F.7 AL Chemistry

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Form: 7S

Topic: Sibutramine

(1).Introduction

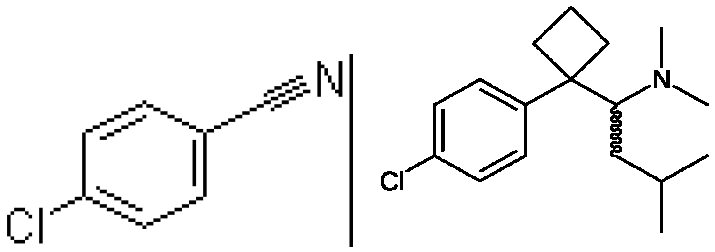
Chemical name: Sibutramine

IUPAC name:

{1-[1-(4-chloro-phenyl)-cyclobutyl]-3-methyl-butyl}
-dimethyl-amine

Sibutramine is a neurotransmitter reuptake inhibitor. It can reduce the reuptake of serotonin by53%, norepinephrine by54% and dopamine by16%. As a result, it helps to enhance satiety due to increasing levels of these substances in synaptic clefts. Serotonin can affect the appetite. Some of older medicines such as amphetamine, fenfluramine force the release of these substances rather than affecting their reuptake to deal with depression. Since it can inhabit the reuptake of serotonin; it should be an effective antidepressant logically. However, it failed to demonstrate antidepressant properties in animal studies. Nowadays, its properties are not fully discovered. Knoll Pharmaceuticals now market sibutramine in its HCl monohydrate form as Meridia. All the drugs which contain Sibutramine are banned by the European Union. Some countries such as America, Australia, Taiwan and Hong Kong do not allowed the import of Sibutramine.

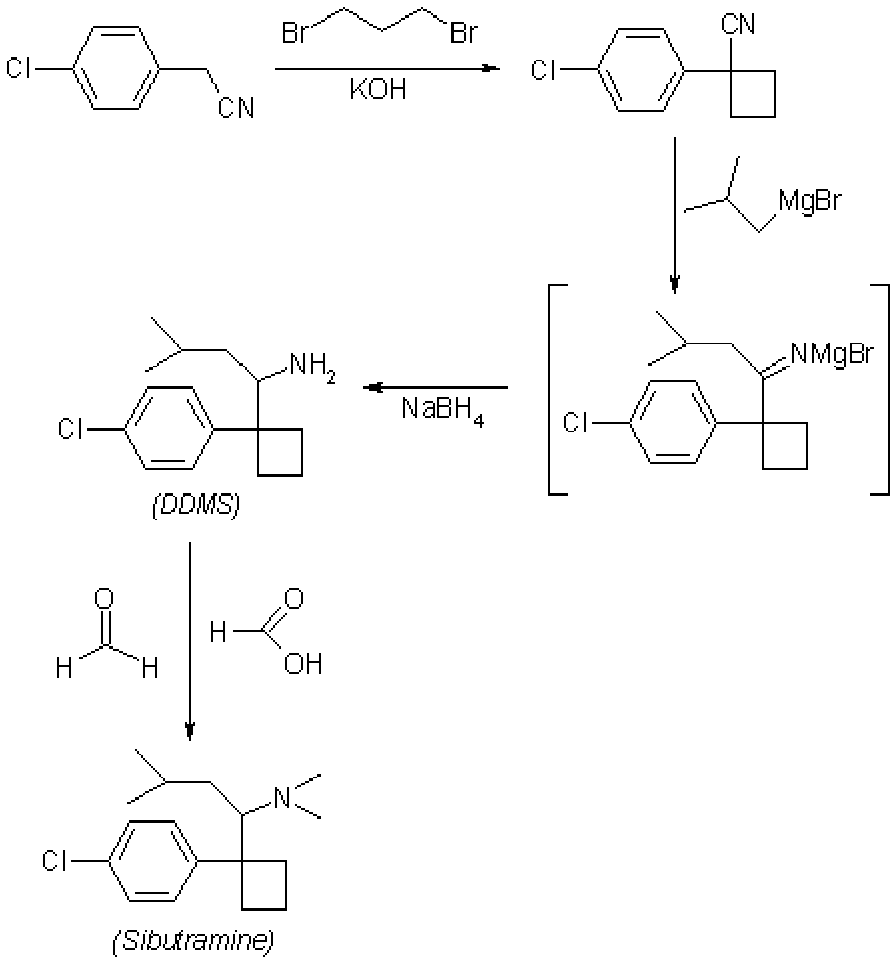
(2)Lead compound discovery



Since Serotonin can promote a feeling of wellbeing and happiness, scientists therefore do researches on it. As a result, in1987, Buckett, W.R., Hopcroft, R.H., Luscombe, G.P., Thomas, P.C are the people who first discovered *BTS 545 24 (Sibutramine)* , a monoamine uptake inhibitor from 4-chlorobenzyl cyanide. The pharmacology of sibutramine hydrochloride (BTS 545 24), a new antidepressant which induces rapid noradrenergic down-regulation. In1995, it is discovered that sibutramine can decrease an obese person's weight. This makes it become an anorexiant to help obese people lose weight. When a surprising discovery showed that Sibutramine was very effective in aiding weight loss, development proceeded in this direction.

(3).Molecular Modification

The four-membered ring is prepared by removal of the benzylic protons of 4-chlorobenzyl cyanide with sodium hydride, followed by reaction with 1,3-dibromopropane. Reaction with isobutylmagnesium bromide, followed by reductive amination via the Leuckart reaction gives an amine. Methylation with formaldehyde gives the dimethylamino product, sibutramine



(4).Formulation development:

Since Sibutramine is so new, very little research has proceeded into the synthesis of Sibutramine and its derivatives, there is no much on its development.

Sibutramine is used capsule for eating since body can absorb more directly.

It was discovered to have potential in treating sexual dysfunction in 2002. Throughout 2002, Sibutramine was discovered that it was effective in treating addictive disorders, pulmonary hypertension, cardiovascular disease, Chronic Fatigue Syndrome, hyperactivity disorders, menstrual dysfunction and orthostatic hypotension.

Also, scientists recently found that Sibutramine has a number of clinically significant interactions. The concomitant use of sibutramine and monoamine oxidase inhibitors (MAOIs, such as selegiline) is not indicated, as it may increase the risk of serotonin syndrome, a somewhat rare but serious adverse drug reaction. Sibutramine should not be taken within two weeks of stopping or starting an MAOI. Taking both sibutramine and certain medications used in the treatment of migraines—such as ergolines and triptans—, as well as opioids, may also increase the risk for serotonin syndrome, as may the use of more than one serotonin reuptake inhibitor at the same time

(5).Safety tests and human trials:

Weight loss was examined in 11 double-blind, placebo-controlled obesity trials (BMI range across all studies 27-43) with study durations of 12 to 52 weeks and doses ranging from 1 to 30 mg once daily. Weight was significantly reduced in a dose-related manner in sibutramine-treated patients compared to placebo over the dose range of 5 to 20 mg once daily. In two 12-month studies, maximal weight loss was achieved by 6 months and statistically significant weight loss was maintained over 12 months. The amount of placebo-subtracted weight loss achieved on sibutramine was consistent across studies. Significant dose-related reductions in waist circumference, which is an indicator of intra-abdominal fat, have also been observed over 6 and 12 months in placebo-controlled clinical trials.

Mean Weight Loss (lbs) in the Six-Month and One-Year Trials

Study/Patient Group	Placebo (n)	Sibutramine(mg) 5 (n)	10 (n)	15 (n)	20 (n)
Study 1					
All patients*	2.0 (142)	6.6 (148)	9.7 (148)	12.1 (150)	13.6 (145)
Completers**	2.9 (84)	8.1 (103)	12.1 (95)	15.4 (94)	18.0 (89)
Early responders***	8.5 (17)	13.0 (60)	16.0 (64)	18.2 (73)	20.1 (76)
Study 2					
All patients*	3.5 (157)		9.8 (154)	14.0 (152)	
Completers**	4.8 (76)		13.6 (80)	15.2 (93)	
Early responders***	10.7 (24)		18.2 (57)	18.8 (76)	
Study 3****					
All patients*	15.2 (78)		28.4 (81)		
Completers**	16.7 (48)		29.7 (60)		
Early responders***	21.5 (22)		33.0 (46)		

(6).Approval for marketing:

Meridia, a Sibutramine product, was approved by the Food and Drug Administration in November 1997 for weight loss and maintenance of weight loss in obese people, as well as in certain overweight people with other risks for heart disease. It is produced by Abbott of America. The approval was based on clinical data showing that more people receiving Sibutramine lost at least 5 percent of their body weight than people on placebo who relied on diet and exercise alone.

There are some side effects of taking Sibutramine. A higher number of

cardiovascular events have been observed in people taking sibutramine versus control (11.4% vs. 10.0%). In 2010 the FDA noted the concerns that sibutramine increases the risk of heart attacks and strokes in patients with a history of cardiovascular disease. Also, Sibutramine can substantially increase blood pressure and pulse in some patients. Therefore regular monitoring needs to be performed.