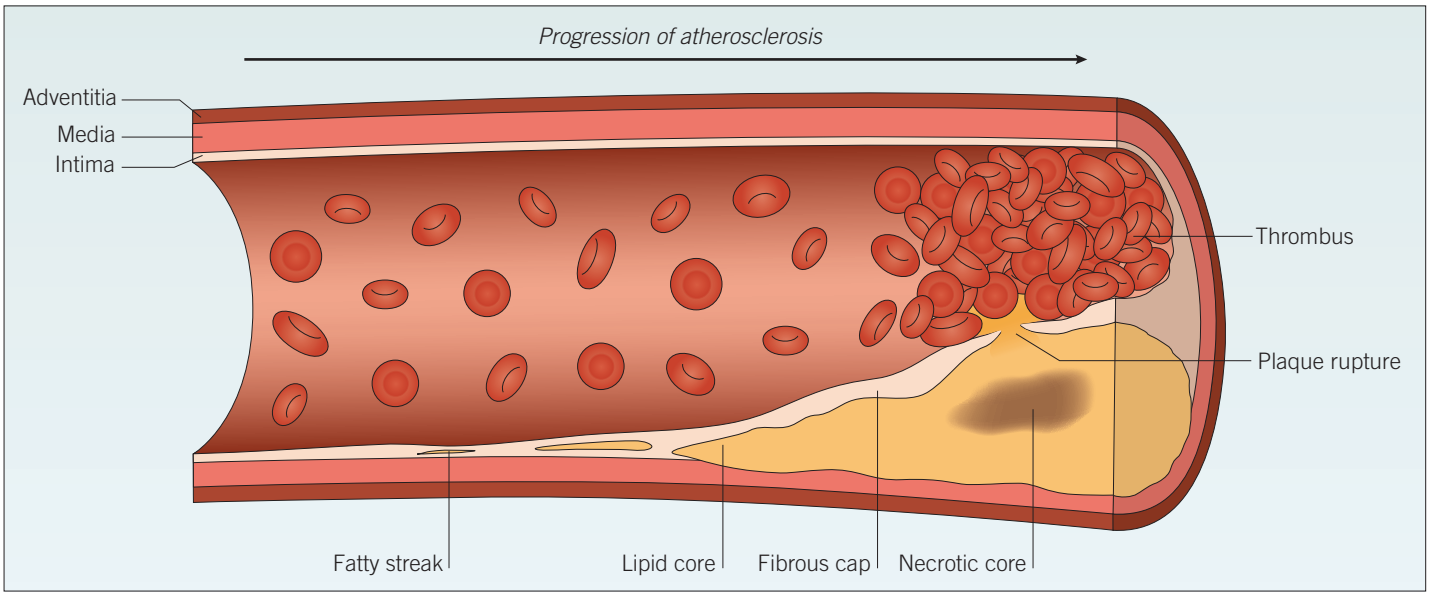
The exact cause of atherosclerosis remains unknown, but the initial process – termed 'atherogenesis' – involves the transmigration of monocytes/macrophages across the endothelium into the intima, where they scavenge oxidized lipid (ox-LDL), forming lipid-laden 'foam cells'. Expression of adhesion molecules 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

Figure 4 | Atherosclerosis

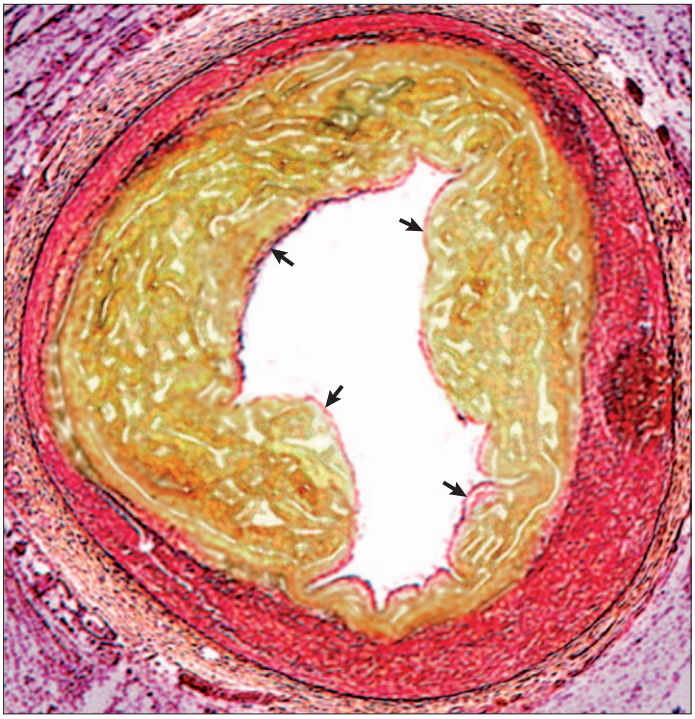


The development of atherosclerosis within a blood vessel wall starts as a fatty streak, composed of a small cluster of lipid-laden macrophages, which progresses over time to form a lipid pool within the vessel wall. Cell debris from apoptotic foam cells within the lipid pool forms a necrotic core. The 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.

Atherosclerosis – continued

present during atherosclerosis. The expression of a number of pro-atherogenic cytokines, including interleukin (IL)-1 and IL-6, are known to be upregulated in atherosclerotic plaques, and therefore targeting the receptors of these cytokines may hinder the progression of atherosclerosis. Whilst activation of the immune response within an atherosclerotic plaque may be detrimental, driving the progression and eventual rupture of a plaque, it may equally be beneficial in resolving the inflammation and clearing necrotic foam cells from the core of the plaque. Therefore, targeting the immune response in atherosclerosis may be a 'double-edged sword'.

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.

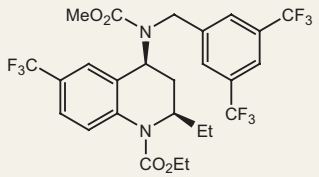
Current therapeutics in atherosclerosis predominantly aim to reduce blood cholesterol, thereby limiting the expansion of an atherosclerotic plaque. The gold standard lipid-lowering drugs are the statins, but other compounds including torcetrapib (Cat. No. 4184), probucol (Cat. No. 2775) and CI 976 (Cat. No. 2227) also exhibit antihypercholesterolemic activity, though their side effect profiles limit their use in the clinic.

Aside from lipid-lowering, a further potential avenue in the treatment of atherosclerosis is the coagulation cascade since it is the formation of an occlusive thrombus, not plaque rupture *per se*, which triggers the pathologies associated with atherosclerosis. Potential targets within the coagulation cascade include thrombin, urokinase plasminogen activator (uPA) and tissue plasminogen activator (tPA). Other mediators involved in platelet activation are also potential therapeutic targets in the prevention and treatment of atherothrombosis; this topic is discussed in greater detail in the 'Thrombosis and Hemostasis' section, page 6.

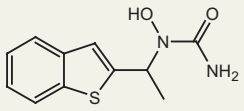
Additional targets with therapeutic potential in atherosclerosis include phospholipases and urotensin II, since the presence of both may trigger foam cell formation, furthering the progression of atherosclerosis.

Box 4: Atherosclerosis Key Products

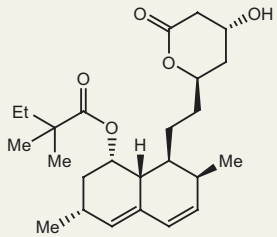
A full list of targets and related products are listed on pages 20-30



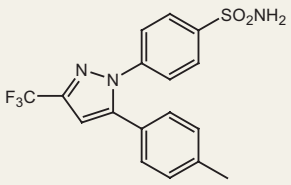
Torcetrapib (4184)
Inhibitor of cholesteryl ester transfer protein (CETP)



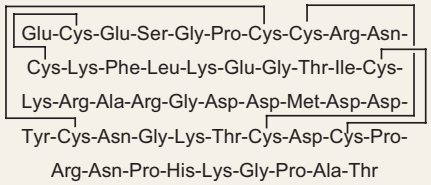
Zileuton (3308)
Orally active 5-LOX inhibitor



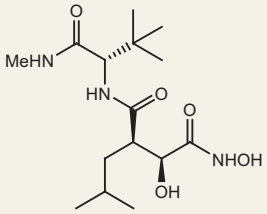
Simvastatin (1965)
HMG-CoA reductase inhibitor



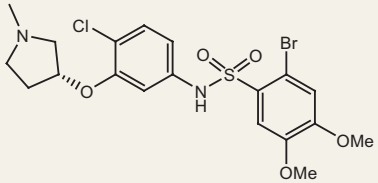
Celecoxib (3786)
Selective COX-2 inhibitor



Echistatin α1 isoform (3202)
Potent, irreversible $\alpha_v\beta_3$ integrin antagonist



Marimastat (2631)
Broad spectrum MMP inhibitor



SB 657510 (3571)
Selective urotensin-II receptor antagonist

Myocardial Infarction

Myocardial Infarction

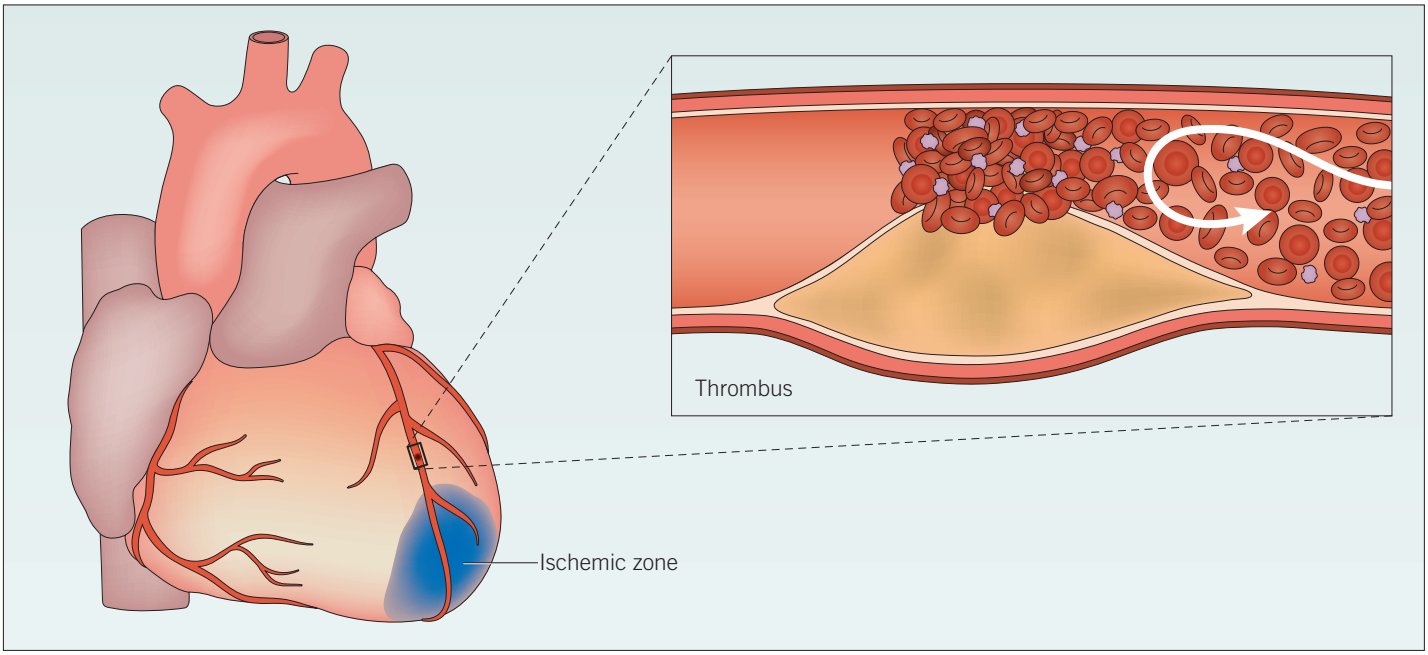
Myocardial infarction (MI) – more commonly referred to as a heart attack – is an acute event caused by the interruption of blood supply to regions of the heart, leading to myocardial necrosis. Infarction of a substantial area of the myocardium can disrupt normal conductance of the heart, leading to cardiac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

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.

Myocardial Infarction Research – continued

mechanism for preventing angina is to increase ATP production whilst maintaining the same oxygen consumption. One of the first antianginal agents, perhexiline, exerts these affects by inhibiting the mitochondrial enzyme, carnitine palmitoyltransferase-1 (CPT1). Newer antianginal 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.

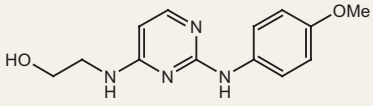
In addition to vasodilators, pharmacological treatment of acute MI also includes antiplatelet and fibrinolytic agents such as recombinant human tPA, uPA and streptokinase in combination with heparin (Cat. No. 2812) in order to break down the occluding thrombus and restore blood supply to the downstream 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 – A_1, A_{2A}, A_{2B} and A_3 – 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.

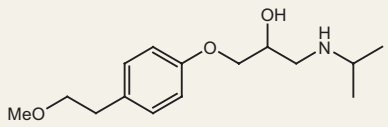
More recent therapy for the treatment of myocardial infarction centers around the use of stem cells to repair damaged myocardium. Following an infarction, damaged myocardium cannot regenerate and so is replaced by non-contractile scar tissue. This alters both the contractility and the conductance of 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

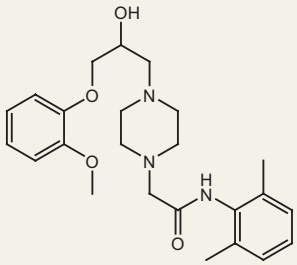
A full list of targets and related products are listed on pages 20-30



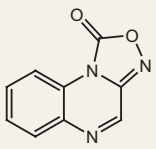
Cardiogenol C (3851)
Induces cardiomyogenesis in ESCs



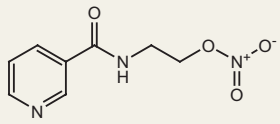
Metoprolol (3256)
Selective β_1 antagonist



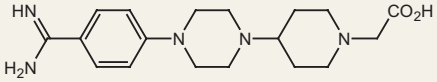
Ranolazine (3118)
Antianginal, activates pyruvate dehydrogenase



ODQ (0880)
Selective inhibitor of NO-sensitive guanylyl cyclase



Nicorandil (2147)
$K_{ir}6$ (K_{ATP}) channel opener and NO donor



GR 144053 (1263)
Glycoprotein IIb/IIIa (integrin $\alpha_{IIb}\beta_3$) receptor antagonist. Antithrombotic

Ischemia/Reperfusion Injury

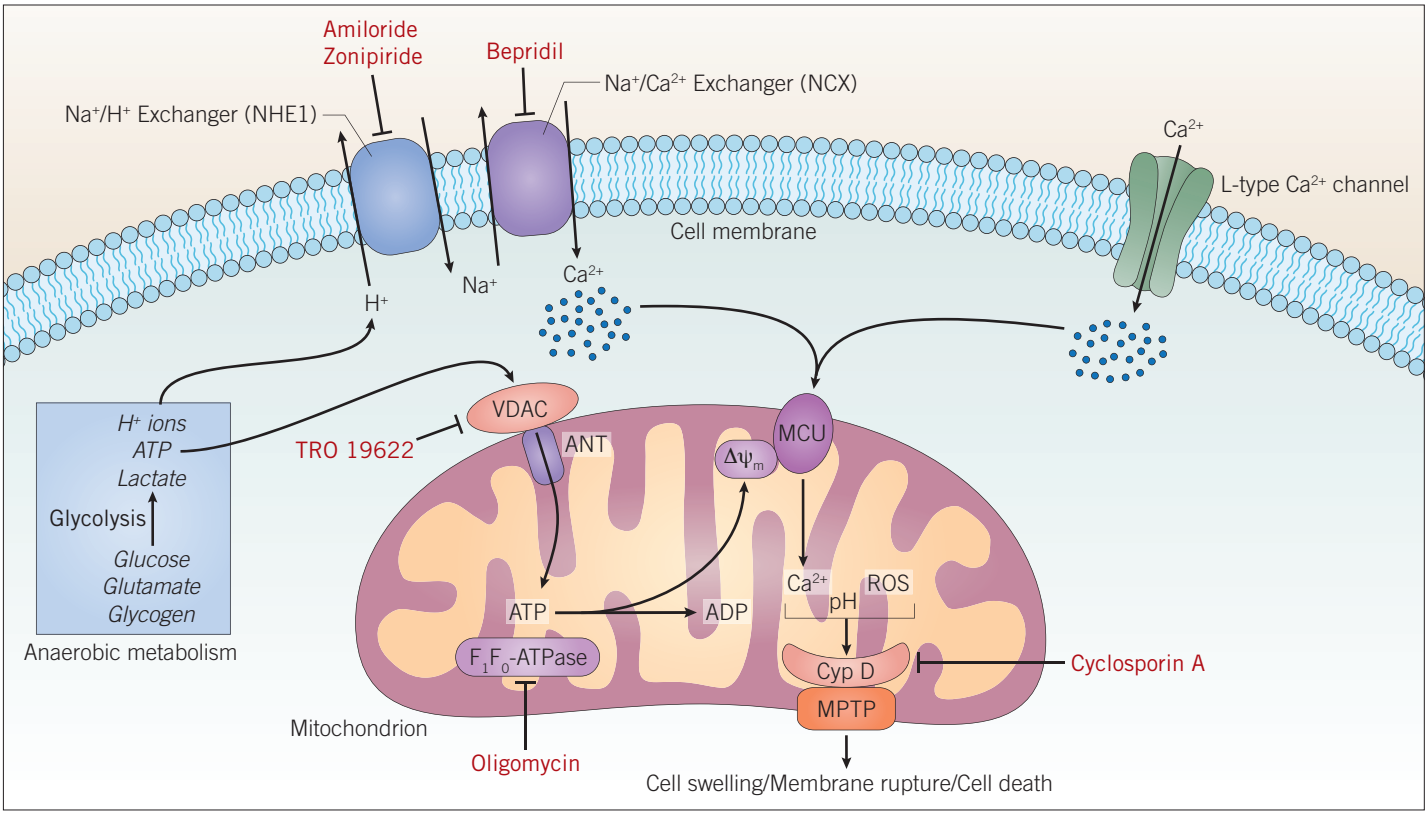
Ischemia/Reperfusion Injury

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

Figure 7 | Ionic disturbances in I/R injury within a cardiac muscle cell



A rise in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) 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^+/Ca^{2+} exchangers, thus increasing $[Ca^{2+}]_i$. ATP, generated by glycolysis, is used by F_1F_0-ATPase to create a mitochondrial membrane potential ($\Delta\psi_m$). This is utilized by the mitochondrial calcium uniporter; an increase in mitochondrial Ca^{2+} 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.

Ischemia/Reperfusion Injury – continued

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.

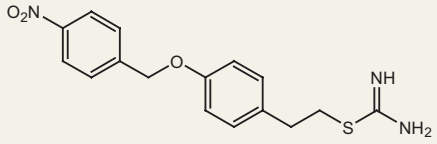
The cell death that underlies I/R injury is characterized by features typical of apoptosis, autophagy and necrosis. A key regulator of both apoptotic and necrotic cell death is the mitochondrial permeability transition pore (MPTP) (Figure 7). Low pH, induced during ischemia, inhibits MPTP opening; only 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 *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 cardiprotective 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.

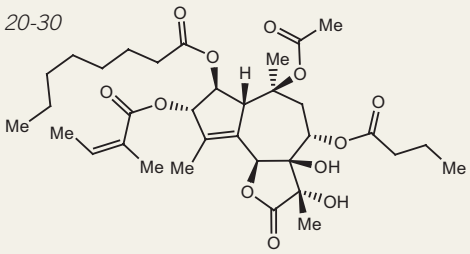
Newer cardioprotective targets include GSK-3β, a multifunctional kinase that has also been linked to protection against I/R damage; the mitochondrial calcium uniporter (MCU), which has been linked to the cardioprotective response to ischemic preconditioning; and the sarco/endoplasmic reticulum Ca^{2+}-ATPase (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

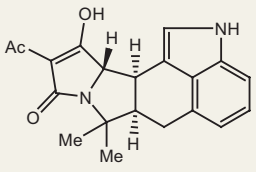
A full list of targets and related products are listed on pages 20-30



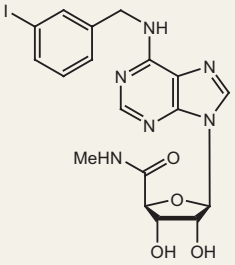
KB-R7943 (1244)
Na^+/Ca^{2+} exchange inhibitor (reverse mode)



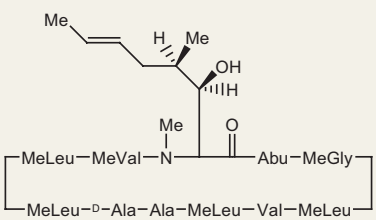
Thapsigargin (1138)
Potent inhibitor of SERCA



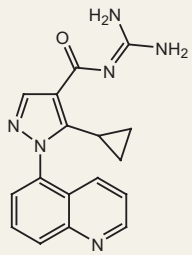
Cyclopiazonic acid (1235)
Inhibitor of SERCA



IB-MECA (1066)
A_3 selective agonist



Cyclosporin A (1101)
Inhibits formation and opening of the MPTP



Zoniporide (2727)
Selective NHE1 inhibitor

Arrhythmias

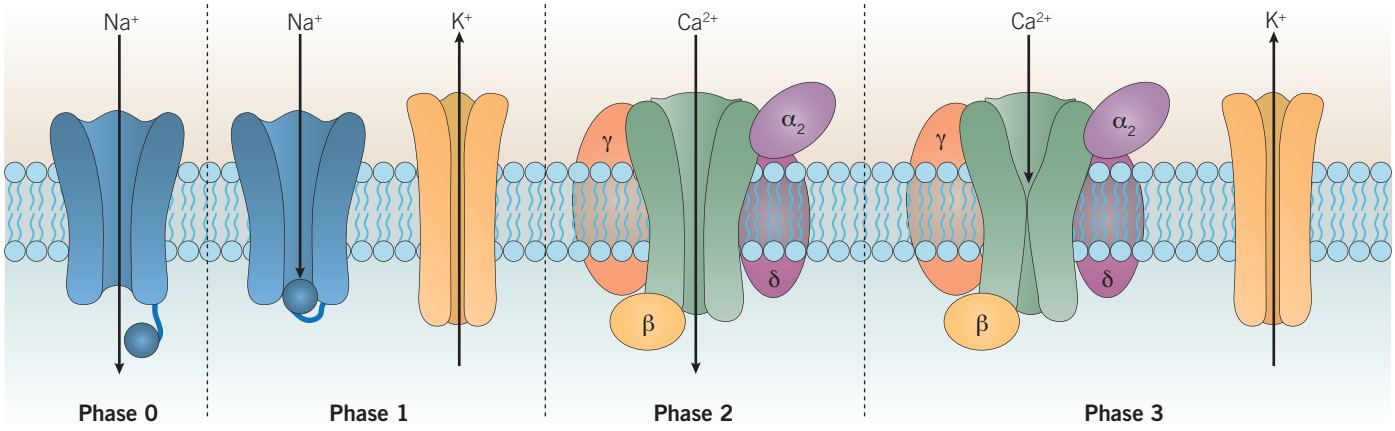
Arrhythmias

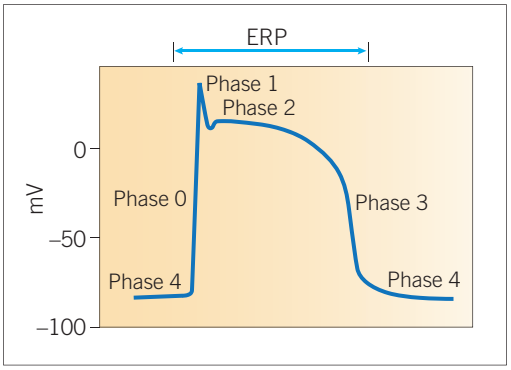
An arrhythmia (also known as cardiac dysrhythmia) is defined as an irregular heartbeat, and results from abnormal electrical activity in the heart. There are various different types of arrhythmia, often resulting in a heartbeat that is too fast (tachycardia) or too slow (bradycardia). Atrial and ventricular 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 4 (Rest): The majority of Na^+ and K^+ channels are closed. Once an action potential is initiated, four phases follow:

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.

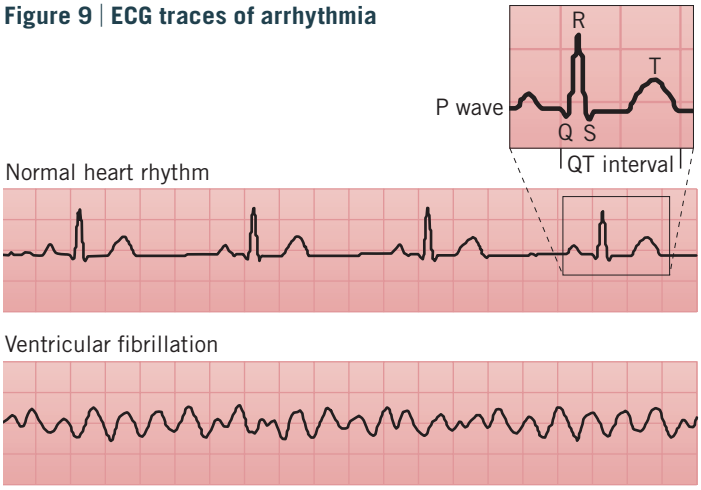
Phase 2: The 'plateau' phase. This is the longest phase, and marks the entry of Ca^{2+} ions into the myocardial cell via L-type Ca^{2+} channels. Reduced outward K^+ current continues.

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

Figure 9 | ECG traces of arrhythmia



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.

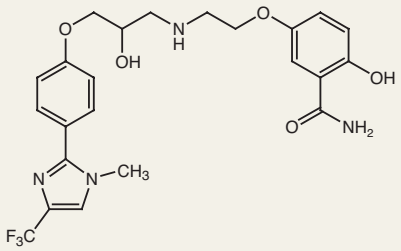
consequently dysregulation of their activity has been linked to the development of arrhythmias. For example, mutations in genes encoding the $K_V11.1$ (hERG) potassium channel, the sodium $Na_V1.5$ channel, and the calcium $Ca_V1.2$ channel have been linked to long QT syndrome (LQTS). In LQTS, the QT 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.

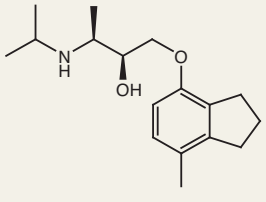
Antiarrhythmic drug therapy aims to restore normal cardiac rhythm and conduction, and to prevent more serious arrhythmias from occurring. Vaughan Williams created one of the most widely used classification schemes for antiarrhythmic drugs. The scheme divides antiarrhythmic drugs into five classes (I-V), 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.

Box 7: Arrhythmia Key Products

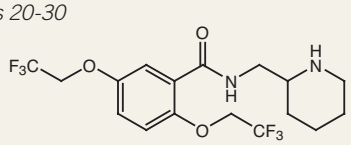
A full list of targets and related products are listed on pages 20-30



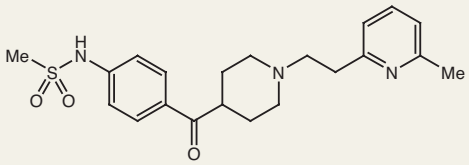
CGP 20712 (1024)
Highly potent and selective β_1 antagonist



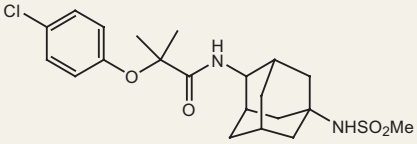
ICI 118,551 (0821)
Very selective β_2 antagonist



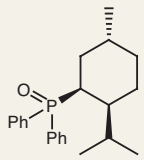
Flecainide (1470)
Cardiac Na^+ channel blocker. Antiarrhythmic



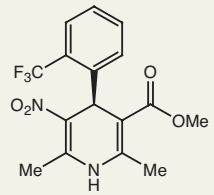
E-4031 (1808)
$K_V11.1$ (hERG) channel blocker; inhibits rapid delayed rectifier K^+ current (I_{Kr})



JNJ 303 (3899)
Potent and selective I_{Ks} blocker



DPO-1 (2533)
Blocker of $K_V1.5$ channel and I_{Kur} current



(*S*)-(-)-Bay K 8644 (1546)
Ca^{2+}-channel activator (L-type)

Heart Failure

Heart Failure

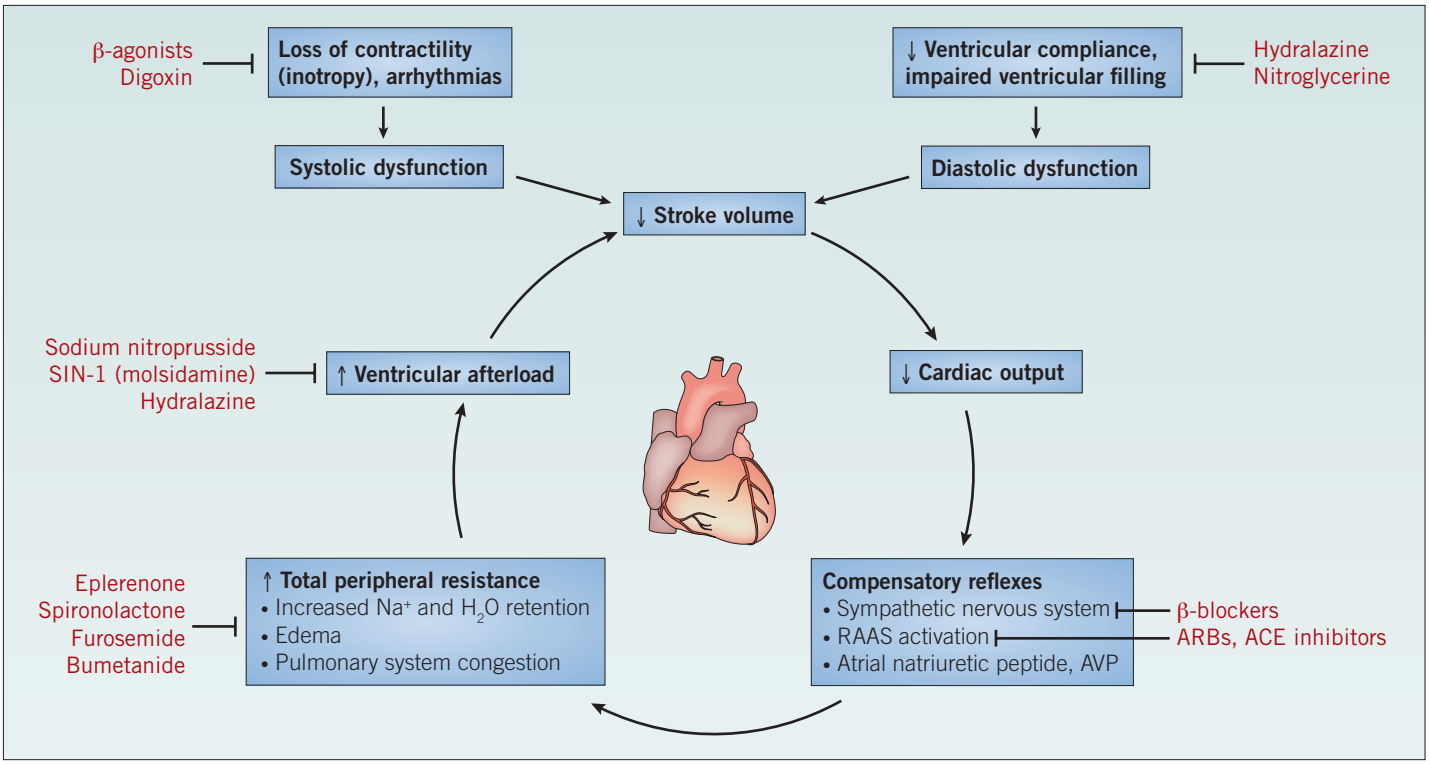
Heart failure, also known as congestive heart failure or CHF, is an inability of the heart to pump sufficient blood around the body. Heart failure typically occurs secondary to an existing pathology that alters cardiac function. Examples of syndromes that can precede heart failure include myocardial 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.

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.

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.

Heart Failure – continued

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 mecarbil – 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.

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.

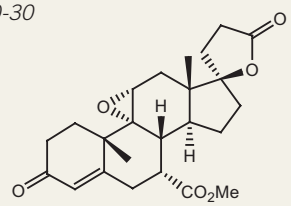
A further therapeutic target in heart failure, central to disease progression, is the activity of G protein-coupled receptor kinases (GRKs), in particular the cardiomyocyte-expressed GRK2. GRK2 activation during heart failure leads to the desensitization of β adrenergic receptors (βARs) and therefore 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 – β_1ARs and β_2ARs – 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.

Box 8: Heart Failure Key Products

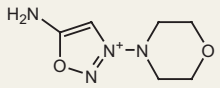
A full list of targets and related products are listed on pages 20-30

Trp-Lys-Lys-Glu-Leu-Arg-Asp-Ala-Tyr-Arg-Glu-Ala-Gln-Gln-Leu-Val-Gln-Arg-Val-Pro-Lys-Met-Lys-Asn-Lys-Pro-Arg-Ser

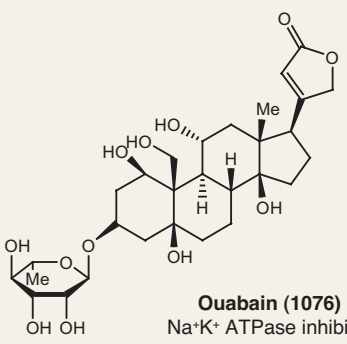
GRK2i (3594)
GRK2 inhibitory polypeptide; Gβγ antagonist



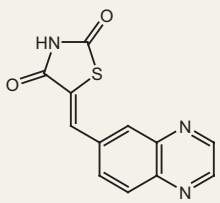
Eplerenone (2397)
Selective mineralocorticoid receptor antagonist



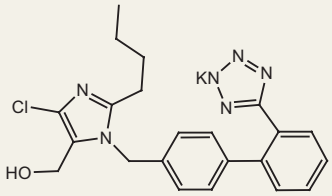
SIN-1 (0756)
Water-soluble NO donor



Ouabain (1076)
Na^+K^+ ATPase inhibitor



AS 605240 (3578)
Potent and selective PI 3-kinase γ (PI3Kγ) inhibitor

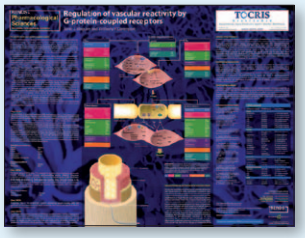


Losartan (3798)
Selective, nonpeptide AT_1 antagonist

List of Acronyms

Acronym	Definition
ACE	Angiotensin-converting enzyme
ACh	Acetylcholine
ANT	Adenine nucleotide translocase
ARB	Angiotensin II receptor blocker
AV	Atrioventricular
AVP	Arginine Vasopressin
βAR	β-androgen receptor
BP	Blood pressure
CaM	Calmodulin
cAMP	Cyclic adenine monophosphate
cGMP	Cyclic guanosine monophosphate
CHF	Congestive heart failure
CK	Creatine kinase
COX	Cyclooxygenase
$cPLA_2$	Cytosolic phospholipase A_2
CPT1	Carnitine palmitoyltransferase 1
cTnI	Cardiac troponin I
cTnT	Cardiac troponin T
DAG	Diacylglycerol
DNA-PK	DNA protein kinase
ECG/EKG	Electrocardiography/Elektrokardiogramm
eNOS	Endothelial nitric oxide synthase
ERP	Effective refractory period
ET	Endothelin
FcRγ	Fc receptor γ-chain
GPVI	Glycoprotein VI
GRK	G protein-coupled receptor kinase
GSK-3β	Glycogen synthase kinase-3β
GTP	Guanosine triphosphate
hERG	Human ether-à-go-go-related gene
HPETE	Hydroperoxyeicosatetraenoic acid
IGF-1	Insulin-like growth factor-1
IL	Interleukin
InsP3R	IP_3 receptor
IP_3	Inositol triphosphate
IPR	I prostanoid receptor
ITAM	Immunoreceptor tyrosine-based activation motif
K_{ATP}	ATP-sensitive potassium channel
K_{ir}	Inward rectifying potassium channel
K_V	Voltage-gated potassium channel
LOX	Lipoxygenase
LQTS	Long QT syndrome
MCU	Mitochondrial calcium uniporter
MLCK	Myosin light chain kinase
MMP	Matrix metalloproteinase
MPTP	Mitochondrial permeability transition pore
mTOR	Mammalian target of rapamycin
NA	Noradrenalin
NCX	Na^+/Ca^{2+} exchanger
NHE	Na^+/H^+ exchanger
NKCC	$Na^+/K^+/2Cl^-$ cotransporter
NO	Nitric oxide
NTS	Nucleus tractus solitarius
ox-LDL	Oxidized low-density lipoprotein
PAR	Protease-activated receptor
PBR	Peripheral benzodiazepine receptor
PDGF	Platelet-derived growth factor
PGH_2	Prostaglandin H_2
PGI_2	Prostacyclin
PI 3-K	Phosphoinositide 3-kinase
PIP_2	Phosphatidylinositol 4,5-bisphosphate
PKG	Protein kinase G
PLC	Phospholipase C
PMN	Polymorphonuclear leukocyte
RAAS	Renin-angiotensin-aldosterone system
ROS	Reactive oxygen species
SA	Sinoatrial
SERCA	Sarco/endoplasmic reticulum Ca^{2+}-ATPase
sGC	Soluble guanylyl cyclase
TGF-BRI	Transforming growth factor-B type I receptor
TIMP	Tissue inhibitor of metalloproteinase
tPA	Tissue plasminogen activator
TXA_2	Thromboxane A_2
uPA	Urokinase plasminogen activator
VDAC	Voltage-dependent anion channel
vWF	von Willebrand factor

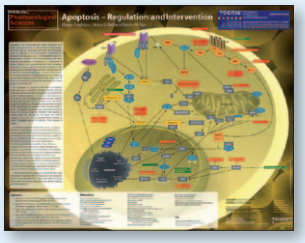
Related literature from Tocris that you may be interested in:



Regulation of Vascular Reactivity by G-protein-coupled Receptors

J. Maguire and A. Davenport, University of Cambridge

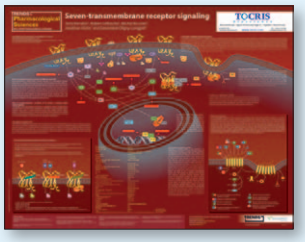
Cardiovascular disease remains one of the major causes of morbidity and mortality in the Western world and therefore this therapeutic area continues to be of great interest to researchers. This poster highlights the key GPCRs regulating vascular reactivity.



Apoptosis – Regulation and Intervention

D. Crighton *et al.* Beatson Institute for Cancer Research

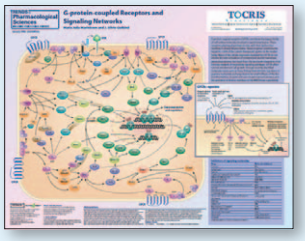
Apoptosis is an orchestrated cell death mechanism that brings about removal of cells without inflammation and stress. The key signaling pathways associated with the regulation of apoptosis are summarized in this poster.



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.

To download or request copies, please visit www.tocris.com/requestliterature

Cardiovascular Research Compounds from Tocris

Class	Cat. No.	Product Name	Primary Action	Unit Size
5-HT Receptors				
Agonists	3428	DMT	5-HT_{2A} agonist; also endogenous σ_1 ligand	10 mg
	2643	DOI	Mixed 5-$HT_{2A/2C}$ agonist	10 mg 50 mg
	2201	PNU 22394	5-HT_{2C} agonist and 5-$HT_{2A/2B}$ partial agonist	10 mg 50 mg
	2592	TCB-2	Potent, high affinity 5-HT_{2A} agonist	10 mg 50 mg
Antagonists	0523	4F 4PP	Selective 5-HT_{2A} antagonist	10 mg 50 mg
	0870	MDL 11,939	5-HT_{2A} antagonist	10 mg 50 mg
	1742	R-96544	Potent, selective 5-HT_{2A} antagonist	10 mg 50 mg
	2865	Risperidone	5-HT_{2A} antagonist	10 mg 50 mg
	3739	Sarpogrelate	Selective 5-HT_{2A} antagonist	10 mg 50 mg
α_1 adrenergic Receptors				
Agonists	0888	Cirazoline	Selective α_1 agonist	10 mg
	2838	(*R*)-(-)-Phenylephrine	α_1 agonist	100 mg
Antagonists	2685	Carvedilol	α_1 and β adrenergic receptor antagonist	50 mg
	0545	Ifenprodil	α_1 antagonist; also NMDA antagonist and σ ligand	10 mg 50 mg
	0623	Prazosin	α_1 and α_{2B} antagonist; MT_3 antagonist	100 mg
α_2 adrenergic Receptors				
Agonists	0690	Clonidine	α_2 agonist. Also I_1 ligand	100 mg
	2749	Dexmedetomidine	Potent, highly selective α_2 agonist; active isomer of medetomidine (Cat. No. 2023)	10 mg 50 mg
	0885	Guanabenz	α_2 agonist; also I_2 selective ligand	100 mg
	1030	Guanfacine	α_{2A} agonist	10 mg 50 mg
	2638	ST 91	α_2 agonist, putative α_{2C} agonist	10 mg 50 mg
	2466	UK 14,304 tartrate	α_2 agonist; water-soluble form of UK 14,304 (Cat. No. 0425)	10 mg 50 mg
Antagonists	2666	JP 1302	Potent and selective α_{2C} antagonist	10 mg 50 mg
β Adrenergic Receptors				
Agonists	0435	Cimaterol	β agonist	10 mg 50 mg
	0515	Dobutamine	α_1, β_1 and β_2 agonist	50 mg
	1448	Formoterol	Potent and selective β_2 agonist	10 mg 50 mg
	1747	Isoproterenol	Standard selective β agonist	100 mg
Antagonists	2685	Carvedilol	α_1 and β adrenergic receptor antagonist	50 mg
	1024	CGP 20712	Highly potent and selective β_1 antagonist	10 mg 50 mg
	0821	ICI 118,551	Very selective β_2 antagonist	10 mg 50 mg
	0832	ICI 89406	β antagonist	10 mg 50 mg
	3256	Metoprolol	Selective β_1 antagonist	50 mg
	0829	Pronethalol	β antagonist	100 mg

Cardiovascular Research Compounds – continued

Class	Cat. No.	Product Name	Primary Action	Unit Size
	0624	Propranolol	β antagonist	100 mg
	0952	Sotalol	β antagonist	10 mg 50 mg
Adenosine Receptors				
Agonists	1705	2-Chloro-N^6-cyclopentyladenosine	Potent, selective A_1 agonist	10 mg 50 mg
	1104	2-Cl-IB-MECA	Highly selective A_3 agonist	10 mg 50 mg
	4472	BAY 60-6583	Potent A_{2B} receptor agonist; cardioprotective	10 mg 50 mg
	1063	CGS 21680	A_{2A} agonist	10 mg 50 mg
	1066	IB-MECA	A_3 selective agonist	5 mg 25 mg
Antagonists	0439	DPCPX	A_1 selective antagonist	100 mg
	1217	MRS 1220	Highly potent, selective hA_3 antagonist	5 mg 25 mg
	2752	MRS 1754	Selective A_{2B} antagonist	10 mg 50 mg
	2009	PSB 1115	Selective human A_{2B} receptor antagonist; water-soluble	10 mg 50 mg
	3198	PSB 603	Highly selective A_{2B} antagonist	10 mg 50 mg
	2270	SCH 58261	Potent, highly selective A_{2A} antagonist	10 mg 50 mg
	1036	ZM 241385	Potent, highly selective A_{2A} antagonist	10 mg 50 mg
Aldosterone Receptors				
Antagonists	3281	Canrenone	Mineralocorticoid receptor antagonist	50 mg
	2397	Eplerenone	Selective mineralocorticoid receptor antagonist	10 mg 50 mg
	2970	RU 26752	Mineralocorticoid receptor antagonist	10 mg
	1672	RU 28318	Potent, selective mineralocorticoid receptor antagonist	10 mg 50 mg
	2968	Spironolactone	Mineralocorticoid receptor antagonist	50 mg
Angiotensin-converting Enzyme				
Inhibitors	2578	Benazepril	Angiotensin-converting enzyme (ACE) inhibitor	50 mg
	4455	Captopril	ACE inhibitor; also inhibits LTA_4 hydrolase	50 mg
	2691	Moexipril	Angiotensin-converting enzyme (ACE) inhibitor	10 mg 50 mg
	4302	Perindopril	Angiotensin-converting enzyme (ACE) inhibitor	50 mg
	2931	Spinorphin	Endogenous peptide inhibitor of ACE; also potent $P2X_3$ antagonist	1 mg
Substrates	1563	Angiotensin I (human, mouse, rat)	Endogenous precursor to angiotensin II (Cat. No. 1158)	1 mg
	1764	Hemopressin (rat)	Endogenous endopeptidase substrate; potent hypotensive *in vivo*	1 mg
Angiotensin II Receptors				
Agonists	2569	CGP 42112	Selective, high affinity AT_2 ligand	1 mg
	3615	Novokinin	Orally active AT_2 agonist	1 mg
Antagonists	3798	Losartan	Selective, non-peptide AT_1 antagonist	50 mg
	1361	PD 123319	Potent, selective non-peptide AT_2 antagonist	10 mg 50 mg
	4216	Valsartan	High affinity, selective AT_1 antagonist	10 mg 50 mg

Class	Cat. No.	Product Name	Primary Action	Unit Size
Apoptosis				
Other	2098	Apoptosis Activator 2	Promotes apoptosome formation and activates caspase-9/caspase-3 pathway; selectively induces tumor cell apoptosis	10 mg 50 mg
	2172	AZ 10417808	Selective non-peptide caspase-3 inhibitor	10 mg 50 mg
	2160	Bax channel blocker	Inhibits Bax-mediated mitochondrial cytochrome c release	10 mg 50 mg
	1786	Bax inhibitor peptide P5	Inhibitor of Bax-mediated apoptosis	1 mg
	1785	Bax inhibitor peptide V5	Inhibitor of Bax-mediated apoptosis	1 mg
	1787	Bax inhibitor peptide, negative control	Negative control peptide for Bax inhibitor peptides V5 and P5 (Cat. Nos. 1785 and 1786)	1 mg
	3590	Gambogic acid	Apoptosis inducer; activates caspases and inhibits Bcl-2 family proteins	10 mg 50 mg
	1541	HA14-1	Bcl-2 inhibitor; induces apoptosis	10 mg 50 mg
	3794	iMAC2	Suppressor of mitochondrial apoptosis	10 mg 50 mg
	2636	Ivachtin	Potent caspase-3 inhibitor	1 mg 10 mg
	2581	PAC 1	Activator of procaspase-3; proapoptotic	10 mg 50 mg
	1758	PETCM	Activator of caspase-3	50 mg
	2775	Probucol	Antioxidant, anti-inflammatory and hypocholesterolemic agent	100 mg
	4038	TW 37	Bcl-2 inhibitor; induces apoptosis	10 mg 50 mg
	2166	Z-DEVD-FMK	Cell-permeable, irreversible caspase-3 inhibitor	1 mg
	2163	Z-VAD-FMK	Cell-permeable, irreversible caspase inhibitor	1 mg
Calcium Channels				
Activators	1544	(±)-Bay K 8644	Ca^{2+}-channel activator (L-type)	10 mg 50 mg
	1546	(*S*)-(-)-Bay K 8644	Ca^{2+}-channel activator (L-type)	10 mg 50 mg
	1403	FPL 64176	Potent activator of Ca^{2+} channels (L-type)	10 mg 50 mg
Blockers	0685	Diltiazem	Ca^{2+} channel blocker (L-type)	1 g
	2004	Isradipine	Ca^{2+} channel blocker (L-type)	10 mg 50 mg
	2198	Mibefradil	Ca^{2+} channel blocker (T-type)	10 mg 50 mg
	1075	Nifedipine	Ca^{2+} channel blocker (L-type)	100 mg
	0600	Nimodipine	Ca^{2+} channel blocker (L-type)	100 mg
	2268	NNC 55-0396	Highly selective Ca^{2+} channel blocker (T-type)	10 mg
	1439	Ruthenium Red	Non-selective Ca^{2+} channel blocker (N- and P-type)	100 mg
	0654	Verapamil	Ca^{2+} channel blocker (L-type)	1 g
Calcium Signaling				
Inhibitors	3954	*trans*-Ned 19	NAADP antagonist; inhibits Ca^{2+} release	10 mg
	1329	Ryanodine	Ca^{2+} release inhibitor	1 mg
	1147	SKF 96365	STIM1-mediated Ca^{2+} influx inhibitor	10 mg 50 mg
	1280	(-)-Xestospongin C	Inhibits IP_3-mediated Ca^{2+} release	10 µg

Cardiovascular Research Compounds – continued

Class	Cat. No.	Product Name	Primary Action	Unit Size
Other	1234	A23187	Calcium ionophore	10 mg
	2786	BAPTA	Selective calcium chelator	100 mg
	2787	BAPTA AM	Cell-permeable Ca^{2+} chelator	25 mg
	2220	FURA-2AM	Fluorescent Ca^{2+} indicator	1 mg
	1704	Ionomycin calcium salt	Calcium ionophore	1 mg
	2092	Ionomycin free acid	Calcium ionophore	1 mg
Cell Adhesion Molecules				
Antagonists	1263	GR 144053	Glycoprotein IIb/IIIa (integrin $\alpha_{IIb}\beta_3$) receptor antagonist; antithrombotic	10 mg 50 mg
Inhibitors	2524	A 205804	Selective inhibitor of E-selectin and ICAM-1 expression	10 mg 50 mg
	4228	A 286982	Potent inhibitor of the LFA-1/ICAM-1 interaction	10 mg 50 mg
	3202	Echistatin, α1 isoform	$\alpha_v\beta_3$ and glycoprotein IIb/IIIa (integrin $\alpha_{IIb}\beta_3$) inhibitor	100 µg
	2748	KF 38789	Selective inhibitor of P-selectin-mediated cell adhesion	10 mg
	2877	MNS	Selective inhibitor of Src and Syk	50 mg
	2710	OGT 2115	Antiangiogenic; heparanase inhibitor	1 mg 10 mg
	4227	RWJ 50271	Inhibitor of LFA-1/ICAM mediated cell adhesion	10 mg 50 mg
Other	2812	Heparin	Anticoagulant	100 mg
	4034	PM 102	Antagonist of heparin (Cat. No. 2812)	1 mg
Chemokine Receptors				
Antagonists	3299	AMD 3100	Highly selective CXCR4 antagonist	10 mg 50 mg
	2423	DAPTA	Chemokine receptor 5 (CCR5) antagonist	1 mg
	2595	J 113863	Potent CCR1 chemokine receptor antagonist	1 mg 10 mg 50 mg
	3756	Maraviroc	Selective CCR5 antagonist	10 mg 50 mg
	2725	SB 225002	Potent and selective CXCR2 antagonist	10 mg 50 mg
	2724	SB 265610	Potent CXCR2 antagonist	1 mg 10 mg 50 mg
Cholesterol Regulation				
Inhibitors	3776	Atorvastatin	HMG-CoA reductase inhibitor	10 mg 50 mg
	1639	AY 9944	Inhibitor of hedgehog (Hh) signaling; inhibits Δ^7-dehydrocholesterol reductase	10 mg
	2227	CI 976	Acyl-CoA:cholesterol acyltransferase (ACAT) inhibitor	10 mg 50 mg
	3540	Orlistat	Pancreatic, gastric and carboxylester lipase inhibitor; antiobesity and antihypercholesterolemic activity	10 mg 50 mg
	2775	Probucol	Antioxidant, anti-inflammatory and hypocholesterolemic agent	100 mg
	1965	Simvastatin	HMG-CoA reductase inhibitor	50 mg
	4184	Torcetrapib	Inhibitor of cholesteryl ester transfer protein (CETP)	10 mg 50 mg
	1638	U 18666A	Inhibitor of hedgehog (Hh) signaling; inhibits cholesterol synthesis	10 mg
	3039	YM 750	Acyl-CoA:cholesterol acyltransferase (ACAT) inhibitor	10 mg 50 mg
Cyclic GMP				
Activators	1089	8-Bromo-cGMP	cGMP analog; activates PKG	10 mg 50 mg

Class	Cat. No.	Product Name	Primary Action	Unit Size
Cyclooxygenases				
Inhibitors	3786	Celecoxib	Selective cyclooxygenase-2 (COX-2) inhibitor	10 mg 50 mg
	4454	Diclofenac	Cyclooxygenase inhibitor; NSAID	50 mg
	1418	Resveratrol	Cyclooxygenase inhibitor	100 mg
	4206	Valdecoxib	Selective and potent COX-2 inhibitor	10 mg 50 mg
Cytokine Receptors				
Antagonists	1793	AF 12198	Potent, selective human type I IL-1 receptor antagonist	1 mg
	2265	Lyn peptide inhibitor	Inhibits Lyn-dependent activities of IL-5 receptor; cell-permeable	1 mg
Elastases				
Inhibitors	3535	Sivelestat	Selective leukocyte elastase inhibitor	10 mg 50 mg
	2506	SSR 69071	Potent, orally active human leukocyte elastase inhibitor	10 mg
Endothelin Receptors				
Agonists	1189	BQ-3020	Selective ET_B agonist	500 µg
	1160	Endothelin 1 (human, porcine)	Potent vasoconstrictor peptide	100 µg
	1899	Sarafotoxin S6a	Endothelin receptor agonist	100 µg
Antagonists	1441	BMS 182874	Highly selective, orally active non-peptide ET_A antagonist	10 mg 50 mg
	1500	BQ 788	Selective ET_B antagonist	1 mg
	1188	BQ-123	Selective ET_A antagonist	500 µg
	1210	FR 139317	Highly potent, selective ET_A antagonist	10 mg 50 mg
Fatty Acid Oxidation				
Other	4539	(*R*)-(+)-Etomoxir	Carnitine palmitoyltransferase I (CPT1) inhibitor	10 mg 50 mg
	0548	(±)-Lauroylcarnitine	Intermediate in lipid metabolism	50 mg
	0567	(±)-Myristoylcarnitine	Intermediate in lipid metabolism	50 mg
	0605	(±)-Octanoylcarnitine	Intermediate in lipid metabolism	50 mg
	0611	(±)-Propionylcarnitine	Intermediate in lipid metabolism	50 mg
	1484	Oleylethanolamide	GPR55 agonist; also PPARα agonist	10 mg 50 mg
	3118	Ranolazine	Antianginal; activates pyruvate dehydrogenase	50 mg
GRK2				
Antagonists	3594	GRK2i	GRK2 inhibitory polypeptide; $G_{\beta\gamma}$ antagonist	1 mg
IGF-1 Receptor				
Inhibitors	2768	PQ 401	IGF1R inhibitor	10 mg 50 mg
	2956	Picropodophyllotoxin	Selective IGF1R inhibitor	10 mg
Lipoxygenases				
Inhibitors	3541	BAY-X 1005	Orally active 5-lipoxygenase activating protein (FLAP) inhibitor	1 mg
	1311	MK 886	Inhibitor of 5-lipoxygenase-activating protein (FLAP)	10 mg 50 mg
	2850	PD 146176	Selective 15-lipoxygenase inhibitor	10 mg 50 mg
	0645	2-TEDC	5-, 12-, 15-Lipoxygenase inhibitor	10 mg 50 mg
	3308	Zileuton	Orally active 5-LOX inhibitor	10 mg 50 mg

Cardiovascular Research Compounds – continued

Class	Cat. No.	Product Name	Primary Action	Unit Size
Matrix Metalloproteinases				
Inhibitors	2961	Batimastat	Potent, broad spectrum MMP inhibitor	1 mg 10 mg
	2631	Marimastat	Broad spectrum MMP inhibitor	1 mg 10 mg
	2628	ONO 4817	Broad spectrum MMP inhibitor	10 mg
	2916	Ro 32-3555	Potent, collagenase-selective MMP inhibitor	10 mg
	4187	UK 356618	Potent and selective MMP-3 inhibitor	10 mg
	2633	WAY 170523	Potent and selective inhibitor of MMP-13	1 mg 10 mg
Mitochondrial Calcium Uniporter				
Inhibitors	3603	Kaempferol	Mitochondrial Ca^{2+} uniporter (MCU) activator; proapoptotic	50 mg
	1244	KB-R7943	MCU inhibitor; also inhibits Na^+/Ca^{2+} exchange	10 mg 50 mg
Mitochondrial Permeability Transition Pore				
Inhibitors	1101	Cyclosporin A	Calcineurin inhibitor	100 mg
	4110	Oligomycin A	Inhibitor of mitochondrial ATPase	5 mg
	2906	TRO 19622	Binds voltage-dependent anion channel (VDAC)	10 mg 50 mg
Muscarinic Receptors (mAChRs)				
Antagonists	1105	AF-DX 116	Selective M_2 antagonist	10 mg 50 mg
	1345	AF-DX 384	Potent M_2/M_4 antagonist	10 mg 50 mg
	0482	4-DAMP	Muscarinic M_3 antagonist	50 mg
	2096	DAU 5884	M_3 receptor antagonist	10 mg 50 mg
	2507	J 104129	Potent, selective M_3 antagonist	10 mg
Na^+/Ca^{2+} Exchanger				
Inhibitors	4117	Bepridil	Nonselective calcium channel blocker	50 mg
	1114	CGP 37157	Antagonist of mitochondrial Na^+/Ca^{2+} exchange	10 mg 50 mg
	1244	KB-R7943	Na^+/Ca^{2+} exchange inhibitor (reverse mode)	10 mg 50 mg
	2184	SN-6	Selective Na^+/Ca^{2+} exchange inhibitor (reverse mode)	10 mg 50 mg
Na^+/H^+ Exchanger				
Inhibitors	0890	Amiloride	Na^+ channel blocker; also I_2 imidazoline ligand	100 mg
	2727	Zoniporide	Selective NHE1 inhibitor	10 mg 50 mg
Na^+/K^+ ATPase				
Inhibitors	4583	Digoxin	Na^+/K^+ ATPase inhibitor	50 mg
	1076	Ouabain	Na^+/K^+ ATPase inhibitor	100 mg
Natriuretic Peptide Receptors				
Agonists	1912	Atrial natriuretic factor (1-28) (rat)	Endogenous pepide regulating blood pressure	1 mg
	1906	Atrial natriuretic factor (1-28) (human, porcine)	Endogenous pepide regulating blood pressure	1 mg
	3520	C-type natriuretic factor peptide (1-22) (human, rat, swine)	Endogenous peptide agonist at NPR2	500 µg

Class	Cat. No.	Product Name	Primary Action	Unit Size
Nitric Oxide				
Donors	2147	Nicorandil	$K_{ir}6$ (K_{ATP}) channel opener and NO donor	50 mg
	0756	SIN-1	Water-soluble NO donor	50 mg
	0603	SNOG	NO carrier, breaks down to release NO	10 mg 50 mg
	1135	Spermine NONOate	Slow NO releasing agent	10 mg 50 mg
Inhibitors	0546	L-NIO	Potent eNOS inhibitor	10 mg 50 mg
Other	0598	SNAP	A stable analog of endogenous S-nitroso compounds	10 mg 50 mg
Substrates	0722	*N*-Acetyl-*N*-acetoxy-4-chlorobenzenesulfonamide	Nitroxyl precursor	10 mg 50 mg
	0663	L-Arginine	Endogenous substrate for NOS	100 mg
NKCC Cotransporter				
Inhibitors	3108	Bumetanide	$Na^+/2Cl^-/K^+$ (NKCC) cotransporter inhibitor	50 mg
	3109	Furosemide	$Na^+/2Cl^-/K^+$ (NKCC) cotransporter inhibitor; also antagonizes $GABA_A$	50 mg
Oxidative Phosphorylation				
Inhibitors	0452	CCCP	Oxidative phosphorylation uncoupler	500 mg
	3612	Enterostatin	Binds to β-subunit of F_1-ATPase; anorexigenic peptide	1 mg
	0453	FCCP	Oxidative phosphorylation uncoupler	10 mg 50 mg
	3616	Rotenone	Inhibits complex I of the mitochondrial electron transport chain	50 mg
PDGF Receptors				
Inhibitors	4274	AP 24534	Potent multi-kinase and pan-BCR-ABL inhibitor	10 mg 50 mg
	1222	DMPQ	Potent, selective inhibitor of PDGFRβ	10 mg 50 mg
	3785	PD 166285	Potent Src inhibitor; also inhibits FGFR1, PDGFRβ and Wee1	1 mg 10 mg
	3304	SU 16f	Potent and selective PDGFRβ inhibitor	10 mg 50 mg
	3335	SU 6668	PDGFR, VEGFR and FGFR inhibitor	10 mg 50 mg
	3768	Sunitinib	Potent VEGFR, PDGFRβ and KIT inhibitor	10 mg 50 mg
Phosphodiesterases				
Inhibitors	0691	Dipyridamole	PDE inhibitor; coronary vasodilator	500 mg
	3053	Mesopram	Orally active PDE4 inhibitor	10 mg 50 mg
	1349	(*R*)-(-)-Rolipram	PDE4 inhibitor; more active enantiomer of rolipram (Cat. No. 0905)	10 mg 50 mg
	3784	Sildenafil	Orally active, potent PDE5 inhibitor	10 mg 50 mg
	1676	T 0156	Highly potent, selective PDE5 inhibitor	10 mg 50 mg
	1046	Zardaverine	PDE3/4 inhibitor	10 mg 50 mg

Cardiovascular Research Compounds – continued

Class	Cat. No.	Product Name	Primary Action	Unit Size
Phospholipases				
Inhibitors	1462	$AACOCF_3$	Phospholipase A_2 inhibitor	5 mg 25 mg
	1437	D609	Selective PC-PLC inhibitor	10 mg 50 mg
	3022	Edelfosine	Selective PI-PLC inhibitor; also PAF receptor agonist	10 mg
	1941	*m*-3M3FBS	Phospholipase C activator	10 mg
	1942	*o*-3M3FBS	Inactive analog of *m*-3M3FBS (Cat. No. 1941)	10 mg
	0606	OBAA	Phospholipase A_2 inhibitor	10 mg 50 mg
	1268	U 73122	Phospholipase C inhibitor	10 mg 50 mg
	4133	U 73343	Inactive analog of U 73122 (Cat. No. 1268)	10 mg 50 mg
PI 3-Kinase				
Activators	1983	740 Y-P	Cell-permeable PI 3-kinase activator	1 mg
Inhibitors	3578	AS 605240	Potent and selective PI 3-kinase γ (PI3Kγ) inhibitor	10 mg 50 mg
	3606	BAG 956	Dual PI 3-kinase and PDK1 inhibitor	10 mg 50 mg
	2814	PI 828	PI 3-kinase inhibitor	1 mg 10 mg 50 mg
Potassium Channels				
Activators	1377	Cromakalim	$K_{ir}6$ (K_{ATP}) channel opener	10 mg 50 mg
	1378	Levcromakalim	$K_{ir}6$ (K_{ATP}) channel opener; active enantiomer of cromakalim (Cat. No. 1377)	10 mg 50 mg
	0583	Minoxidil	$K_{ir}6$ (K_{ATP}) channel opener	100 mg
	4519	ML 213	$K_V7.2$ and $K_V7.4$ channel opener	10 mg 50 mg
	2147	Nicorandil	$K_{ir}6$ (K_{ATP}) channel opener and NO donor	50 mg
	4462	NS 3623	$K_V11.1$ (hERG) channel activator; antiarrhythmic	10 mg 50 mg
	1355	P1075	Potent $K_{ir}6$ (K_{ATP}) channel opener	10 mg 50 mg
Blockers	2533	DPO-1	Blocker of $K_V1.5$ channels; prevents atrial arrhythmia	10 mg 50 mg
	1808	E-4031	$K_V11.1$ (hERG) channel blocker; class III antiarrhythmic agent	10 mg 50 mg
	0911	Glibenclamide	$K_{ir}6$ (K_{ATP}) channel blocker	100 mg
	2396	Glimepiride	$K_{ir}6$ (K_{ATP}) channel blocker	10 mg 50 mg
	3899	JNJ 303	Potent and selective I_{Ks} blocker	10 mg 50 mg
	4231	Nateglinide	$K_{ir}6$ (K_{ATP}) blocker; displays high affinity for SUR1/$K_{ir}6.2$ channels	10 mg 50 mg
	2095	PNU 37883	Vascular $K_{ir}6$ (K_{ATP}) channel blocker	10 mg 50 mg
	3805	Repaglinide	$K_{ir}6$ (K_{ATP}) channel blocker	50 mg
	3948	Terfenadine	$K_V11.1$ (hERG) and $K_{ir}6$ (K_{ATP}) channel blocker; also H_1 receptor antagonist	50 mg

Class	Cat. No.	Product Name	Primary Action	Unit Size
PPAR				
Agonists	1307	Ciglitazone	Selective PPARγ agonist	10 mg 50 mg
	2229	GW 0742	Highly selective, potent PPARδ agonist	10 mg 50 mg
	1664	GW 1929	Selective PPARγ agonist; orally active	10 mg 50 mg
	1677	GW 7647	Highly selective, potent PPARα agonist; orally active	10 mg 50 mg
	4124	Pioglitazone	Selective PPARγ agonist; antidiabetic agent	10 mg 50 mg
	3114	Troglitazone	Selective PPARγ agonist; antidiabetic agent	10 mg 50 mg
Antagonists	3961	GSK 3787	Potent and selective PPARδ antagonist	10 mg 50 mg
	4618	GW 6471	PPARα antagonist	10 mg 50 mg
Prostanoid Receptors				
Agonists	1442	BMY 45778	Non-prostanoid prostacyclin IP receptor partial agonist	10 mg 50 mg
	2989	Epoprostenol	Endogenous IP receptor agonist	10 mg
	1932	U 46619	Potent, stable thromboxane A_2 (TP) receptor agonist	1 mg
Antagonists	0671	AH 6809	EP_1 and EP_2 receptor antagonist	10 mg 50 mg
	2514	L-161,982	Selective EP_4 receptor antagonist	10 mg
	3342	L-798,106	Potent and highly selective EP_3 antagonist	10 mg 50 mg
Other	1620	Alprostadil	Prostaglandin; vasodilator and antiplatelet agent *in vivo*	10 mg 50 mg
	2296	Prostaglandin E_2	Major endogenous prostanoid	10 mg
	4214	Prostaglandin $F_{2\alpha}$	Naturally-occurring prostanoid; potent vasoconstrictor	10 mg
Protease-activated Receptors				
Agonists	1464	TFLLR-NH_2	PAR_1-activating peptide	1 mg
	3497	TRAP-6	PAR_1 peptide fragment (residues 42-47); acts as a PAR_1 agonist	5 mg
Antagonists	3643	FR 171113	PAR_1 antagonist	10 mg 50 mg
	2614	RWJ 56110	Selective PAR_1 antagonist	1 mg
	1592	SCH 79797	Potent, selective non-peptide PAR_1 antagonist	10 mg 50 mg
	1488	tcY-NH_2	Selective PAR_4 antagonist	1 mg
Other	3393	RLLFT-NH2	Control peptide for TFLLR-NH_2 (Cat. No. 1464)	1 mg
	1185	Thrombin Receptor Agonist Peptide	Causes platelet aggregation and secretion	1 mg
Purinergic P2 Receptors				
Agonists	3312	BzATP	$P2X_7$ agonist; also $P2X_1$ and $P2Y_1$ partial agonist	1 mg
	2157	MRS 2365	Highly potent and selective $P2Y_1$ agonist	1 mg
	2915	MRS 2690	Potent $P2Y_{14}$ agonist	1 mg
Antagonists	3321	AR-C 66096	Potent and selective $P2Y_{12}$ antagonist	1 mg
	2490	(±)-Clopidogrel	Selective $P2Y_{12}$ antagonist	10 mg 50 mg
	0900	MRS 2179	Selective $P2Y_1$ antagonist	10 mg 50 mg
	2159	MRS 2500	Extremely potent and selective $P2Y_1$ antagonist	1 mg
	1240	NF 023	Selective, competitive $P2X_1$ antagonist	10 mg 50 mg

Cardiovascular Research Compounds – continued

Class	Cat. No.	Product Name	Primary Action	Unit Size
	3983	PSB 0739	Highly potent $P2Y_{12}$ receptor antagonist	10 mg 50 mg
	1472	Suramin	Non-selective P2 antagonist	100 mg
	3931	Ticlopidine	Selective $P2Y_{12}$ antagonist	50 mg
	2464	TNP-ATP	Potent, selective P2X antagonist	5 mg
Rho-kinase				
Inhibitors	0541	Fasudil	Inhibitor of cyclic nucleotide dependent- and Rho-kinases	10 mg 50 mg
	4009	GSK 269962	Potent and selective ROCK inhibitor	10 mg 50 mg
	2414	H 1152	Selective Rho-kinase (ROCK) inhibitor	1 mg
	4118	SB 772077B	Potent Rho-kinase inhibitor; vasodilator	10 mg 50 mg
	1254	Y-27632	Selective p160ROCK inhibitor	1 mg 10 mg 50 mg
SERCA				
Inhibitors	1235	Cyclopiazonic acid	Inhibitor of SERCA	10 mg 50 mg
	2006	Paxilline	SERCA blocker; also potent BK_{Ca} channel blocker	10 mg
	1138	Thapsigargin	Potent inhibitor of SERCA	1 mg
Sodium Channels				
Activators	2918	Veratridine	Voltage-gated Na^+ channel opener	10 mg 50 mg
Blockers	1470	Flecainide	Cardiac Na^+ channel blocker; antiarrhythmic	10 mg 50 mg
	3251	KC 12291	Orally active atypical Na^+ blocker; cardioprotective	10 mg 50 mg
	1014	QX 314	Na^+ channel blocker	100 mg
	2313	QX 314 chloride	Na^+ channel blocker	50 mg
	4435	TC-N 1752	Selective $Na_v1.7$ blocker	10 mg 50 mg
	1078	Tetrodotoxin	Na^+ channel blocker	1 mg
	1069	Tetrodotoxin citrate	Na^+ channel blocker; citrate salt of tetrodotoxin (Cat. No. 1078)	1 mg
Soluble Guanylyl Cyclase				
Activators	2753	A 350619	Soluble guanylyl cyclase (sGC) activator	10 mg 50 mg
	4430	BAY 41-2272	Soluble guanylyl cyclase (sGC) activator	10 mg 50 mg
Inhibitors	4517	NS 2028	Potent soluble guanylyl cyclase (sGC) inhibitor	10 mg 50 mg
	0880	ODQ	Selective inhibitor of NO-sensitive guanylyl cyclase	10 mg 50 mg
Stem Cells				
Other	3842	5-Azacytidine	DNA methyltransferase inhibitor; induces cardiomyogenesis in MSCs	50 mg
	3851	Cardiogenol C	Induces cardiomyogenesis in ESCs	10 mg 50 mg
	3748	XAV 939	Inhibits Wnt signaling; promotes cardiomyogenesis	10 mg 50 mg
	2293	Zebularine	DNA methyltransferase inhibitor; induces cardiomyogenesis in MSCs	10 mg

Class	Cat. No.	Product Name	Primary Action	Unit Size
TGF-β Receptors				
Inhibitors	2939	A 83-01	Selective inhibitor of TGF-βRI, ALK4 and ALK7	10 mg 50 mg
	3264	GW 788388	Selective inhibitor of TGF-βRI	10 mg 50 mg
	2718	LY 364947	Selective inhibitor of TGF-βRI	1 mg 10 mg
	1614	SB 431542	Potent, selective inhibitor of TGF-βRI, ALK4 and ALK7	1 mg 10 mg
	3263	SB 505124	Selective inhibitor of TGF-βRI, ALK4 and ALK7	10 mg 50 mg
	3211	SB 525334	Selective inhibitor of TGF-βRI	10 mg 50 mg
	3269	SD 208	Potent ATP-competitive TGF-βRI inhibitor	10 mg 50 mg
	3742	SJN 2511	Selective inhibitor of TGF-βRI	10 mg 50 mg
Urokinase				
Inhibitors	4372	BC 11	Selective urokinase (uPA) inhibitor	10 mg 50 mg
	0442	4-Chlorophenylguanidine	Urokinase inhibitor	100 mg
Urotensin II				
Agonists	2484	(±)-AC 7954	Non-peptide UT receptor agonist	10 mg 50 mg
	1642	Urotensin II (human)	Endogenous vasoactive agonist for the UT receptor	1 mg
Antagonists	3162	[Orn^{5}]-URP	Urotensin-II (UT) receptor antagonist	1 mg
	1839	BIM 23127	NMB receptor antagonist; also UT receptor antagonist	1 mg
	3571	SB 657510	Selective urotensin-II (UT) receptor antagonist	10 mg 50 mg

Further Reading

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

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