Critically discuss why a nitric oxide donating moiety has been used to modify COX-2 inhibitors.

An approach used to minimise adverse effects of therapeutic agents consists of covalently binding a carrier group to the agent to alter its physiochemical properties and then subsequent enzymatic or non-enzymatic cleavage to release the active drug molecule. The coupling of this moiety to the parent drug creates a carrier-linked prodrug. A carrier-linked prodrug can be defined as an active drug covalently linked to an inert carrier. The general advantages of prodrugs include improving bioavailability of poorly absorbed drugs, increasing the duration of action of a drug that is eliminated rapidly, reducing adverse effects, promoting site-specific drug delivery, improving patient compliance and increasing water solubility of poorly water soluble drugs to aid formulation development.

An example of a carrier group is the nitric oxide (NO) donating moiety, which can be used in conjunction with NSAID’s (non-steroidal anti-inflammatory drugs); to form drugs called NO-NSAIDs. The aim of this strategy is to synthesise prodrugs that retain the pharmacological activity of the parent drug molecule in addition to, the benefits of the biological actions of NO in reducing adverse effects of the parent drug molecule. As a result, the addition of the NO-releasing moiety to NSAIDs does not impair their ability to supress cyclooxygenase enzymes (COX1 and COX2) and thus all the beneficial effects of the NSAID are retained. The nitric oxide released is able to counteract some of the detrimental effects of cyclooxygenase inhibition such as the development of gastric mucosal injury by the inhibition of COX-1, or the development of cardiovascular problems by the inhibition of COX-2. Therapeutic agents coupled to the NO-donating moiety must contain at least one carboxylic acid group. NO-NSAIDs are synthesised by an ester linkage formed through coupling of the NO-releasing moiety to the carboxylic acid group of an NSAID.

In vivo, a typical NO-NSAID is initially hydrolysed into the parent NSAID and a nitrate-containing alcohol. A two-electron reduction cascade of the nitrate group followed by dehydration leads to the formation of a nitrite derivative. Hydrolysis of this nitrite derivative liberates a diol and a nitrite anion. Finally, the nitrite anion is further reduced to form a nitric oxide molecule.

Nitric oxide is a signalling molecule involved in many physiological and pathological processes. Nitric oxide regulates cardiovascular function due to its vasodilatory, antihypertensive, cardioprotective and anti-platelet effects. The vasodilatory effects are principally due to NO-induced activation of cytosolic guanylate cyclase in the vascular smooth muscle, with a consequent rise in the intracellular concentration of cGMP, and direct activation of potassium channels.

COX-2 inhibitors are a form of NSAID which act to inhibit the COX-2 enzyme responsible for inflammation. Examples of COX-2 inhibitors include Celecoxib and Rofecoxib. The COX-2 enzyme is responsible for catalysing prostaglandin biosynthesis from arachidonic acid. The prostaglandins formed lead to the production of prostacyclin and thromboxane A2. Prostacyclin is a potent vasodilator and thromboxane A2 is responsible for platelet aggregation and therefore thrombus formation. COX-2 inhibitors cause selective blockade of the vasodilator prostacyclin and therefore COX-2 inhibitors are associated with vasoconstriction which elevates systemic blood pressure. Via a negative feedback mechanism, a decrease in prostacyclin causes an increase in prothrombotic thromboxane A2. So COX-2 inhibitors are associated with high BP and high risk of thrombosis. The administration of exogenous nitric oxide (NO) through NO-releasing drugs can mimic the effects of endogenous nitric oxide. Therefore, nitric oxide can counteract the effects of a decrease in