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Clarivate Analytics

Monograph

Praliciguat

Rec INNM; Rec INN; USAN

Soluble guanylate cyclase activator
Treatment of heart failure with preserved ejection fraction
Treatment of diabetic nephropathy

K. Rana[1], J. Reid[1], R.R. Choksi[1], T. Lewis[2] and R.F. Goldfaden[1]

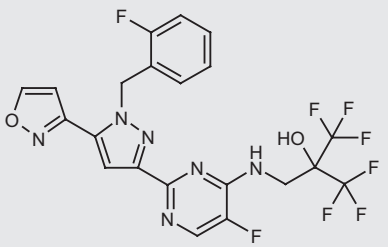
[1]East Coast Institute for Research, Jacksonville, Florida, USA; [2]Baker-Gilmour Cardiovascular Institute, Jacksonville, Florida, USA

Contents

Summary

Disruption in the nitric oxide–soluble guanylate cyclase–cyclic guanosine monophosphate (NO–sGC–cGMP) pathway due to endothelial damage may play a role in the pathogenesis of chronic heart failure (HF) with preserved ejection fraction (HFpEF) and diabetic nephropathy (DN). HF is defined as a chronic progressive condition in which the heart is unable to pump an adequate volume of blood to meet the necessities of the body. Two major types of HF prevail: HF with reduced ejection fraction (HFrEF) and HFpEF. HFrEF has numerous approved therapies to reduce morbidity and mortality, while HFpEF does not have any approved therapies with such demonstrated benefits and remains a large unmet need in the United States. In relation to DN, about 40% of patients with diabetes develop this complication which can progress to end-stage renal disease (ESRD) and/or need for renal transplant. Treatment with neurohumoral antagonists is used in addition to antidiabetic therapies to slow the progression of DN in patients with proteinuria. Nevertheless, the risk of progression to ESRD still remains high and better treatment options are necessary. Praliciguat (IW-1973), a novel sGC stimulator, may have a potential therapeutic effect in chronic HFpEF and DN as it directly stimulates sGC and increases the production of endogenous cGMP.

Key words: IW-1973 – Praliciguat – Soluble guanylate cyclase stimulator – Heart failure – Diabetic nephropathy



IW-1973
R1S0H458SA (UNII code)

1,1,1,3,3,3-Hexafluoro-2-[[(5-fluoro-2-[1-[(2-fluorophenyl)methyl]-5-(1,2-oxazol-3-yl)-1*H*-pyrazol-3-yl]pyrimidin-4-yl)amino]methyl]propan-2-ol

InChI = 1S/C21H14F8N6O2/c22-12-4-2-1-3-11(12)9-35-16(14-5-6-37-34-14)7-15(33-35)18-30-8-13(23)17(32-18)31-10-19(36,20(24,25)26)21(27,28)29/h1-8,36H,9-10H2,(H,30,31,32)

$C_{21}H_{14}F_8N_6O_2$; Mol wt: 534.3621

Integrity Entry Number: 878774

Synthesis*

Praliciguat (IW-1973) can be prepared by two different routes:

a) Chlorination of isoxazole-3-carboxylic acid (I) with $(COCl)_2$ in the presence of catalytic DMF in toluene/DMF gives acid chloride (II), which is coupled with *N*,*O*-dimethylhydroxylamine hydrochloride (III) in the presence of K_2CO_3 in H_2O to produce amide (IV). Alkylation of amide (IV) with ethyl propiolate (V) in the presence of NaHMDS in THF affords β-enamino keto ester (VI), which upon

Correspondence: Rebecca F. Goldfaden, PharmD, 3550 University Blvd. South, Suite 101, Jacksonville, FL 32216, USA. E-mail: Rebecca.goldfaden@ecirmed.com.

*Synthesis prepared by V. Carceller, Clarivate Analytics, Barcelona, Spain.

cyclocondensation with 2-fluorobenzylhydrazine (VII) in the presence of K_2CO_3 in EtOH/H_2O furnishes pyrazole ethyl ester intermediate (VIII) (1). Amination of ester (VIII) with NH_4Cl in the presence of Me_3Al in toluene at 110 °C provides carboximidamide (IX), which is cyclized with diethyl fluoromalonate (X) in the presence of NaOMe in MeOH to produce pyrimidine diol derivative (XI). Chlorination of diol (XI) with $POCl_3$ in the presence of DMA in acetonitrile gives dichloride (XII), which is treated with NaOMe in MeOH to obtain monomethoxy compound (XIII). Dechlorination of intermediate (XIII) using H_2 over Pd/C in the presence of Et_3N in THF affords 5-fluoro-2-[1-(2-fluorobenzyl)-5-isoxazol-3-ylpyrazol-3-yl]-4-methoxypyrimidine (XIV), which is demethylated with HCl in MeOH/H_2O to furnish alcohol (XV). Alternatively, selective displacement of chloride (XII) with NaOH in the presence of Bu_4NBr in THF provides compound (XVI), which is dechlorinated using H_2 over Pd/C in the presence of Et_3N in THF to generate 5-fluoro-2-[1-(2-fluorobenzyl)-5-isoxazol-3-ylpyrazol-3-yl]pyrimidin-4-ol (IWP-051) (XV) (1). Scheme 1a.

Chlorination of alcohol (XV) with $POCl_3$ in the presence of DMA in acetonitrile gives chloride (XVII) (1-3), which is coupled with 2-(aminomethyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (XVIII) (prepared by the amination of 2,2-bis(trifluoromethyl)oxirane (XIX) with NH_4OH in MTBE/H_2O [1]) in the presence of DIEA in DMSO at 128 °C or Et_3N in dioxane/H_2O at 100 ° C (1, 3). Scheme 1b.

Alternative synthesis to intermediate IWP-051 (XV)

Claisen condensation of 1-isoxazol-3-ylethanone (XX) with diethyl oxalate (XXI) in the presence of NaOEt in EtOH gives intermediate (XXII), which is cyclized with hydrazine hydrate (XXIII) in the presence of AcOH in MeOH to yield ethyl 5-isoxazol-3-ylpyrazole-3-carboxylate (XXIV). N-Alkylation of pyrazole derivative (XXIV) with mesylate (XXV) in the presence of NaH in THF provides compound (VIII). Aminolysis of ethyl ester (VIII) with NH_3 in the presence of NaCN in MeOH affords amide (XXVI), which is dehydrated with $(CF_3CO)_2O$ in pyridine to provide pyrazole-3-carbonitrile derivative (XXVII) (4). Reaction of nitrile (XXVII) with NaOMe in MeOH at 65 °C, followed by treatment with NH_4Cl in the presence of AcOH produces pyrazole-3-carboximidamide derivative (XXVIII) (2, 4). Alternatively, reaction of ethyl ester (VIII) with NH_4Cl in the presence of $AlMe_3$ in toluene at 100 °C furnishes amidine (XXVIII) (3, 5), which is finally cyclocondensed with ethyl 3-(dimethylamino)-2-fluoroacrylate (XXIX) (2, 4, 5) or sodium 3-ethoxy-2-fluoro-3-oxoprop-1-en-1-olate (XXX) (3) in EtOH at 85 °C (2-5). Scheme 2.

Alternative route to nitrile intermediate (XXVII)

Claisen condensation of 1-isoxazol-3-ylethanone (XX) with diethyl oxalate (XXI) in the presence of LiHMDS in THF at −78°C affords ketoester (XXXI), which upon cyclocondensation with 1-(2-fluorobenzyl)hydrazine hydrochloride (XXXII) in the presence of HCl in EtOH at 70°C furnishes ethyl 1-(2-fluorobenzyl)-5-isoxazol-3-ylpyrazole-3-carboxylate (VIII) (2, 3, 5). Hydrolysis of ethyl ester (VIII) by means of LiOH produces the corresponding acid (XXXIII), which is sequentially treated with *t*-$BuNH_2$, Et_3N, T_3P in EtOAc and $POCl_3$ (2). Scheme 3.

b) Selective condensation of 4,6-dichloro-5-fluoro-2-[1-(2-fluorobenzyl)-5-isoxazol-3-ylpyrazol-3-yl]pyrimidine (XII) with 2-(aminomethyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (XVIII) in DMSO at 60 °C gives secondary amine (XXXIV), which is dechlorinated using H_2 gas or hydrogenated optionally in the presence of a metal catalyst and a base (1). Scheme 4.

Background

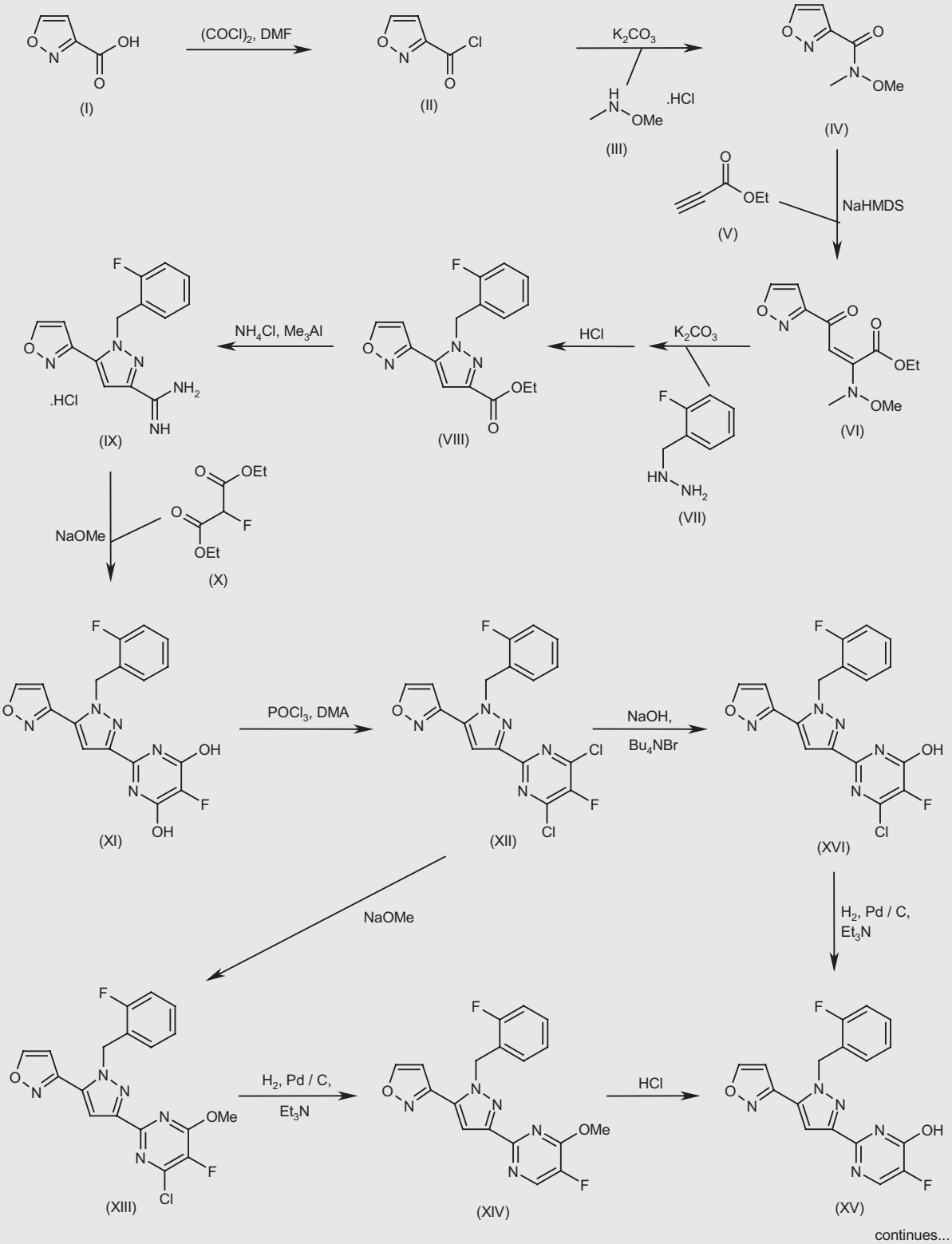
Heart failure

The number of people living with heart failure (HF) in the United States was estimated to be 5.7 million for the year 2012 and by the year 2030, the number is expected to drastically rise by 46% (6, 7). In addition, due to the symptomatic burden of this disease, the hospitalization rates for HF have increased by 125% over the last 25 years and about one-third of HF hospitalized patients are either re-admitted or expire within 90 days after discharge (8). Abundant therapies are available for the management of this disease; however, the amount of acute HF exacerbations resulting in mortality or mandating urgent therapy is unacceptably high and remains an unmet need in the United States.

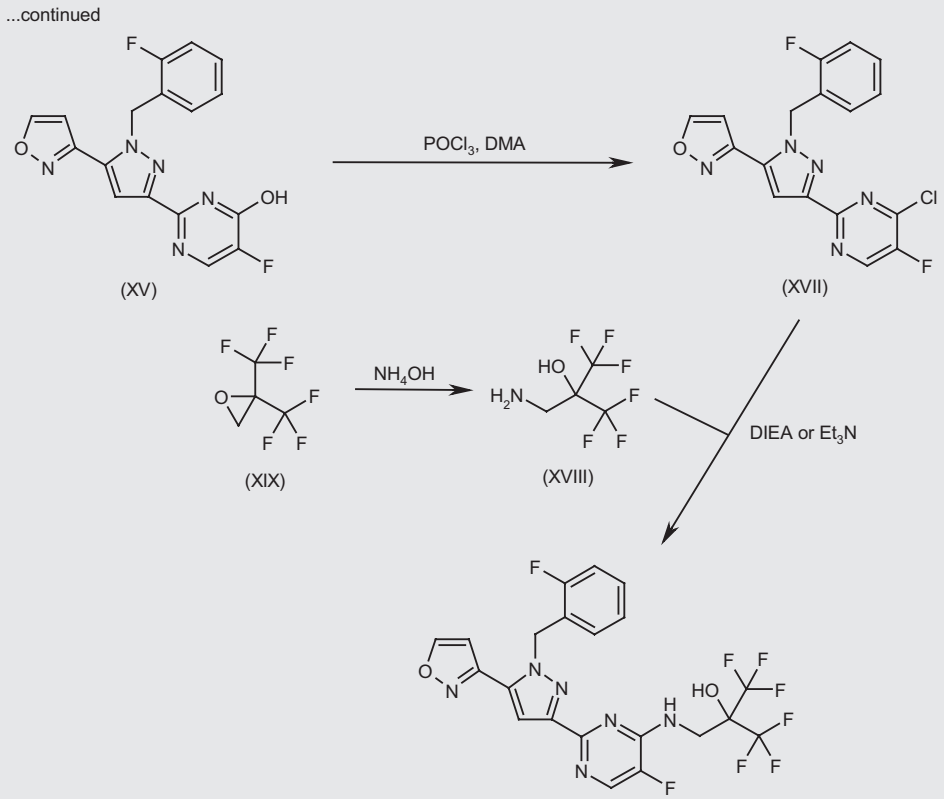
HF occurs when the cardiac muscle does not have the capacity to pump a sufficient amount of blood to meet the requirements of the body (9). This cardiac dysfunction is divided into two major subcategories: HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). HFrEF develops from systolic dysfunction with impaired ventricular contraction that results in an EF of less than 40% (6). Contrarily, HFpEF stems from diastolic left ventricle (LV) dysfunction resulting from decreased LV relaxation and increased LV wall stiffness. These abnormalities lead to impaired filling of the LV which does not allow the myocardium to pump an adequate supply of blood to the body (10). For this reason, patients with HFpEF present with normal ventricular systolic contraction and have an EF of 40% or greater (6).

In the treatment landscape for HF, there are numerous therapies available to reduce morbidity and mortality for patients with HFrEF, such as angiotensin-converting enzyme inhibitors (ACEis), angiotensin II receptor blockers (ARBs) and β-blockers (BBs) (9). However, there are currently no Food and Drug Administration (FDA) approved treatments to provide these same benefits in patients with HFpEF (9). It is presumed that the reasons behind the ineffectiveness of these therapies in HFpEF are the differences in the structural abnormalities of the LV between the two classes (i.e., HFpEF and HFrEF). For example, ACEis, ARBs and BBs have all shown to reverse LV remodeling in HFrEF by improving

Scheme 1a. Synthesis of Praliciguat



Scheme 1b. Synthesis of Praliciguat



the weakened ventricular walls; but due to the stiffened morphology of the LV walls in HFpEF, this effect is not beneficial in this population (11).

Diabetic nephropathy

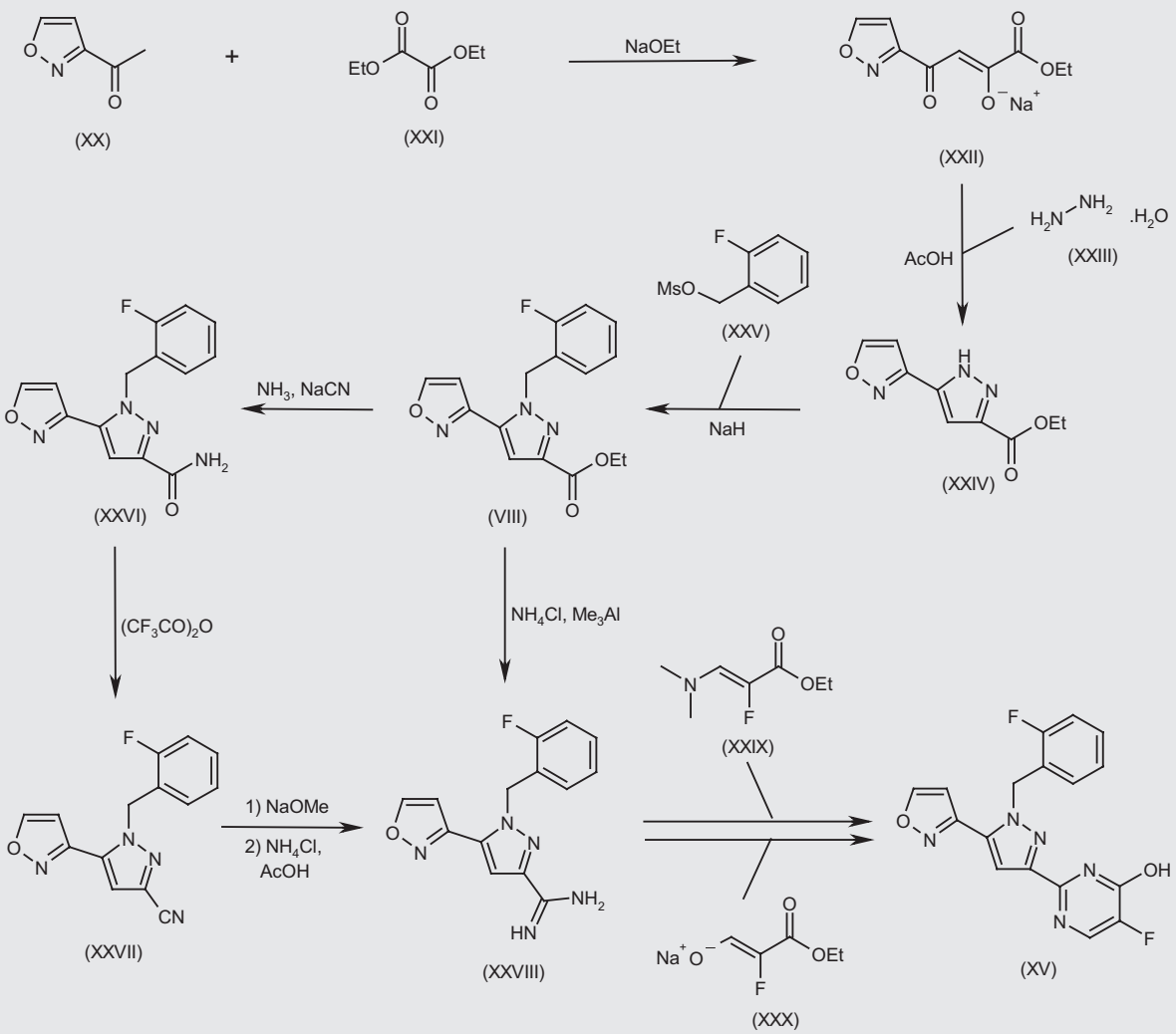
In the year 2015, approximately 30.3 million people in the U.S. were diagnosed with diabetes mellitus (DM) with roughly 40% developing diabetic nephropathy (DN) (12, 13). DN is a consequence of glomerulosclerosis and tubulointerstitial fibrosis caused by an increase in both systemic and glomerular pressure. Due to the damaged glomerulus membrane seen in DN, albuminuria is often used as marker to determine the prognosis and severity of the renal impairment. Increased excretion of albumin in the urine is indicative of the progression of DN, which can advance to end-stage renal disease (ESRD) and kidney transplant (13).

Among patients with type 1 DM (T1DM) and untreated microalbuminuria (urinary albumin excretion of 30-300 mg/day), approximately 80% will progress to overt DN, whereas only 20-40% of patients with type 2 DM (T2DM) will develop this complication (13). In patients with microalbuminuria, inhibiting the renin–angiotensin–aldosterone system (RAAS) through the utilization of neurohumoral antagonists has been found to slow the progression of DN. However, both T1DM and T2DM patients have a poor prognosis with a progressive decline in kidney function despite use of current recommended treatments, such as ACEis or ARBs (14). The increased need in medical attention and the potential requirement of hemodialysis and/or renal transplant results in an increased economic burden. This, together with the medical severity of the disease, mandates a need for a novel therapy that can either further slow or prevent the development of ESRD in patients with diabetes.

Drug Discovery and Mechanism

Under healthy conditions, the endothelium of the blood vessels undergoes constant stress due to the pressure produced by blood flow. This triggers the endothelial nitric oxide (NO) synthase (eNOS) to produce NO. NO, in turn, stimulates soluble guanylate cyclase (sGC) by binding to its heme prosthetic group resulting in the conversion of guanosine-5′-triphosphate (GTP) to cyclic guanosine

Scheme 2. Alternative synthesis to Intermediate IWP-051 (XV)

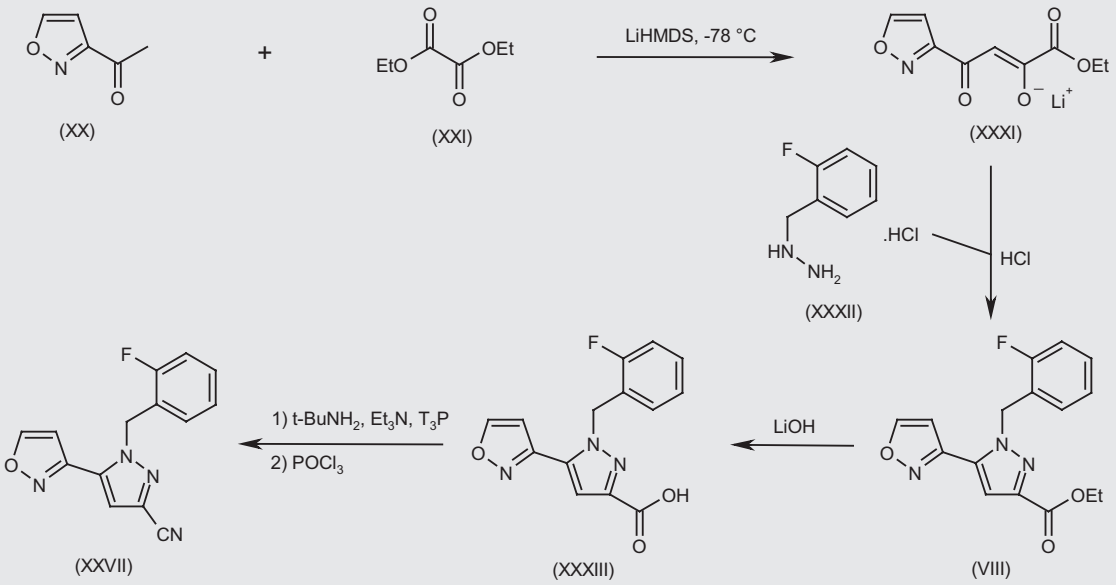


monophosphate (cGMP) leading to subsequent relaxation of the vascular smooth muscle (15, 16). sGC also acts as a receptor for NO in nonvascular tissues, such the myocardium, and therefore, the elevation of cGMP correspondingly regulates the contractility and relaxation of the myocardial muscle (16) (Fig. 1).

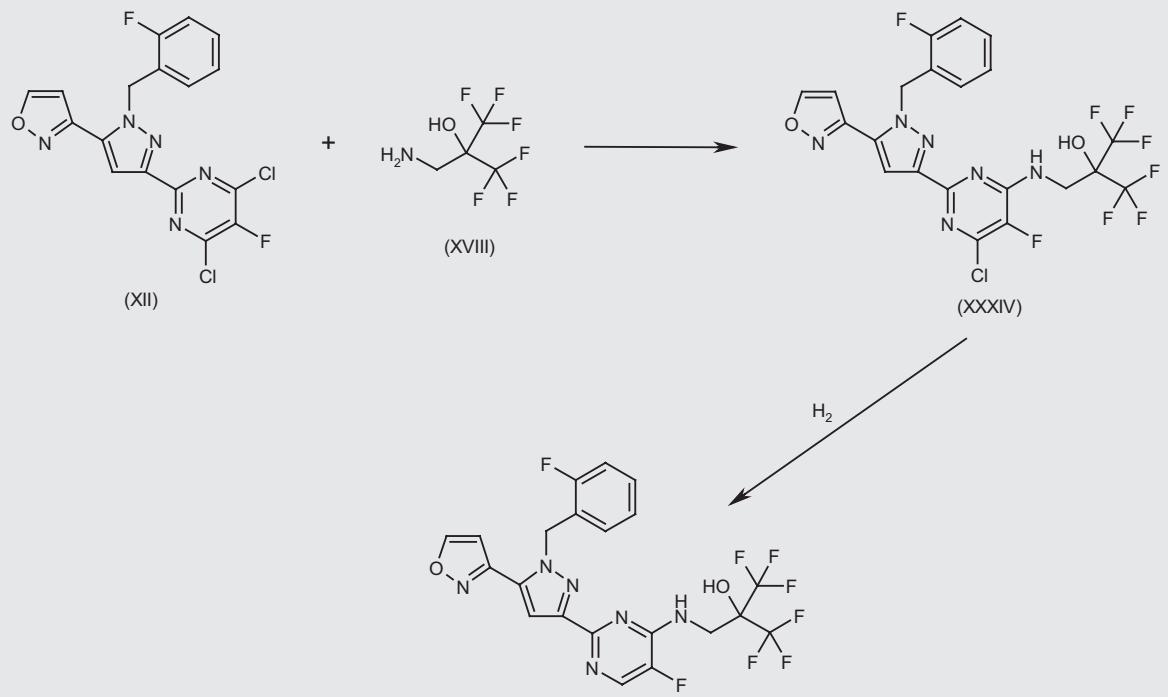
In the presence of DM and cardiovascular diseases, such as hypertension and HF, there is an increase in oxidative stress resulting in endothelium dysfunction and NO imbalance caused by decreased NO production and increased NO degradation (17). Impaired NO–sGC–cGMP pathway signaling reduces the availability of NO and, therefore, results in decreased sGC simulation. In addition, under such conditions, sGC is converted to an oxidized form, making it insensitive to NO and NO donors. This, in turn, leads to a decreased cGMP production and causes undesirable vasoconstriction, inflammation and fibrosis of the myocardium muscle and blood vessels (16).

The NO–sGC–cGMP pathway in the kidneys aids in the regulation of renal blood flow and renin release. This process helps maintain blood pressure (BP) through fluid retention and electrolyte transport through the activation of the RAAS (18). Oxidative stress due to the pathogenesis of diabetes can result in inflammation of the endothelium and impair the production of NO that is needed to maintain renal vascular tone and BP. Additionally, the disease progression may be associated with an increased production of asymmetric dimethylarginine, an inhibitor of eNOS, leading to a further decrease in the production of endogenous NO and increased glomerulosclerosis (19, 20).

Scheme 3. Alternative route to nitrile Intermediate (XXVII)



Scheme 4. Synthesis of Praliciguat



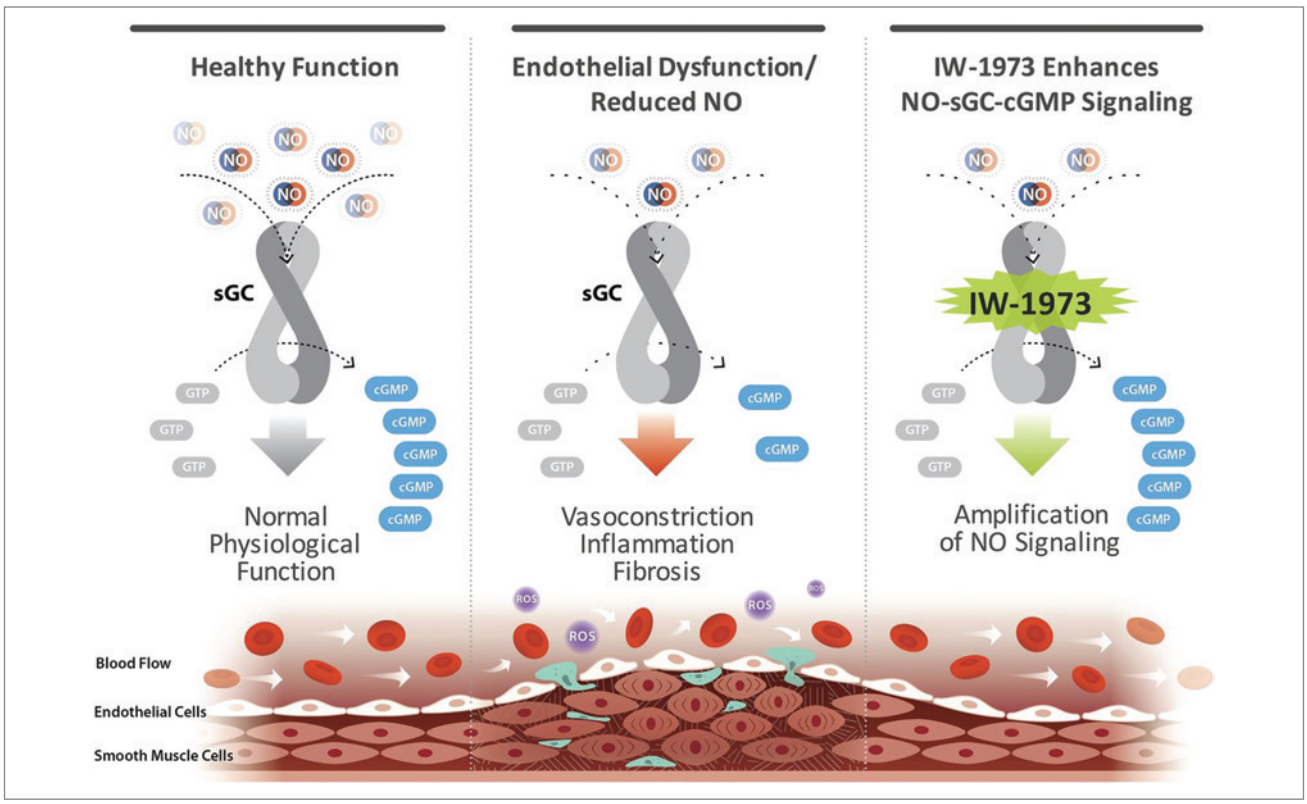


Figure 1. Mechanism of action of praliciguat. (Reproduced from Tobin, J.V. et al. *Pharmacological characterization of IW-1973, a novel soluble guanylate cyclase stimulator with extensive tissue distribution, antihypertensive, anti-inflammatory, and antifibrotic effects in preclinical models of disease.* J Pharmacol Exp Ther 2018, 365(3): 664-75 (15), © 2018 The Author[s], used under CC BY Attribution 4.0 International license.)

As NO potentiates a variety of beneficial effects through the stimulation of the NO–sGC–cGMP pathway, pharmacological agents that target this pathway may provide a powerful approach in the management of diseases such as chronic HFpEF and DN. sGC stimulators are a class of unique agents that directly act upon the NO–sGC pathway and modulate NO-mediated cGMP production. As a result, sGC stimulators are heme dependent and require heme-containing sGC to achieve full activity. Furthermore, in addition to their potential to increase sGC activity and directly increase cGMP production, sGC stimulators work synergistically with NO to further amplify cGMP production (15).

Currently, there are three sGC stimulators either approved by the FDA or being studied in clinical trials. Riociguat (Adempas; Bayer) is the only sGC stimulator approved by the FDA, but it is only indicated for the management of chronic thromboembolic pulmonary hypertension and pulmonary arterial hypertension and is dosed three times a day. Vericiguat (Bayer, Merck & Co.) is another sGC stimulator currently undergoing phase III clinical trials in patients with HFrEF and phase II studies in HFpEF. Praliciguat (IW-1973) is the most novel of all sGC stimulators and is being developed by Ironwood Pharmaceuticals with currently ongoing phase II clinical trials in both chronic HFpEF and DN.

Preclinical Pharmacology

A preclinical study conducted by Tobin et al. evaluated the production of cGMP through the stimulation of sGC by praliciguat in HEK-293 cells. In the absence of a NO donor (DETA-NONOate), a concentration-dependent increase in cGMP was observed with praliciguat 30 pM to 30 µM. Furthermore, in the presence of the NO donor DETA-NONOate (10 µM), a greater increase in cGMP production was observed compared with praliciguat 30 µM alone (cGMP = 431 nM vs. 96 nM). Such demonstration indicates that praliciguat not only directly increases the production of cGMP, but also has the ability to work synergistically with NO (15).

Tobin et al. evaluated the effects of praliciguat on BP, heart rate (HR), inflammation, proteinuria and renal fibrosis in male rats. BP was evaluated utilizing mean arterial pressure (MAP) and HR with praliciguat 0.3, 1, 3 and 10 mg/kg versus placebo. The animals were dosed orally via gavage. Each rat received one concentration of praliciguat for 4 days, then, following a 3-day washout period, received the next concentration of praliciguat. The MAP and HR were collected 1 day prior to therapy initiation and continued for 3 days after. A significant decrease in MAP from baseline was observed for praliciguat 1, 3 and 10 mg/kg in both normotensive rats

($P \leq 0.01$ for all doses) and hypertensive rats ($P \leq 0.01$, $P \leq 0.001$ and $P \leq 0.001$, respectively) (15). In addition, praliciguat 10 mg/kg resulted in a greater change in MAP from baseline in hypertensive rats compared to normotensive rats (25.2 ± 0.8 mmHg vs. 11.9 ± 0.9 mmHg, respectively). Moreover, there was a significant increase in HR in normotensive rats at praliciguat doses 0.3, 3 and 10 mg/kg compared to placebo at day 3 ($P \leq 0.05$, $P \leq 0.01$ and $P \leq 0.05$, respectively), while a significant increase in HR in hypertensive rats was only observed at the praliciguat 10 mg/kg dose ($P \leq 0.05$) (15).

Tobin et al. also examined praliciguat in Dahl salt-sensitive (DSS) male rats by splitting them into 2 groups, 1 receiving a normal salt (NS) diet (0.3% NaCl for 8 weeks) and the other receiving a high salt (HS) diet. HS diet rats were placed on 8% NaCl and further split into 3 groups: 1 control and 2 treatment groups—praliciguat (1, 3 or 10 mg/kg/day) and losartan 30 mg/kg/day. For all 3 groups, the DSS rats were dosed orally via gavage. At baseline, HS diet rats had a higher MAP compared to NS diet rats (145.5 ± 4.5 mmHg vs. 113.25 ± 1.75 mmHg, respectively) (15). In the praliciguat HS diet-treated rats, a dose-dependent decrease in MAP was observed within the first week of treatment and was maintained throughout 6 weeks of treatment. A decrease in inflammatory response demonstrated by reduced levels of interleukin-6 (IL-6) was also observed in HS diet rats treated with praliciguat 10 mg/kg/day compared with the HS control group ($P \leq 0.01$). Nevertheless, IL-6 levels in HS diet rats receiving praliciguat were similar to those in rats on NS diet and HS diet treated with losartan 30 mg/kg/day ($P \leq 0.05$) (15).

Furthermore, Tobin et al. identified that HS diet rats treated with praliciguat 10 mg/kg/day showed lower urinary protein levels compared to the HS diet control rats ($P \leq 0.05$) (15). This study also found the expression of transforming growth factor-β1 (TGF-β1) and collagen type I α 1 (Col1α1) genes to be lower in kidneys of rats on HS diet treated with either praliciguat 3 mg/kg/day or 10 mg/kg/day compared to HS diet control rats ($P \leq 0.001$) indicating a potential reduction in renal fibrosis. In addition, when compared to losartan, praliciguat 3 mg/kg was shown to be comparable in significantly reducing the expression of TGF-β1 and Col1α1 compared to HS diet control rats ($P \leq 0.001$) (15).

Lastly, another preclinical study by Shea et al. evaluated the efficacy of praliciguat in DSS rats with HFpEF and rats with HFrEF post-myocardial infarction. Compared to placebo, DSS rats treated with praliciguat had a lower heart/body mass ratio ($P < 0.05$) and liver/body ratio ($P < 0.05$) indicating less cardiac hypertrophy. In addition, the EF, which is often reduced in HFrEF patients, was shown to be unaffected in DSS rats treated with praliciguat compared to placebo ($P < 0.05$) (21). Lastly, N-terminal pro B-type natriuretic peptide (NT-proBNP), a marker used for the diagnosis and prognosis of HF, was observed to be lower in DSS rats treated with praliciguat than in those given placebo ($P < 0.05$) (21).

Pharmacokinetics and Metabolism

A preclinical study conducted in rats demonstrated that praliciguat reached its maximum concentration (C_{max}) of 254 ng/mL in 8 h. When administered orally, praliciguat had a half-life ($t_{½}$) of 9.2 h with a bioavailability of 102% and, when administered intravenously, its systemic clearance rate was 13.8 mL/min/kg with a large volume of distribution of 10.5 L/kg. Furthermore, the tissue concentration of oral praliciguat 10 mg/kg administered daily for 5 days displayed higher levels in organs such as the heart, kidneys and lungs, with the highest concentration present in the liver compared to the plasma (15).

In a phase Ia study conducted by Hanrahan et al., praliciguat demonstrated dose-proportional pharmacokinetics in 6 healthy volunteers with minimal intersubject variability. The study also showed a high volume of distribution and insignificant renal clearance (22). Additionally, in a phase Ib study conducted in healthy volunteers, praliciguat remained at its C_{max} for 2-4 h with a $t_{½}$ of 24 to 37 h (23).

Clinical Studies

A phase Ib study conducted by Hanrahan et al. evaluated the safety, pharmacokinetics and pharmacodynamics of praliciguat at ascending doses. A total of 44 healthy volunteers were equally randomized into 4 successive cohorts of which 8 received praliciguat and 3 received placebo. After 14 days of treatment, the mean change in systolic BP from baseline was −0.85 ± 1.32 mmHg in the placebo arm, −7.29 ± 1.62 mmHg in the praliciguat 15-mg arm, −3.27 ± 1.61 mmHg in the praliciguat 20-mg arm, −6.75 ± 1.62 mmHg in the praliciguat 30-mg arm, and −5.23 ± 1.61 mmHg in the praliciguat ≤ 40-mg arm (23). A dose-related increase in cGMP was also observed at day 21 in subjects that received praliciguat (23). This was demonstrated by change in systolic BP of −8.21 ± 1.46 mmHg in the praliciguat 15- to 30-mg arm, −6.29 ± 1.45 mmHg in the praliciguat 20- to 40-mg arm, and −9.05 ± 1.56 mmHg in the praliciguat 30- to 40-mg arm (23).

One phase IIa study that evaluated the safety, tolerability, pharmacokinetics and pharmacodynamics of praliciguat demonstrated a positive effect of praliciguat on BP, cholesterol, triglycerides and endothelial dysfunction in patients with T2DM and hypertension. A total of 26 subjects were randomized to 3 arms: 1) praliciguat 40 mg orally in the morning and placebo orally in evening for 14 days, 2) praliciguat 20 mg orally in the morning and praliciguat 20 mg orally in the evening for 7 days, followed by praliciguat 40 mg orally taken in the morning and placebo orally taken in the evening daily for the remaining 7 days, and 3) placebo in the morning and evening for 14 days (24). Results of the study were released by Ironwood Pharmaceuticals and demonstrated a decrease in MAP from baseline in the praliciguat groups compared to placebo at day 14 (6.3 vs. 1.6 mmHg). Also, a decrease in serum cholesterol, especially

in LDL cholesterol and triglycerides was observed at day 15 in subjects treated with praliciguat compared to placebo from baseline (24.7 vs. 0.8 mg/dL and 46.2 vs. 32.0 mg/dL). Additionally, asymmetric dimethylarginine (ADMA), an endothelial dysfunction biomarker and a cardiovascular disease risk factor, was reduced in subjects in the praliciguat arms compared with the placebo arm (25).

Currently, there are two ongoing phase II trials being conducted by Ironwood Pharmaceuticals with praliciguat. A multicenter, randomized, double-blind, placebo-controlled, phase II study evaluating the safety and efficacy of different doses of praliciguat over 12 weeks in patients with HFpEF (CAPACITY-HFpEF) enrolled its first patient in 2017 and is still enrolling patients at the time of this publication. This study will evaluate the safety and efficacy of praliciguat as well as its effect on peak exercise capacity in subjects with HFpEF with an EF of 40% or more who are 45 years of age or older meeting at least two of the following criteria: prediabetic, T2DM, history of hypertension, body mass index > 30 kg/m^2, or ≥ 70 years of age (26). The other ongoing trial is a randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of praliciguat in patients with T2DM with albuminuria treated with renin–angiotensin system inhibitors. This study was initiated in August 2017 and is evaluating the efficacy of praliciguat on albuminuria and kidney function when used concurrently with a stable dose of an ACEi or an ARB in subjects with T2DM (HbA_{1c} ≤ 11%), estimated glomerular filtration rate 30 to 75 mL/min/1.73 m^2, and albuminuria > 200 mg/g (27).

Safety and Tolerability

A phase Ia, randomized, placebo-controlled study with 46 healthy subjects measuring the safety profiles of ascending doses of praliciguat (3-100 mg in solution) did not report any cases of serious adverse events (SAEs) (22). More specifically, praliciguat up to 35 mg was well tolerated and AEs, such as headaches, tachycardia, nausea, vomiting and dizziness, were mostly mild or moderate in severity and seen mainly with praliciguat 45 and 100 mg (22). These AEs are consistent with the sGC stimulation mechanism and are in harmony with the other medications within this drug class. Furthermore, in a phase Ib study, praliciguat 15-40 mg was well tolerated by 32 healthy subjects, with AEs occurring with praliciguat 30 mg and greater. Of all the subjects receiving praliciguat, 15 experienced headaches, 6 suffered dizziness and 4 experienced orthostatic hypotension (23). However, no subjects dosed with praliciguat reported any SAEs or discontinued treatment due to an AE (23).

In a phase IIa study, evaluating the tolerability and safety of praliciguat in hypertensive T2DM patients, the most common AEs reported in the praliciguat treatment arms were headache, hypoglycemia and nausea. In addition, when compared to placebo, only a higher incidence of nausea with praliciguat versus placebo was noted. Lastly, only 1 SAE of an upper gastrointestinal hemorrhage with erosive esophagitis occurred in 1 subject in the praliciguat arm (25).

Drug Interactions

Data on drug–drug interactions specific to praliciguat are limited due to its current investigational drug status (i.e., phase II). However, riociguat, another sGC stimulator that is approved by the FDA, may be a good indicator of potential drug–drug interactions due to its similar mechanism of action (28). Since riociguat causes vasodilation and has the potential to reduce BP, the concurrent use of nitrates, nitrate oxide donors, phosphodiesterase PDE5 inhibitors, dipyridamole and theophylline are contraindicated with riociguat due to the increased risk of hypotension (28). Furthermore, praliciguat use in preclinical and clinical studies to date has demonstrated its similar ability to decrease BP and, due to this, it should be used cautiously with other BP-lowering therapies, such as those that are contraindicated with riociguat.

Conclusions

Praliciguat is a novel investigational sGC stimulator demonstrating promising preclinical effects on BP, HR, HF and renal fibrosis. Its multifactorial effect within the human body through a direct increase in endogenous cGMP may prove to have positive beneficial effects in patients with these comorbidities. Furthermore, its half-life and potential for once-daily dosing establishes a benefit over other agents within its drug class. Phase II clinical trials are currently underway, and these results will determine the drug's potential clinical benefit and possible progression to phase III trials.

Disclosures

The authors state no conflicts of interests.

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