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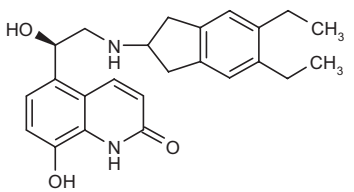
Indacaterol

Prop INN

Asthma Therapy
Treatment of COPD
β_2-Adrenoceptor Agonist

QAB-149

5-[2-(5,6-Diethyl-2,3-dihydro-1*H*-inden-2-ylamino)-1(*R*)-hydroxyethyl]-8-hydroxyquinolin-2(1*H*)-one



$C_{24}H_{28}N_2O_3$
Mol wt: 392.4908

CAS: 312753-06-3

EN: 298713

Abstract

The chronic inflammatory syndromes asthma and chronic obstructive pulmonary disease (COPD) are significant causes of morbidity, mortality, increased healthcare costs and hospital admissions. β_2-Adrenoceptor agonists are among the first-line therapies for asthma and COPD due to their bronchodilating effects, but currently available therapeutics are associated with a short duration of action and a broad side effect profile. Indacaterol (QAB-149) is currently undergoing phase II development for the treatment of asthma and COPD. Clinical studies have demonstrated that it is well tolerated and associated with improved cardiovascular safety in both patient populations. Furthermore, it is the first β_2-adrenoceptor agonist to provide rapid improvements in bronchodilatory control and FEV_1, with a sustained (24 h) duration of action. Indacaterol could therefore provide substantial improvement in the life-threatening symptoms of breathlessness and bronchoconstriction associated with asthma and COPD.

Synthesis

Friedel Crafts acylation of 1,2-diethylbenzene (I) with 3-chloropropionyl chloride (II) in the presence of $AlCl_3$ in nitromethane gives 3-chloro-1-(3,4-diethylphenyl)-1-propanone (III), which is cyclized by means of concentrated H_2SO_4 at 90 °C to yield 5,6-diethylindan-1-one (IV). Reaction of compound (IV) with butyl nitrite in methanol affords 5,6-diethylindan-1,2-dione 2-oxime (V), which is reduced with H_2 over Pd/C in H_2SO_4/AcOH to provide 5,6-diethylindan-2-amine (VI) (1).

Chiral epoxide (VII) is prepared by chlorination of commercially available methyl ketone (VIII) with benzyltrimethylammonium dichloroiodate in dichloroethane at 60 °C to yield ketone (IX), which is reduced with BH_3 in THF in the presence of the chiral boron catalyst (*R*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-c][1,3,2]oxazaborole and then reaction of the corresponding alcohol (X) with K_2CO_3 in refluxing acetone/water (1, 2).

Finally, alkylation of amine (VI) with the chiral epoxide (VII) in diethylene glycol dimethyl ether at 110 °C gives the adduct (XI), which is debenzylated by hydrogenation with H_2 over Pd/C in AcOH (1, 3). Scheme 1.

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) both involve chronic inflammation and constriction of the bronchioles, leading to limited or obstructed airflow and difficulty in breathing (4, 5). While asthma involves episodes of reversible bronchoconstriction, bronchoconstriction in COPD is progressive and only partially reversible (6).

Both diseases are an important cause of morbidity, mortality, increased healthcare costs and hospital admissions. Epidemiological data from 2000 indicate that approximately 10 million adults have been diagnosed with COPD in the United States, although the fact that about 24 million present with impaired lung function suggests a marked underdiagnosis of COPD. COPD is the fourth leading cause of death in the U.S. and COPD adult mortality was recorded as 119,000 for the year 2000. The complicated and progressive morbidity of COPD also puts the estimated total cost of care in 2002 at USD 32.1 billion (5, 7, 8). In 2003, asthma was estimated to affect

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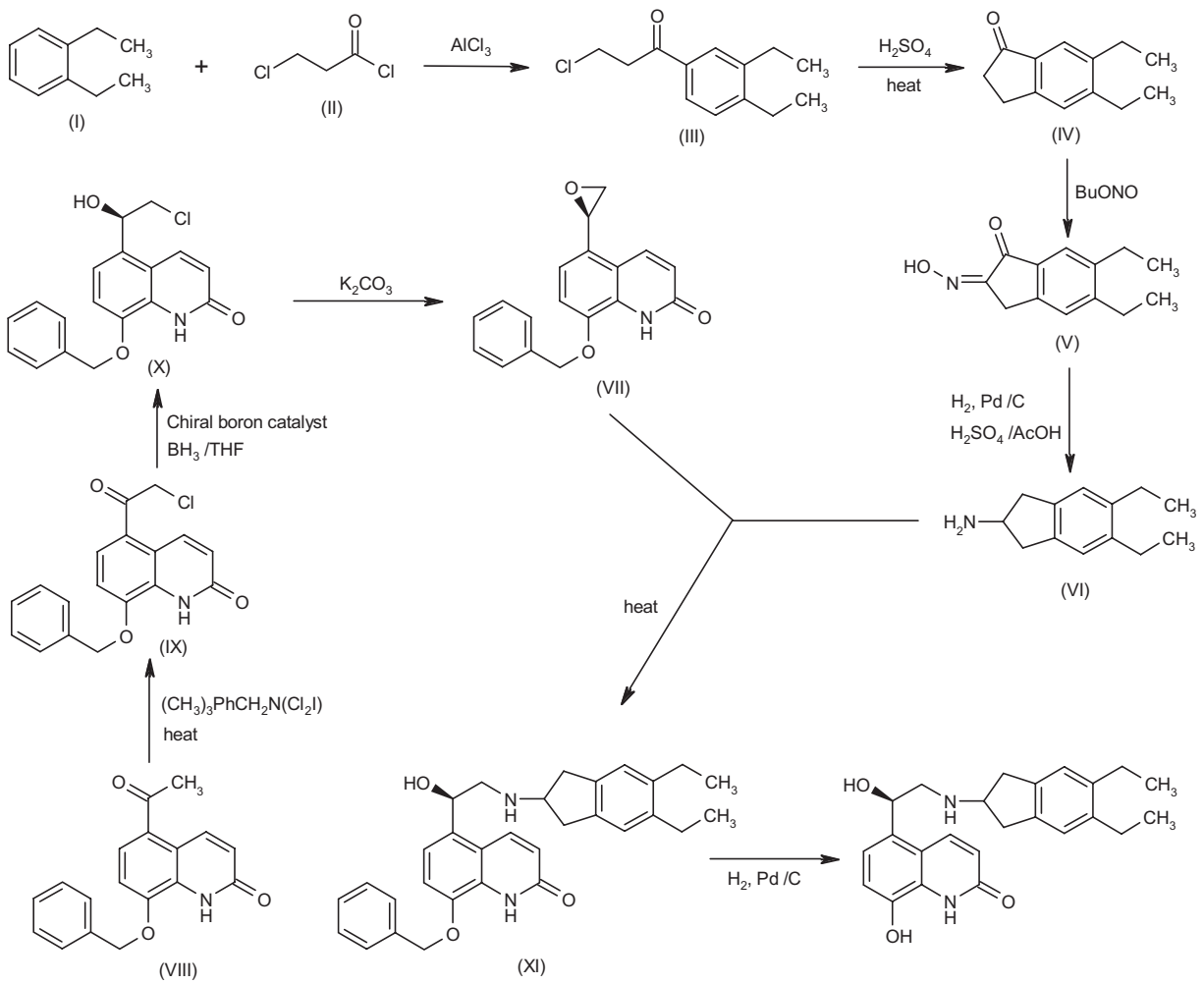
Scheme 1: Synthesis of Indacaterol



20 million Americans and its prevalence continues to increase. The economic cost of asthma is considerable both in terms of direct medical costs (such as hospital admissions and cost of pharmaceuticals) and indirect medical costs (such as time lost from work and premature death). According to the American Lung Association, direct healthcare costs in the U.S. are about USD 11.5 billion, with indirect costs of about USD 5 billion (4, 7).

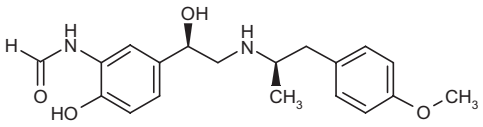
Optimal therapy for many patients requires control of pathological mechanisms via the use of inhaled bronchodilators and corticosteroids, which exert localized, site-specific therapeutic effects on the bronchiolar smooth muscle (9). β_2-Adrenoceptor agonists are among the first-line therapies for asthma and COPD due to their bronchodilating effects. Table I outlines β_2-adrenoceptor agonists that are currently under active clinical development.

Because of their rapid onset of action, β_2-adrenoceptor agonists are especially helpful for an acute attack of breathlessness. However, because of the short duration of action of currently available agents, several daily doses are often necessary for optimal effect, and newer, longer acting agents are associated with the development of tolerance to their effect and cross-tolerance with short-acting β_2-agonists. Furthermore, cautionary use of β_2-adrenoceptor agonists is advised, as they can cause severe side effects. Stimulation of other populations of β_2-adrenoceptors in the heart, blood vessels, genitourinary tract, uterus, gastrointestinal tract, liver, skeletal muscle and pancreas can result in side effects such as tachycardia, anxiety, tremor, palpitations, low blood potassium, hyperglycemia, glycogenolysis and gluconeogenesis (10).

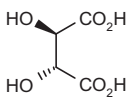
Indacaterol (QAB-149) is the first β_2-adrenoceptor agonist to provide bronchodilatory control upon once-daily dosing with a rapid onset, sustained duration (24 h) and improved cardiovascular safety. It is currently undergoing phase II development for the treatment of asthma and COPD. Indacaterol is expected to enter phase III clin-

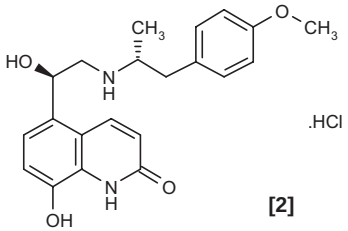
Table I: β_2-Adrenoceptor agonists under active clinical development (from Prous Science Integrity®).

Drug	Source	Phase
1. Arformoterol Tartrate	Sepracor	Prereg.
2. Carmoterol hydrochloride (CHF-4226/TA-2005)	Chiesi; Tanabe Seiyaku	II
3. Indacaterol	Novartis	II
4. 159797/TD-3327*	GlaxoSmithKline; Theravance	II
5. 597901*	GlaxoSmithKline; Theravance	II
6. 678007*	GlaxoSmithKline; Theravance	II
7. 159802*	GlaxoSmithKline; Theravance	I
8. 642444*	GlaxoSmithKline; Theravance	I

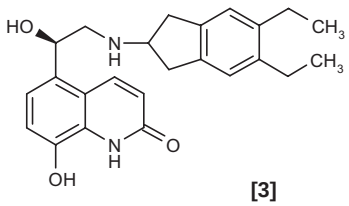


[1]





[2]



[3]

* Structure not available.

ical trials in 2006 as monotherapy or in combination with other Novartis respiratory compounds (11).

Pharmacological Actions

The effect of indacaterol on β_1- and β_2-adrenoceptors was assessed *in vitro* in isolated guinea pig trachea and left atria and compared to formoterol and salmeterol. In isolated trachea (measure of β_2-adrenoceptor activity), all compounds produced a concentration-dependent inhibition of electrically induced contractions, with EC_{50} values of 45, 1.1 and 15 nM, respectively. In electrically stimulated atria preparations (measure of β_1-adrenoceptor activity), the respective EC_{50} values were reported to be 21.6, 0.28 and > 30 μM. These results demonstrate that indacaterol exhibits a greater margin for cardiovascular safety, as effective doses of the compound are not likely to mediate β_1-adrenoceptor-associated cardiovascular side effects. Further studies in electrically stimulated isolated guinea pig trachea revealed that indacaterol demonstrates a maximum inhibitory effect similar to salmeterol and formoterol (74.7%, 78.5% and 76.7%, respectively), although indacaterol exhibited a faster onset of action (33 min *vs.* 86 and 38 min, respectively); all three compounds displayed a long duration of action of > 7 h (12-15).

The duration and onset of action of indacaterol were assessed In isolated human bronchial rings extracted from 34 patients. At resting tone, the average onset of action (defined as the time to induce 50% maximal relaxation) was 9.2 min for indacaterol, 5.8 min for formoterol, 11.0 min for salbutamol and 18.0 min for salmeterol. All four compounds concentration-dependently inhibited electrical field stimulation-induced contractions (pD_2 = 8.61, 9.71, 8.14 and 8.18 respectively; IC_{50} = 104, 0.95, 676 and 3160 nM, respectively), but duration of action was significantly longer with indacaterol and salmeterol (> 700 min) compared to formoterol (35.3 min) or salbutamol (14.6 min). Indacaterol therefore demonstrates a fast onset and long duration of action (16-19).

In further experiments in human bronchial ring preparations, precontraction with histamine had no effect on the potency and efficacy of the compounds, whereas pre-

contraction with carbachol significantly reduced the efficacy of salmeterol and salbutamol, but not that of indacaterol and formoterol. Importantly, in contrast to salbutamol, indacaterol did not antagonize the bronchorelaxant effects of the short-acting β_2-adrenoceptor agonist isoprenaline (18, 19).

In guinea pig studies, indacaterol significantly and dose-dependently inhibited 5-HT-induced bronchoconstriction in conscious animals, as did formoterol, salbutamol and salmeterol, at 2 h postdosing. Application of ED_{80} doses intratracheally (3.3, 0.8, 82.7 and 14.9 μg/kg, respectively) showed that indacaterol was superior to the other compounds with respect to duration of action (55% at 12 h *vs.* 71% at 4 h, 98% at 2 h and 71% at 9 h for the other compounds, respectively) (14, 15). With repeated dosing, no development of tachyphylaxis was seen (20, 21).

In anesthetized rhesus monkeys, aerosolized indacaterol and formoterol demonstrated more potent inhibition of methacholine-induced bronchoconstriction than salmeterol, with ED_{50} values of 1.7 and 0.14 μg/kg, respectively. Doses of 12.5 μg/kg indacaterol and 1.2 μg/kg formoterol provided maximal (70-80%) inhibition of methacholine-induced bronchoconstriction for more than 3 h. However, indacaterol had the additional advantage of less treatment-associated tachycardia (maximum change 5 min following administration was reported as 13% for indacaterol and 27% for formoterol). In contrast, an aerosolized dose of 54 μg/kg salmeterol induced a maximal inhibition of 50%, increased heart rate by an average of 43% and was associated with significant decreases in serum potassium concentrations (12, 13).

Clinical Studies

A multicenter, randomized, double-blind, parallel-group, placebo-controlled study investigated the safety and tolerability of indacaterol (400 or 800 μg once daily over 28 days) given as a dry powder inhaler to 163 patients with mild to moderate COPD. Pre- and postdose assessments were carried out on days 1, 14 and 28. Adverse events were reported in 35%, 51% and 25%, respectively, of patients receiving 400 and 800 μg and placebo, although no serious drug-related adverse events were reported. Indacaterol did not evoke a significant change in $Q\text{-}T_c$ interval or affect hematology, glucose or potassium levels, pulse rate or blood glucose. Both doses of indacaterol significantly increased FEV_1 compared to placebo for 24 h (22). The results from this and the following studies are summarized in Table II.

Thirteen patients with mild to moderate COPD participated in a double-blind, randomized trial involving administration of placebo or indacaterol 800 μg using an HFA metered-dose inhaler once daily for 14 days. Indacaterol induced clinically meaningful improvements in FEV_1 at 1 h postdosing and FEV_1 values were increased from baseline by an average of 15% at the end of the study. Pharmacokinetic data (median) on day 14 were reported as follows: t_{max} = 1 h; C_{max} = 0.7 ng/ml; $AUC_{0\text{-}24h}$ = 6.7 ng.h/ml; Cl/F = 131 l/h; and $t_{1/2}$ = 48.4 h. This profile indicates that indacaterol is rapidly absorbed, and although serum accumulation was apparent, it was not thought to be problematic, as most adverse events were mild and no patients discontinued the study due to safety issues (23).

In another randomized, double-blind, placebo-controlled study, 25 male patients with mild intermittent or mild persistent asthma received two single ascending doses of indacaterol (25, 100, 300, 600, 1200 and 2000 μg). Single doses up to 2000 μg were well tolerated and induced few systemic β_2-adrenoceptor agonist-mediated adverse events. Pharmacokinetic analysis at doses of 600, 1200 and 2000 μg revealed that C_{max} was reached rapidly, within approximately 15 min, with an apparent half-life of 6-10 h. AUC values increased with dose and the drug showed a large volume of distribution. FEV_1 analysis revealed that all doses of indacaterol provided effective bronchodilatation, with a rapid onset and a long duration of action (24).

A multiple-dose (14-day) treatment regimen of indacaterol (400 or 800 μg once daily) was also associated with a favorable safety profile in 25 male and female patients with mild intermittent or persistent asthma. All adverse events were mild or moderate, with an indicence of 38% on placebo, 22% on low-dose indacaterol and 63% on high-dose indacaterol. No clinically significant effects were found on serum potassium and glucose levels or $Q\text{-}T_c$ values. Both doses of indacaterol were rapidly absorbed, with an elimination half-life of over 30 h. $AUC_{0\text{-}24h}$ data revealed apparent accumulation of indacaterol, but this was not linked to adverse events (25).

A double-blind study randomized 115 patients with moderate persistent asthma to receive inhaled placebo or indacaterol (100, 200, 300, 400 or 600 μg) once daily for 7 days. Compared to placebo, all indacaterol doses significantly improved baseline FEV_1 values throughout the study and all doses except 100 μg provided a rapid onset of action (by day 1). Mean differences in FEV_1 AUC (22-24 h) were reported as 80, 160, 150, 110 and 160 ml for the respective doses. Indacaterol treatment appeared to be well tolerated and safe, as most adverse events were mild and no serious drug-related adverse events were reported (26).

Measurement of FEV_1, forced vital capacity (FVC) and forced expiratory flow ($FEF_{24\text{-}75\%}$) was carried out in 156 asthmatic patients receiving once-daily treatment (200, 400 or 600 μg) over 28 days. This multicenter, double-blind, randomized, placebo-controlled study revealed clinically relevant treatment-related bronchodilatation (within 30 min) that was sustained for 24 h (FEV_1 increased in 46%, 65% and 81% of patients receiving the respective doses *vs.* 23% on placebo) and these effects did not weaken after 28 days of treatment. The cardiovascular safety of indacaterol was also investigated in this trial. Assessment 60 min postdosing revealed no significant difference between treatment or placebo $Q\text{-}T_c$ and no dose-related increase. Pulse rate and blood pressure changes were minimal and were not significantly different among groups. Adverse events were reported in

Table II: Clinical studies of indacaterol (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Chronic obstructive pulmonary disease	Randomized Double-blind Multicenter	Indacaterol, 400 µg inhal. o.d. x 28 d Indacaterol, 800 µg inhal. o.d. x 28 d Placebo	163	Once-daily indacaterol was well tolerated and had no significant effects on Q-T_c values, pulse rate, blood pressure or serum glucose or potassium levels in patients with moderate to severe chronic obstructive pulmonary disease	22
Chronic obstructive pulmonary disease	Randomized Double-blind	Indacaterol, 800 µg inhal. o.d. x 14 d Placebo	13	Administration of multiple doses of indacaterol was effective in increasing FEV_1 in patients with mild to moderate chronic obstructive pulmonary disease. Most adverse events were mild and not drug-related	23
Asthma	Randomized Double-blind Crossover	Indacaterol, 25 µg Indacaterol, 100 µg Indacaterol, 300 µg Indacaterol, 600 µg Indacaterol, 1200 µg Indacaterol, 2000 µg Placebo	24	Single doses of up to 2000 µg of indacaterol were well tolerated and did not induce any significant systemic effects in patients with mild intermittent/persistent asthma	24
Asthma	Randomized Double-blind	Indacaterol, 400 µg inhal. o.d. x 14 d Indacaterol, 800 µg inhal. o.d. x 14 d Placebo	25	Once-daily indacaterol was well tolerated and had no significant effects on Q-T_c values or serum glucose or potassium levels in patients with mild intermittent/persistent asthma	25
Asthma	Randomized Double-blind Crossover	Indacaterol, 100 µg inhal. o.d. x 7 d Indacaterol, 200 µg inhal. o.d. x 7 d Indacaterol, 300 µg inhal. o.d. x 7 d Indacaterol, 400 µg inhal. o.d. x 7 d Indacaterol, 600 µg inhal. o.d. x 7 d Placebo	115	Indacaterol was well tolerated and more effective than placebo in improving FEV_1 values in patients with moderate persistent asthma	26
Asthma	Randomized Double-blind Multicenter	Indacaterol, 200 µg inhal. o.d. x 28 d Indacaterol, 400 µg inhal. o.d. x 28 d Indacaterol, 600 µg inhal. o.d. x 28 d Placebo	156	Once-daily Indacaterol at doses up to 600 µg was well tolerated and induced no significant changes on Q-T_c intervals in ECG measurements, vital signs or laboratory tests in patients with stable asthma	27, 28
Asthma	Randomized Double-blind Crossover	Indacaterol, 50 µg inhal. Indacaterol, 100 µg inhal. Indacaterol, 200 µg inhal. Indacaterol, 400 µg inhal. Placebo	42	Once-daily indacaterol was well tolerated and effective in inducing bronchodilatation in patients with intermittent/persistent asthma. The effects of indacaterol were dose-dependent and were detected at 5 min after dosing	29, 30

39%, 41%, 37% and 39% of those receiving 200, 400 and 600 µg and placebo, respectively. No serious drug-related adverse events were reported (27, 28).

Another double-blind, crossover trial randomized 42 patients with intermittent or persistent asthma to receive single doses of placebo or indacaterol (50, 100, 200 or 400 µg) using an HFA metered-dose inhaler to determine the optimal clinical dose. Doses of 200 and 400 µg were the most effective in increasing FEV_1 at both 5 min and 24 h after administration (29, 30).

Source

Novartis AG (CH).

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