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(54) **Title:** NOVEL SALTS OF TEGOPRAZAN AND ITS POLYMORPHS

(57) **Abstract:** The present invention relates to novel salts of Tegoprazan, its polymorphs and process for their preparation.

WO 2024/228133 A1

"NOVEL SALTS OF TEGOPRAZAN AND ITS POLYMORPHS"

Related applications:

This application claims the benefit under Indian Patent Application No. 202341031289 filed on May 2, 2023, the contents of which are incorporated by reference herein.

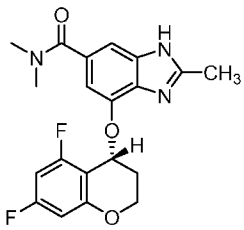
Field of the invention:

The present invention relates to novel salts of Tegoprazan, its polymorphic forms and process for their preparation.

Background of the invention:

Tegoprazan was approved by Ministry of Food and Drug safety (MFDS) Korea, in July, 2018, which is used for the treatment of gastroesophageal reflux disease and erosive esophagitis. Gastric proton pump hydrogen ion/potassium ion exchange ATPase is the main pharmacological target for the treatment of gastric acid-related diseases. Potassium-competitive acid blocker (P-CAB) can inhibit gastric acid secretion by binding to H^+/K^+-ATPase competitively with K^+. It is found in studies that Tegoprazan is such a potassium-competitive acid blocker, which is considered the most advanced drug for the treatment of gastroesophageal reflux disease, because proton pump inhibitors is the most commonly used drugs for the treatment of gastroesophageal reflux disease, and Tegoprazan can exactly overcome the shortcomings of proton pump inhibitors. The approval of this drug on the market provides new options for the treatment of such diseases, and to a certain extent makes up for the shortcomings of other drugs, so that such diseases can be better treated.

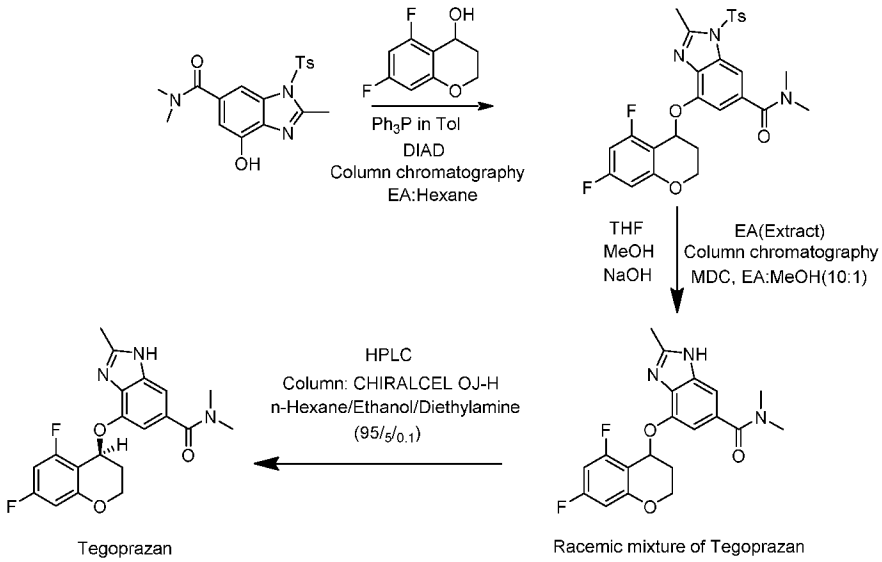
Tegoprazan, chemically known as (S)-4-((5,7-difluorochroman-4-yl) oxy)-N, N, 2-trimethyl-1H-benzo (d) imidazole-6-carboxamide, and structurally represented by the following Formula-I



Formula I

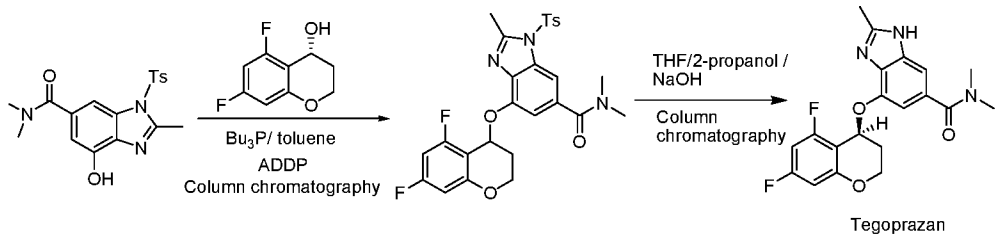
Tegoprazan and process for its preparation was first reported in US 7723321 and in the disclosed process Tegoprazan residue was purified by column chromatography on silica gel (gradient elution from dichloromethane only to ethyl acetate: methanol 10:1) to afford racemic Tegoprazan and the required isomer obtained using chiral HPLC. The process disclosed is schematically shown in the below scheme 1:

Scheme 1:



Similar process also reported in US 7723321, which is schematically shown in the below scheme 2:

Scheme 2:



The US9908870 patent discloses crystalline form A of Tegoprazan and process for the preparation of crystalline Form A of Tegoprazan.

The US11535610 patent discloses succinic acid, Fumaric acid, Oxalic acid, Citric acid, L-pyroglutamic acid, 1.5-naphinalene disulfonic acid, p-toluenesulfonic acid, Benzene sulfonic acid, L-malic acid, nicotinic acid, 2,5-dihydroxybenzoic acid and L-tartaric acid salts of Tegoprazan.

It has now surprisingly been found that the some other salts of Tegoprazan have numerous advantages over the free base of Tegoprazan as well as reported salts of Tegoprazan. The free base is poorly soluble in water and other organic solvents. This poor solubility adversely affects the ability of the free base to be formulated into pharmaceutical dosage forms and reduces the bioavailability of the compound in vivo. The discovery of new salt form of a pharmaceutically useful compound provides a new opportunity to improve the performance characteristics of a pharmaceutical product such as Tegoprazan. Hence the main object of the present invention is to provide novel salts of Tegoprazan.

Summary of the invention:

In one aspect, the present invention provides novel salts of Tegoprazan selected from acetic acid, benzoic acid, methanesulfonic acid, phosphoric acid, maleic acid, lactic acid and hippuric acid.

In another aspect, the present invention provides novel salts of Tegoprazan selected from acetic acid, benzoic acid, methanesulfonic acid, phosphoric acid, maleic acid, lactic acid, and hippuric acid in an amorphous form or in crystalline form.

In another aspect, the present invention provides acetate salt of Tegoprazan.

In another aspect, the present invention provides amorphous form of acetate salt of Tegoprazan.

In another aspect, the present invention provides amorphous form of acetate salt of Tegoprazan characterized by a powder X-ray diffractogram as shown in Figure 1.

In another aspect, the present invention provides benzoate salt of Tegoprazan.

In another aspect, the present invention provides amorphous form of benzoate salt of Tegoprazan.

In another aspect, the present invention provides amorphous form of benzoate salt of Tegoprazan characterized by a powder X-ray diffractogram as shown in Figure 2.

In another aspect, the present invention provides mesylate salt of Tegoprazan.

In another aspect, the present invention provides amorphous form of mesylate salt of Tegoprazan.

In another aspect, the present invention provides amorphous form of mesylate salt of Tegoprazan characterized by a powder X-ray diffractogram as shown in Figure 3.

In another aspect, the present invention provides phosphate salt of Tegoprazan.

In another aspect, the present invention provides amorphous form of phosphate salt of Tegoprazan.

In another aspect, the present invention provides amorphous form of phosphate salt of Tegoprazan characterized by a powder X-ray diffractogram as shown in Figure 4.

In another aspect, the present invention provides a process for the preparation of novel salts of Tegoprazan, which comprises;

a) dissolving or suspending Tegoprazan in a suitable solvent;
b) adding one or more equivalents of acid selected from acetic acid, benzoic acid, methanesulfonic acid, phosphoric acid, maleic acid, lactic acid, and hippuric acid; and
c) isolating the corresponding salt of Tegoprazan.

In another aspect, the present invention provides a process for the preparation of amorphous form of acetate salt of Tegoprazan, which comprises;

a) dissolving Tegoprazan in a suitable solvent;
b) adding acetic acid to the step a) solution; and
c) isolating the acetate salt of Tegoprazan in amorphous form.

In another aspect, the present invention provides a process for the preparation of amorphous form of benzoate salt of Tegoprazan, which comprises;

a) dissolving Tegoprazan in a suitable solvent;
b) adding benzoic acid to step a) solution; and
c) isolating the benzoate salt of Tegoprazan in amorphous form.

In another aspect, the present invention provides a process for the preparation of amorphous form of mesylate salt of Tegoprazan, which comprises;

a) dissolving Tegoprazan in a suitable solvent;
b) adding methanesulfonic acid to the step a) solution; and
c) isolating the mesylate salt of Tegoprazan in amorphous form.

In another aspect, the present invention provides a process for the preparation of amorphous form of phosphate salt of Tegoprazan, which comprises;

a) dissolving Tegoprazan in a suitable solvent;
b) adding phosphoric acid to the step a) solution; and
c) isolating the phosphate salt of Tegoprazan in amorphous form.

In one more aspect, the present invention provides co-crystal/salt form of L-proline and Tegoprazan.

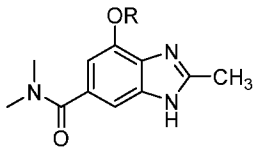
In another aspect, the present invention provides co-crystal form of L-proline and Tegoprazan characterized by a powder X-ray diffractogram as shown in Figure 5.

In another aspect, the present invention provides a process for the preparation of co-crystal form of L-proline and Tegoprazan, which comprises;

a) dissolving Tegoprazan in a suitable solvent;
b) adding L-proline to step-a) solution; and
c) isolating the co-crystal form of L-proline and Tegoprazan.

In a further aspect, the present invention provides a pharmaceutical composition comprising novel salts of Tegoprazan or its amorphous form or co-crystal form of L-proline and Tegoprazan of the present invention and at least one pharmaceutically acceptable excipient.

In one more aspect, the present invention provides a process for the preparation of a compound of formula II, which is an intermediate useful for the preparation of Tegoprazan and its salts;

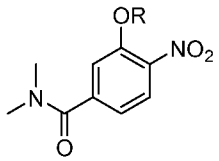


Formula II

wherein R is hydroxyl protecting group;

which comprises;

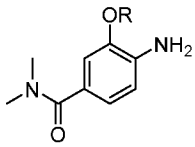
a) reducing a compound of formula III with a suitable reducing agent;



Formula III

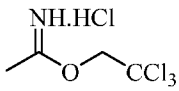
wherein R is hydroxyl protecting group;

to provide a compound of formula IV; wherein R is hydroxyl protecting group;



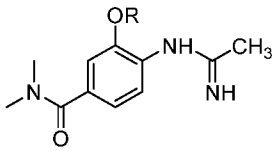
Formula IV

b) reacting the compound of formula IV with a compound of formula V



Formula V

to provide a compound of formula VI; and



Formula VI

wherein R is hydroxyl protecting group;

c) cyclizing the compound of formula VI to provide a compound of formula II; and

d) optionally converting the compound of formula II into Tegoprazan of formula I.

Brief Description of Drawings:

Figure 1: Illustrates the Powder X-Ray Diffraction (PXRD) pattern of amorphous form of acetate salt of Tegoprazan.

Figure 2: Illustrates the Powder X-Ray Diffraction (PXRD) pattern of amorphous form of benzoate salt of Tegoprazan.

Figure 3: Illustrates the Powder X-Ray Diffraction (PXRD) pattern of amorphous form of mesylate salt of Tegoprazan.

Figure 4: Illustrates the Powder X-Ray Diffraction (PXRD) pattern of amorphous form of phosphate salt of Tegoprazan.

Figure 5: Illustrates the Powder X-Ray Diffraction (PXRD) pattern of co-crystal form L-proline and Tegoprazan.

The Powder X-ray diffraction (PXRD) pattern measured on an X-ray diffractometer (Instrument name Bruker D8 Advance) with measured using CuKα radiation of wavelength 1.54060A° step size of 0.02°/min; total time/step 57.60s; scan range of 3-40°A.

Detailed description of the invention:

Accordingly, the present invention provides novel salts of Tegoprazan, process for its preparation and pharmaceutical compositions comprising the same. The novel salts of Tegoprazan of the present invention may have advantageous properties selected from at least one of: chemical purity, flowability, solubility, morphology or crystal habit, stability - such as storage stability.

The novel salts of Tegoprazan of the present invention are characterized by X-ray powder diffraction ("XRPD") patterns, differential scanning calorimetry ("DSC") curves, infrared ("IR") absorption spectra, and H^1 NMR spectra.

In one aspect, the present invention provides novel salts of Tegoprazan selected from acetic acid, benzoic acid, methanesulfonic acid, phosphoric acid, maleic acid, lactic acid and hippuric acid.

In another aspect, the present invention provides novel salts of Tegoprazan selected from acetic acid, benzoic acid, methanesulfonic acid, phosphoric acid, maleic acid, lactic acid and hippuric acid is in amorphous form or in crystalline form.

In another aspect, the present invention provides acetate salt of Tegoprazan.

In another aspect, the present invention provides amorphous form of acetate salt of Tegoprazan.

In another aspect, the present invention provides amorphous form of acetate salt of Tegoprazan characterized by powder X-ray diffractogram as shown in Figure 1.

In another aspect, the present invention provides benzoate salt of Tegoprazan.

In another aspect, the present invention provides amorphous form of benzoate salt of Tegoprazan.

In another aspect, the present invention provides amorphous form of benzoate salt of Tegoprazan characterized by powder X-ray diffractogram as shown in Figure 2.

In another aspect, the present invention provides mesylate salt of Tegoprazan.

In another aspect, the present invention provides amorphous form of mesylate salt of Tegoprazan.

In another aspect, the present invention provides amorphous form of mesylate salt of Tegoprazan characterized by powder X-ray diffractogram as shown in Figure 3.

In another aspect, the present invention provides phosphate salt of Tegoprazan.

In another aspect, the present invention provides amorphous form of phosphate salt of Tegoprazan.

In another aspect, the present invention provides amorphous form of phosphate salt of Tegoprazan characterized by powder X-ray diffractogram as shown in Figure 4.

In another aspect, the present invention provides a process for the preparation of novel salts of Tegoprazan, which comprises;

a) dissolving or suspending Tegoprazan in a suitable solvent;
b) adding one or more equivalents of acid selected from acetic acid, benzoic acid, methanesulfonic acid, phosphoric acid, maleic acid, lactic acid and hippuric acid; and
c) isolating the corresponding salt of Tegoprazan.

In the foregoing process, the step a) involves dissolution or suspension of Tegoprazan in a suitable solvent selected from alcoholic solvents, ketone solvents, ester solvents, ether solvents, nitrile solvents or mixtures thereof; preferably methanol, ethanol, isopropanol, acetone, acetonitrile, ethyl acetate, isopropyl acetate, tetrahydrofuran or mixtures thereof; more preferably methanol; and is carried out at a suitable temperature from about 10°C to about 40°C or reflux temperature of the solvent used; preferably at about 20-30°C; In step b) the addition of suitable acid selected from acetic acid, benzoic acid, methanesulfonic acid, phosphoric acid, maleic acid, lactic acid and hippuric acid to step a) solution or vice versa; is carried out at a suitable temperature from about 10°C to about reflux temperature of the solvent used; preferably at 20-30°C; followed by stirring the reaction mass for a sufficient period of time at a suitable temperature; then the isolation of novel salts of Tegoprazan in step c) is carried out by removing of the solvent from step b) solution or optionally adding suitable anti-solvent to step b) solution followed by filtration and drying of the obtained solid. The removal of solvent from the step b) solution is carried out by known techniques such as distillation, spray drying, agitated thin film drying ("ATFD"), and freeze drying or optionally adding anti-solvent; for example, the removal of solvent is carried out by distillation of the solvent completely from the reaction mass in a rotary evaporator, optionally adding a second solvent in which obtained salts are not soluble, for example n-heptane, hexane, cyclopentane, cyclohexane and the like; then filtering off the solid followed by drying.

In a further aspect, the obtained novel salts of Tegoprazan are in amorphous in nature.

In another aspect, the present invention provides a process for the preparation of amorphous form of acetate salt of Tegoprazan, which comprises;

a) dissolving Tegoprazan in a suitable solvent;
b) adding acetic acid to the step a) solution; and
c) isolating the acetate salt of Tegoprazan in amorphous form.

In another aspect, the present invention provides a process for the preparation of amorphous form of benzoate salt of Tegoprazan, which comprises;

a) dissolving Tegoprazan in a suitable solvent;
b) adding benzoic acid to step a) solution; and
c) isolating the benzoate salt of Tegoprazan in amorphous form.

In another aspect, the present invention provides a process for the preparation of amorphous form of mesylate salt of Tegoprazan, which comprises;

a) dissolving Tegoprazan in a suitable solvent;
b) adding methanesulfonic acid to the step a) solution; and
c) isolating the mesylate salt of Tegoprazan in amorphous form.

In another aspect, the present invention provides a process for the preparation of amorphous form of phosphate salt of Tegoprazan, which comprises;

a) dissolving Tegoprazan in a suitable solvent;
b) adding phosphoric acid to the step a) solution; and
c) isolating the phosphate salt of Tegoprazan in amorphous form.

All steps involved in the forgoing process of novel salts of Tegoprazan is carried out at a suitable temperature from about 10°C to about 40°C or reflux temperature of the solvent used; preferably at room temperature; for a sufficient period of time till complete formation of the salt. The suitable solvent is selected from alcoholic solvents, ketone solvents, ester solvents, ether solvents, nitrile solvents or mixtures thereof; preferably methanol, ethanol, isopropanol, acetone, acetonitrile, ethyl acetate, isopropyl acetate, tetrahydrofuran or mixtures thereof; more preferably methanol. Further the isolation of novel salt is carried out by the methods known in the art such as removing the solvent, filtration, adding anti-solvent, cooling to low temperature; preferably, removing the solvent by distillation followed drying the obtained solid.

In one more aspect, the present invention provides co-crystal form of L-proline and Tegoprazan.

In another aspect, the present invention provides co-crystal form of L-proline and Tegoprazan characterized by a powder X-ray diffractogram as shown in Figure 5.

In another aspect, the present invention provides a process for the preparation of co-crystal form of L-proline and Tegoprazan, which comprises;

a) dissolving Tegoprazan in a suitable solvent;
b) adding L-proline to step-a) solution; and
c) isolating the co-crystal form of L-proline and Tegoprazan.

In the foregoing process, the step a) involves the dissolution of Tegoprazan in a suitable solvent, such as alcoholic solvent selected from methanol, ethanol, isopropanol, butanol, isobutanol, t-butanol and the like; preferably methanol; and is carried out at a suitable temperature from about 10°C to about 40°C or reflux temperature of the solvent used; preferably at room temperature; in step b) addition of L-proline to step a) solution or vice versa; is carried out at a suitable temperature from about 10°C to about 40°C or reflux temperature of the solvent used; preferably at room temperature; followed by stirring the reaction mass for a sufficient period of time at a suitable temperature; then the isolation of co-crystal form of L-proline and Tegoprazan in step c) is carried out by methods known in the art; for example, distilling off the solvent completely from the reaction mass.

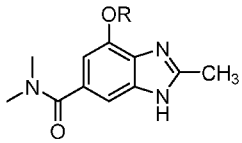
The starting compound Tegoprazan is known in the art and commercially available. The same can be procured from commercial sources or can be prepared by the methods known in the art. Further, the staring Tegoprazan may be in any form such as amorphous or any other crystalline or solvated forms known in the art.

In a further aspect, the present invention provides a pharmaceutical composition comprising novel salts of Tegoprazan of the present invention or its amorphous form or co-crystal form of L-proline and Tegoprazan and at least one pharmaceutically acceptable excipient. The novel salts of Tegoprazan of the present invention may readily be incorporate into

pharmaceutical compositions for immediate or delayed or modified release for the treatment of erosive & non-erosive gastroesophageal reflux disease.

In another aspect, the stoichiometry of each component in the salt can vary and the ratio of the compound to salt is from 1:0.5 to 1:3 preferably mono salt means 1:1 ratio.

In one more aspect, the present invention provides a process for the preparation of a compound of formula II, which is an intermediate useful for the preparation of Tegoprazan and its salts;

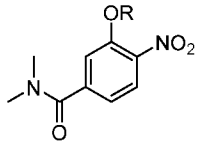


Formula II

wherein R is hydroxyl protecting group;

which comprises;

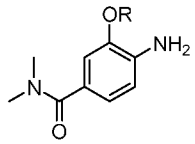
a) reducing a compound of formula III with a suitable reducing agent,



Formula III

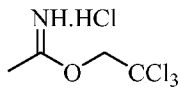
wherein R is hydroxyl protecting group;

to provide a compound of formula IV; wherein R is hydroxyl protecting group;



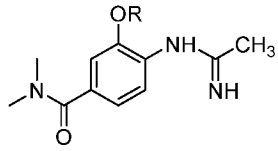
Formula IV

b) reacting the compound of formula IV with a compound of formula V,



Formula V

to provide a compound of formula VI; and



Formula VI

wherein R is hydroxyl protecting group;

c) cyclizing the compound of formula VI to provide a compound of formula II; and

d) optionally converting the compound of formula II into Tegoprazan of formula I.

The starting compound of formula III is known in the art and commercially available. The same can be prepared by the methods known in the art or obtained from the commercial sources.

The step a) of the forgoing process involves reduction of a compound of formula III, wherein R is hydroxyl protecting group, may selected from benzyl or p-methoxybenzyl; preferably benzyl; with a suitable reducing agent selected from Zn powder, Fe (iron) powder, $SnCl_2$, sodium hydrosulfite, Pd/C and the like; preferably iron powder; in a suitable solvent selected from alcoholic solvents, ether solvents, nitrile solvents, ester solvents, ketone solvents, chloro solvents, water and/or mixtures thereof; under appropriate reaction conditions to provide a compound of formula IV. The step a) reaction is carried out at a suitable temperature from about 25°C to about reflux temperature of the solvent used and maintain for a sufficient period of time for completion of the reaction, preferably carried out at 70-90°C for a time period of 1-2 hours.

The step b) of the forgoing process involves reaction of the compound of formula IV, wherein R is hydroxyl protecting group, may selected from benzyl or p-methoxybenzyl; preferably benzyl; with a compound of formula V to provide a compound of formula VI, wherein R is hydroxyl protecting group may selected from benzyl or p-methoxybenzyl; preferably benzyl; and is carried out in the presence of a base or alkali salt of weak organic acid such as sodium acetate or potassium acetate and the like; preferably sodium acetate in a suitable solvent selected from alcoholic solvents, ether solvents, nitrile solvents, ester solvents, ketone solvents, chloro solvents, water and/or mixtures thereof; preferably methylene dichloride; at a temperature from about 25°C to reflux temperature of the solvent

used for a sufficient period of time for completion of the reaction, preferably carried out at 20-40°C for a time period of 5-7 hours.

The step c) of the forgoing process involves cyclisation of the compound of formula VI and is carried out in the presence of suitable N-halo succinamide such as N-chloro succinamide or N-bromo succinamide; preferably N-chloro succinamide in the presence of a base selected from inorganic bases like sodium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate; preferably sodium hydroxide, in a suitable solvent selected from alcoholic solvents, ether solvents, nitrile solvents, ester solvents, ketone solvents, chloro solvents, water and/or mixtures thereof; preferably acetonitrile and/or water; at a temperature from about 25°C to reflux temperature of the solvent used for a sufficient period of time for completion of the reaction, preferably carried out at 20-40°C for a time period of 4-5 hours.

In step d), the conversion of formula II into Tegoprazan can be carried out by the methods known in the art, for example as per the methods disclosed in US7723321.

The term "suitable solvent" used in the present invention until unless specified is selected from, but are not limited to "alcoholic solvents" such as methanol, ethanol, isopropyl alcohol, n-propanol, butanol and the like; "ester solvents" such as ethyl acetate, methyl acetate, n-butyl acetate, isobutyl acetate, sec-butyl acetate, isopropyl acetate and the like, "ether solvents" such as tetrahydrofuran, diethyl ether, methyl tert-butyl ether, dioxane and the like; "hydrocarbon solvents" such as toluene, xylene, cyclohexane, hexane, heptane, n-pentane, petroleum ether and the like; "chloro solvents" such as dichloromethane, ethylene dichloride, carbon tetrachloride, chloroform and the like; "polar aprotic solvents" such as dimethylformamide, dimethylacetamide, dimethylsulfoxide and the like; "nitrile solvents" such as acetonitrile and the like; "ketone solvents" such as acetone, methyl isobutyl ketone, methyl ethylketone and the like; and water and/or mixtures thereof.

The term "suitable base" used herein the present invention until unless specified is selected from inorganic bases like "alkali metal hydroxides" such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; "alkali metal carbonates" such sodium carbonate, potassium carbonate, lithium carbonate and the like; "alkali metal bicarbonates"

such as sodium bicarbonate, potassium bicarbonate, lithium bicarbonate and the like; "alkali metal hydrides" such as sodium hydride, potassium hydride, lithium hydride and the like; "alkali metal alkoxides" such as sodium methoxide, sodium ethoxide, sodium tertbutoxide, potassium methoxide, potassium ethoxide, potassium tert-butoxide and the like; ammonia.

The process details of the invention are provided in the examples given below, which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention.

Examples:

Example-1: Preparation of acetate salt of Tegoprazan:

To a clean and dry RBF, Tegoprazan (5 g) and methanol (25 ml) were added at room temperature and stirred for 15 minutes at the same temperature. Acetic acid (0.82 g) was added to this solution at room temperature and maintained for 2 hours at the same temperature. The reaction mass was distilled off completely under vacuum at below 50°C to get the title compound.

Yield: 5.5 g. Purity by HPLC: 99.65%

The PXRD of Tegoprazan acetate obtained by the process is set forth in Figure 1.

Example-1a: Preparation of acetate salt of Tegoprazan:

To a clean and dry RBF, Tegoprazan (100 g) and methanol (500 ml) were added at room temperature and stirred for 15 minutes at the same temperature. Acetic acid (20 g) was added to this solution at room temperature and maintained for 2 hours at the same temperature. The reaction mass was filtered through hyflow bed and washed with methanol. The filtrate was distilled off under vacuum at below 50°C. n-Heptane was added to the obtained compound at 20-30°C and stirred for 30 minutes. The solid obtained was filtered; washed with n-heptane and dried to get the title compound.

Yield: 110 g.

The PXRD of Tegoprazan acetate obtained by the process is set forth in Figure 1.

Example-2: Preparation of benzoate salt of Tegoprazan:

To a clean and dry RBF, Tegoprazan (5 g) and methanol (25 ml) were added at room temperature and stirred for 15 minutes at the same temperature. Benzoic acid (1.65 g) was added to this solution at room temperature and maintained for 2 hours at the same temperature. The reaction mass was distilled off completely under vacuum at below 50°C to get the title compound.

Yield: 5.2 g.

The PXRD of Tegoprazan benzoate obtained by the process is set forth in Figure 2.

Example-3: Preparation of mesylate salt of Tegoprazan:

To a clean and dry RBF, Tegoprazan (5 g) and methanol (25 ml) were added at room temperature and stirred for 15 minutes at the same temperature. Methanesulfonic acid (1.32 g) was added to this solution at room temperature and maintained for 2 hours at the same temperature. The reaction mass was distilled off completely under vacuum at below 50°C to get the title compound.

Yield: 5.48 g. Purity by HPLC: 99.53%

The PXRD of Tegoprazan mesylate obtained by the process is set forth in Figure 3.

Example-4: Preparation of phosphate salt of Tegoprazan:

To a clean and dry RBF, Tegoprazan (5 g) and methanol (25 ml) were added at room temperature and stirred for 15 minutes at the same temperature. Phosphoric acid (0.82 g) was added to this solution at room temperature and maintained for 2 hours at the same temperature. The reaction mass was distilled off completely under vacuum at below 50°C to get the title compound.

Yield: 5.82 g. Purity by HPLC: 99.72%

The PXRD of Tegoprazan phosphate obtained by the process is set forth in Figure 4.

Example-5: Preparation of co-crystal form of L-Proline and Tegoprazan:

To a clean and dry RBF, Tegoprazan (10 g) and methanol (50 ml) were added at room temperature and stirred for 15 minutes at the same temperature. L-proline (3.18 g) was added to this solution at room temperature and maintained for 2 hours at the same temperature. The reaction mass was distilled off completely under vacuum at below 50°C to get the title compound.

Yield: 12 g.

The PXRD of L-Proline and Tegoprazan co-crystal obtained by the process is set forth in Figure 5.

Example-6: Preparation of 4-amino-3-(benzyloxy)-N,N-dimethylbenzamide (formula IV; R is benzyl):

To a clean and dry RBF, ammonium formate (154.4 g), water (166 ml) followed by 3-benzyloxy-N,N-dimethyl-4-nitro-benzamide (116 g) in toluene was added at 25-35°C. To this, THF (49 ml) and ethanol (50 ml) were added at 25-35°C and stirred for 20 minutes. The reaction mass was heated to 75-85°C and Iron powder (185 g) was added lot wise for every 15 mins at the same temperature. After the reaction completion, the reaction mass was cooled to 25-35°C, filtered through hyflow and washed with toluene. Water was added to the obtained filtrate, stirred for 15 minutes. The organic and aqueous layers were separated; organic layer was washed with sodium chloride solution, dried over sodium sulphate and distilled off the solvent under vacuum to get title compound.

Yield: 72.5 g.

Example-7: Preparation of 4-acetimidamido-3-(benzyloxy)-N,N-dimethyl benzamide (formula VI; R is benzyl):

To a clean and dry RBF, 4-amino-3-benzyloxy-N,N-dimethylbenzamide (15 g) and methylene dichloride (150 ml) was added at 25-35°C and stirred for 15 minutes. Sodium acetate (9.2 g) and 2,2,2-trichloroethyl acetimidate hydrochloride (22.6 g) were added lot wise to the reaction mass at 25-35°C and stirred maintained for 6 hours. After reaction completion, water (150 ml) was added to this reaction mixture at 25-35°C and stirred for 15 minutes. The organic and aqueous layers separated; the aqueous layer washed with diisopropylether; the organic layer washed with water. Aqueous layers were combined, pH adjusted to 8-9 with potassium carbonate and then extracted with methylene dichloride. The extracted methylene chloride layer was washed with sodium chloride solution, dried over sodium sulphate and distilled off the solvent completely under vacuum to get title compound. Yield: 14.3 g.

Example-8: Preparation of 4-(benzyloxy)-N,N,2-trimethyl-1H-benzo[d] imidazole-6-carboxamide (formula II; R is benzyl):

To a clean and dry RBF, 4-acetimidamido-3-(benzyloxy)-N,N-dimethylbenzamide (14 g), acetonitrile (140 ml) and N-chlorosuccinamide (7.14 g) were added at 25-35°C, stirred, cooled to 0-5°C and maintained for 40 minutes at the same temperature. After reaction completion, sodium hydroxide solution (18 ml) was added to the reaction mixture at 0-5°C and maintained for 2 hours at the same temperature. After completion of the reaction, the reaction mass was distilled off completely under vacuum at below 45°C. Water (70 ml) was added to obtained crude and pH of the reaction mass adjusted to 1-2 with hydrochloric acid solution at 0-5°C. Then reaction mass temperature was raised to 25-35°C, ethyl acetate (70 ml) was added and stirred for 15 minutes. The organic and aqueous layers were separated; aqueous layer washed with ethyl acetate and pH was adjusted to 9-10 with sodium carbonate at 0-5°C. Then the aqueous layer was extracted twice with methylene dichloride at 25-35°C; the extracted methylene chloride layer was washed with sodium chloride solution and distilling off the solvent completely under vacuum to get title compound. Yield: 7.6 g.

WE CLAIM:

1. Novel salts of Tegoprazan selected from acetic acid, benzoic acid, methanesulfonic acid and phosphoric acid.

2. The novel salts of Tegoprazan as claimed in claim 1 are in amorphous form or in crystalline form.

3. A process for the preparation of novel salts of Tegoprazan, which comprises;
   a) dissolving or suspending Tegoprazan in a suitable solvent;
   b) adding one or more equivalents of acid selected from acetic acid, benzoic acid, methanesulfonic acid and phosphoric acid; and
   c) isolating the corresponding salt of Tegoprazan.

4. The process as claimed in claim 3, wherein the suitable solvent comprises alcoholic solvents, ketone solvents, ester solvents, ether solvents, nitrile solvents and/or mixtures thereof.

5. The process as claimed in claim 3, wherein the suitable solvent comprises methanol, ethanol, isopropanol, acetone, acetonitrile, ethyl acetate, isopropyl acetate, tetrahydrofuran and/or mixtures thereof.

6. An amorphous form of acetate salt of Tegoprazan characterized by a powder X-ray diffractogram substantially as shown in Figure 1.

7. An amorphous form of benzoate salt of Tegoprazan characterized by a powder X-ray diffractogram substantially as shown in Figure 2.

8. An amorphous form of mesylate salt of Tegoprazan characterized by a powder X-ray diffractogram substantially as shown in Figure 3.

9. An amorphous form of phosphate salt of Tegoprazan characterized by a powder X-ray diffractogram substantially as shown in Figure 4.

10. The process for the preparation of amorphous form of acetate salt of Tegoprazan as claimed in claim 6, which comprises;
    a) dissolving Tegoprazan in a suitable solvent;
    b) adding acetic acid to the step a) solution; and
    c) isolating the acetate salt of Tegoprazan in amorphous form.

11. The process for the preparation of amorphous form of benzoate salt of Tegoprazan as claimed in claim 7, which comprises;
    a) dissolving Tegoprazan in a suitable solvent;
    b) adding benzoic acid to step a) solution; and
    c) isolating the benzoate salt of Tegoprazan in amorphous form.

12. The process for the preparation of amorphous form of mesylate salt of Tegoprazan as claimed in claim 8, which comprises;
    a) dissolving Tegoprazan in a suitable solvent;
    b) adding methanesulfonic acid to the step a) solution; and
    c) isolating the mesylate salt of Tegoprazan in amorphous form.

13. The process for the preparation of amorphous form of phosphate salt of Tegoprazan as claimed in claim 9, which comprises;
    a) dissolving Tegoprazan in a suitable solvent;
    b) adding phosphoric acid to the step a) solution; and
    c) isolating the phosphate salt of Tegoprazan in amorphous form.

14. The process as claimed in the claims 10 to 13, wherein the suitable solvent comprises alcoholic solvents, ketone solvents, ester solvents, ether solvents, nitrile solvents or mixtures thereof.

15. The process as claimed in the claims 10 to13, wherein the isolation in step c) is carried out by removing of the solvent from step b) solution.

16. A co-crystal form of L-proline and Tegoprazan.

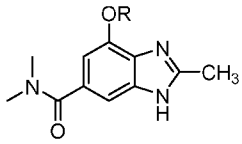
17. The co-crystal form of L-proline and Tegoprazan of claim 16 characterized by a powder X-ray diffractogram substantially as shown in Figure 5.

18. The process for the preparation of co-crystal form of L-proline and Tegoprazan as claimed in claim 16, which comprises;
    a) dissolving Tegoprazan in a suitable solvent;
    b) adding L-proline to step-a) solution; and
    c) isolating the co-crystal form of L-proline and Tegoprazan.

19. The process as claimed in claim 18, wherein the suitable solvent comprises methanol, ethanol, isopropyl alcohol, n-propanol, butanol, isobutanol, t-butanol and/or mixtures thereof.

20. A pharmaceutical composition comprising novel salts of Tegoprazan or its amorphous form as claimed in claim 1 and claim 2, or the co-crystal form of L-proline and Tegoprazan as claimed in claim 16, and at least one pharmaceutically acceptable excipient.

21. A process for the preparation of a compound of formula II, which is an intermediate useful for the preparation of Tegoprazan and its salts;

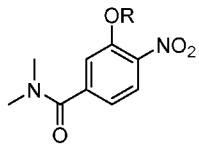


Formula II

wherein R is hydroxyl protecting group;

which comprises;

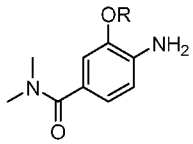
a) reducing a compound of formula III with a suitable reducing agent;



Formula III

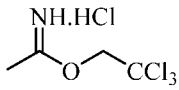
wherein R is hydroxyl protecting group;

to provide a compound of formula IV; wherein R is hydroxyl protecting group;



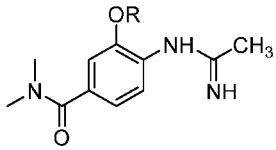
Formula IV

b) reacting the compound of formula IV with a compound of formula V



Formula V

to provide a compound of formula VI; and



Formula VI

wherein R is hydroxyl protecting group;

c) cyclizing the compound of formula VI to provide a compound of formula II; and

d) optionally converting the compound of formula II into Tegoprazan of formula I.

22. The process as claimed in claim 21, wherein the reducing agent in step a) comprises Zn powder, Fe powder, $SnCl_2$, sodium hydrosulfite, Pd/C and/or mixtures thereof; and cyclisation in step c) is carried out in the presence of N-halo succinamide and a base selected from sodium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate and/or mixtures thereof.

METROCHEM API PVT. LTD.

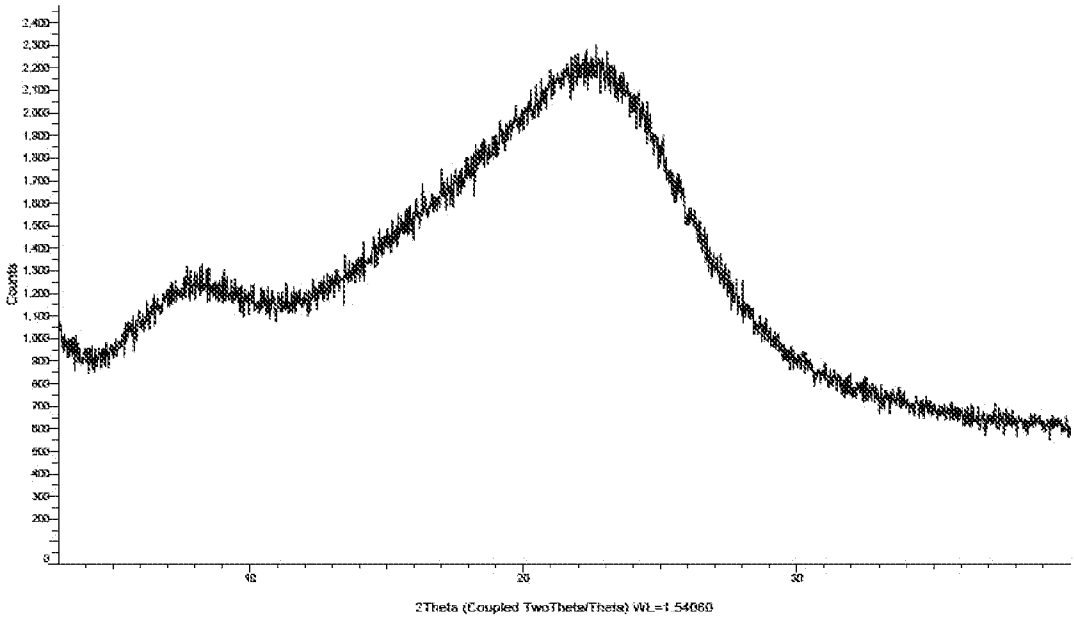


FIGURE 1

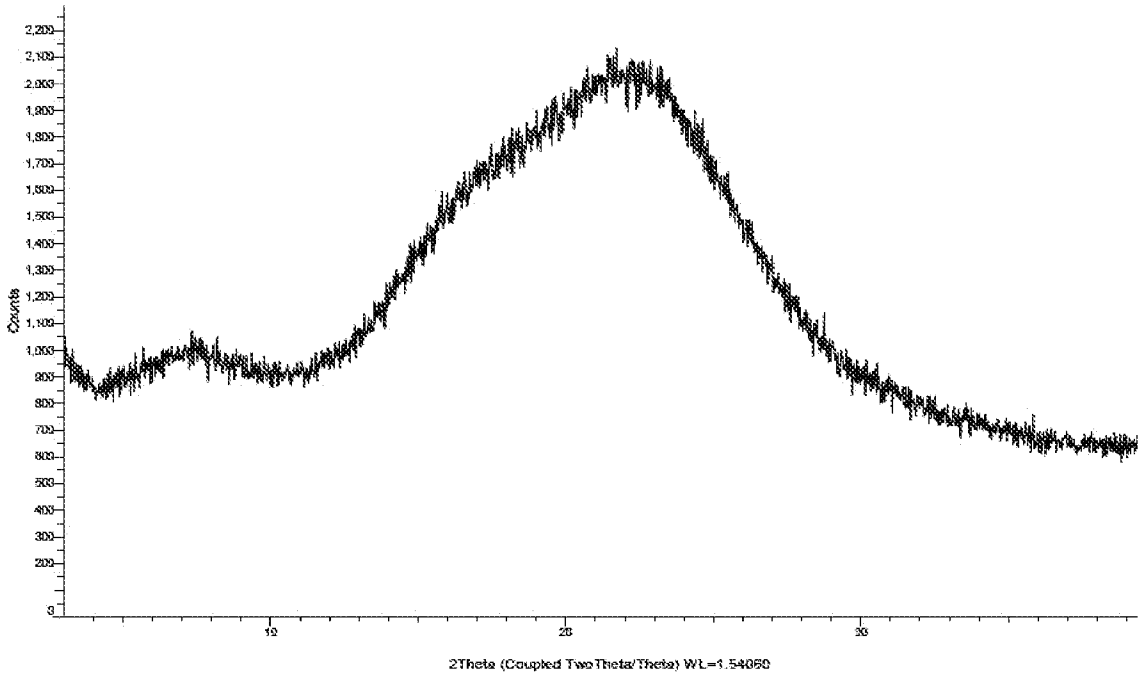


FIGURE 2

METROCHEM API PVT. LTD.

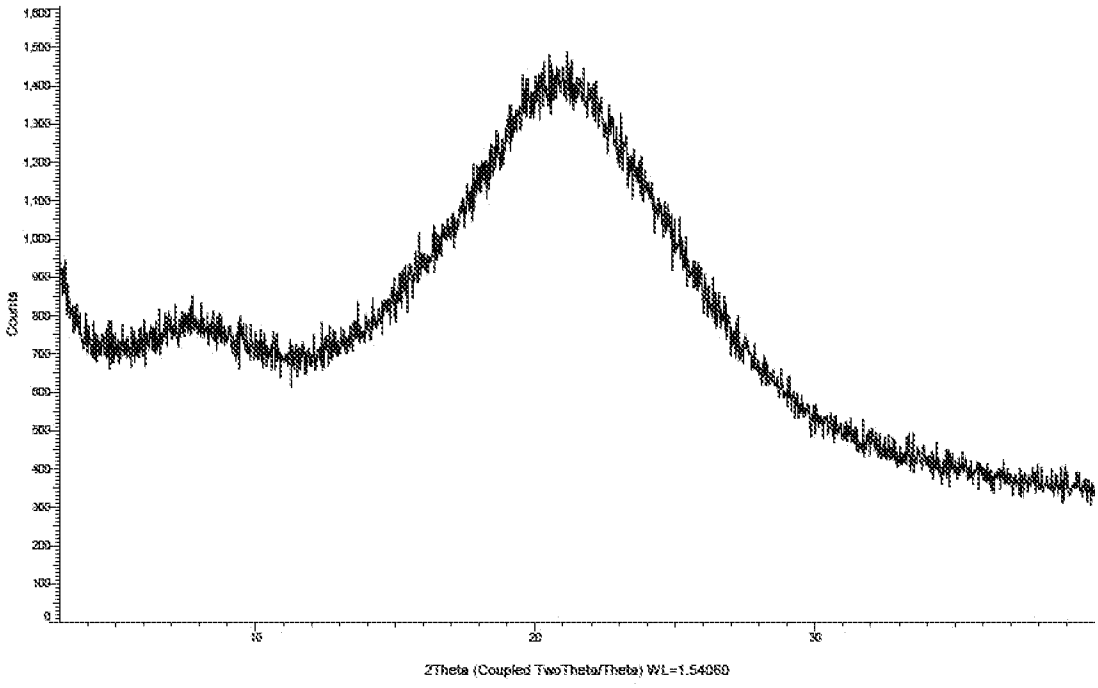


FIGURE 3

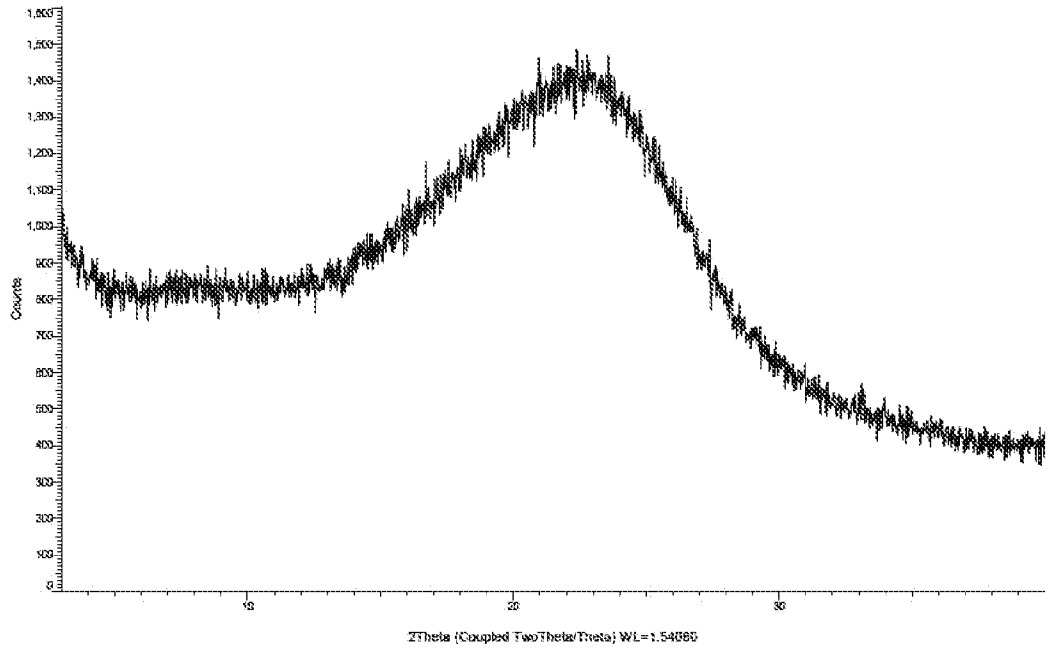


FIGURE 4

METROCHEM API PVT. LTD.

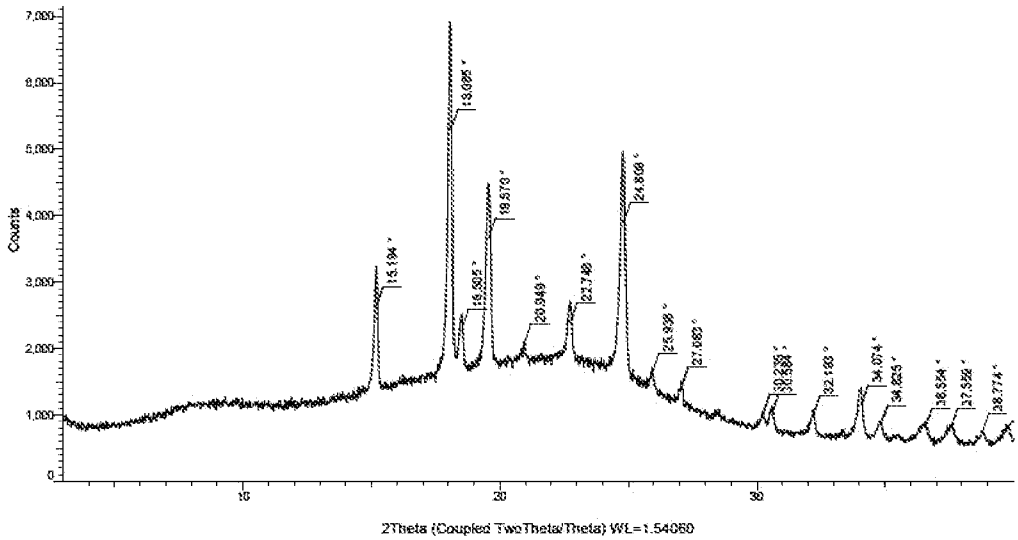


FIGURE 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2024/054243

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/4184,C07D405/12,A61P1/04 Version=2024.01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K,C07D,A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

PatSeer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US2020392120A1 (HK INNO N CORP) 17-Dec-2020 (17-12-2020) abstract ; para 0008,0013,0014 , claim 1	1,20 (partially)
Y	abstract ; para 0008, 0013,0014 ,0038 , claim 1-9	2-15
Y	EP3517528A1(CJ HEALTHCARE CORP) 31-Jul-2019 (31-07-2019) abstract , para 0001, 0002 , 0040-0049,0050-0054; Example 1-2, table 3 , 0061-0063 ; claim 1-13	2-15

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22-08-2024	22-08-2024
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Ravi Shankar Kumar Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2024/054243

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.Group- I- Claims 1-15, 20(partially)

Salts of Tegoprazan selected from acetic acid, benzoic acid, methanesulfonic acid and phosphoric acid in amorphous form or in crystalline form ;

their preparation process and pharmaceutical composition comprising salts of Tegoprazan.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-15,20 (partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Continuation of Observations where unity of invention is lacking(Box III)

2.Group-II-Claims 16-19 , 20(partially)

A co-crystal form of L-proline and Tegoprazan, the process for the preparation of co-crystal form of L-proline and Tegoprazan and pharmaceutical composition comprising co-crystal form of L-proline and Tegoprazan.

3.Group-III- Claims 21-22

A process for the preparation of a compound of formula II, which is an intermediate useful for the preparation of Tegoprazan and its salts.

The subject matter of claims 1-22 of present application do not meet the criteria of Rule 13.1 of PCT due to the following reason:

Group- I- Claims 1-15, 20(partially)

Group-II-Claims 16-19 , 20(partially)

Group-III- Claims 21-22

The common technical link between these groups of inventions appears to be the compound, i.e. Tegoprazan . However, it appears from the disclosure of D1 or D2 that Tegoprazan is already known.
In view of the above facts, it appears that the common technical link is not novel.
Consequently, the subject matter of claims 1-22 of the present application do not meet the criteria of Rule 13.1 PCT, because the subject matter of claims 1-22 lacks unity 'a posteriori'.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2024/054243

Citation	Pub.Date	Family	Pub.Date
US 2020392120 A1	17-12-2020	WO 2018124700 A1	05-07-2018
EP 3517528 A1	31-07-2019	WO 2018056697 A1	29-03-2018