CCC Heep Woh College

2010-2011 F.7 AL Chemistry Group Project (TAS)

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I. Topic: Drug development - Sibutramine

II. Introduction:

Advertisements on the diet products and keep fit services saturate all public media in recent years. Having a slim figure becomes the dream of many ladies and even gentlemen, people who are stunt are teased. Slim and thin become the trend of today's society. Some people, in order to keep fit and have "beautiful" or "perfect" figures, try all means to loss weight in the shortest period of time. Taking diet drugs, of course, is the fastest way people can think of. Diet drugs are medications that may help people lose weight, most of them are intended to reduce calorie intake or increase calorie usage. Usually, the drugs are used together with a program of diet and exercise. However, nowadays, people often misuse diet drugs without the aids of diet programs. So, we will investigate the development of one of the current using diet drugs in Hong Kong. That is Sibutarmine (西布曲明) .

III. Fact about Sibutramine:

Medical name: Sibutramine

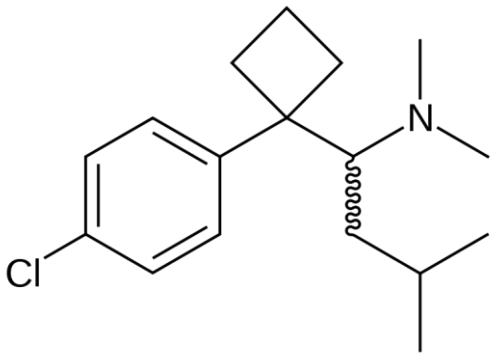


Fig 1 Simplified structure of Sibutramine

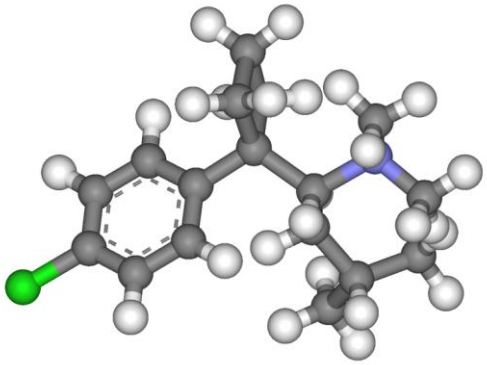


Fig 2 Molecular structure of Sibutramine

Trade name in the USA : Meridia
Trade name in Europe : Reductil
Dosage form: Capsule

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

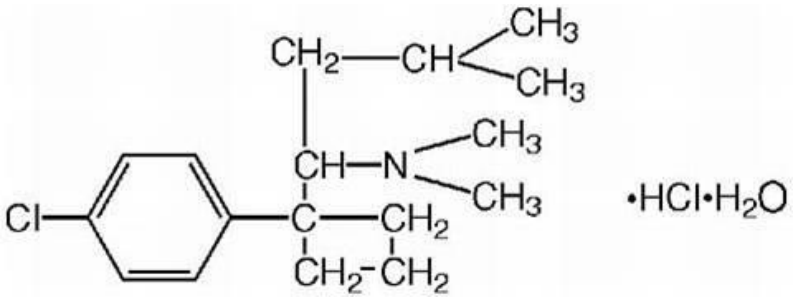


Fig 3 Detailed structure of Sibutramine

Molecular formula: $C_{17}H_{26}ClN$
Molecular mass : 279.85 g/mol

Sibutramine is an **appetite suppressant (食慾抑制藥)** that is consumed orally for the treatment of obesity. It is recommended that patients with BMI of 30kg m^{-2} or more for having weight loss by Sibutramine to reduce appetite and increase satiety. Sibutramine increases blood pressure in some patients and therefore blood pressure must be monitored during treatment to ensure that it does not become dangerously high. Serious concerns have been expressed about its safety and has been suspended from use in the US and EU.
Sibutramine is also indentified as a member of **SNRI (Seratonin/Norepinephrine Reuptake Inhibitors) (抗抑鬱藥)** . SNRI is a new class of drugs that works by stopping the patient body from re-absorbing neurotransmitters (神經傳送素), in particular, seratonin (血清素) and noradrenaline(甲腎上腺素). This can be used to control the levels of these neurotransmitters in the body and therefore produce therapeutic effects without having to introduce the neurotransmitters directly, but it has been shown to be very ineffective in practice.

IV. Key stages of development:

(i) Lead compound discovery

The discovery of sibutramine as a diet drug was a complicated and unexpected process from 1987 to 1995. After the discovery, the development of Sibutramine still continues until now.

Sibutramine was first discovered as a potential drug in 1987 by a scientist,Beckett et al. He first investigated for Sibutramine's potential properties as an **antidepressant (**抗抑鬱藥**)**. As mentioned in the above section (Fact about Sibutramine), it behaves as a serotonin and norepinephrine uptake inhibitor. In particular, the ability of Sibutramine to **reduce the uptake of serotonin** was of particular noticed. So, scientists started to investigate the compound **Serotonin(**血清素**)** in the hope for further development of Sibutramine.

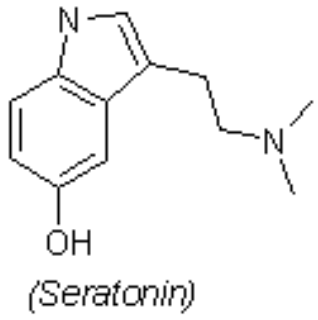


Fig 4 Structure of Serotonin

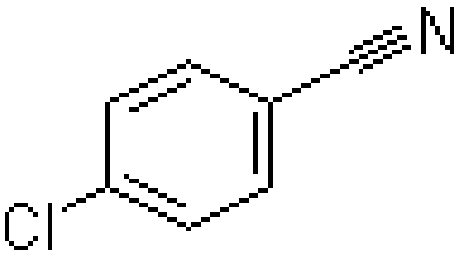


Fig 5 Structure of 4-chlorobenzonitrile

They discovered that serotonin (Fig4) is a neurotransmitter, and promotes a feeling of wellbeing and happiness. However the concentration is carefully controlled by the body. If its level is too high, the production is stopped and the existing level in the body are reabsorbed. With the researches on serotonin, scientists started to use **4-chlorobenzonitrile** (Fig5) to develop Sibutramine . Sibutramine(as an antidepressant) works by blocking this last mechanism; if the body never recovers the neurotransmitters from the bloodstream, the person continues to feel happy.

While work was proceeding to investigate the potential as an antidepressant, a patient was filed in the US in 1990 by Kiyoharu Ukai et al. The case noted Sibutramine's effectiveness in the **treatment of cerebral function disorders** such as Parkinson's disease. It was another breakthrough in 1990.

However In 1995, Kelly et al. discovered that amongst Sibutramine's other effects was a noticeable decrease in weight amongst obese patients, leading to its modern use as an **anorexiant (**減食慾劑**)** to help clinically obese patients lose weight. When a surprising discovery showed that Sibutramine was very effective in aiding weight loss, development proceeded in this direction, leading to Sibutramine being one of the **leading weight loss drugs** on the market.

(ii) Molecular modification

The following is one of the modification of Sibutramine from 4-chlorobenzonitrile.

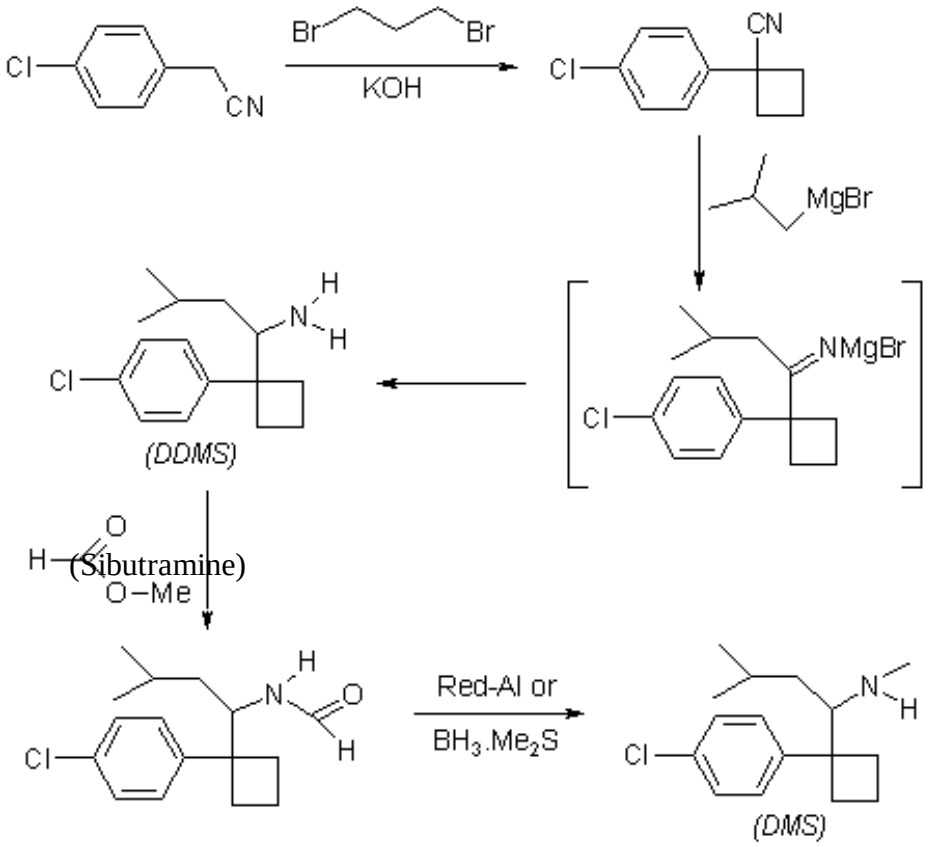
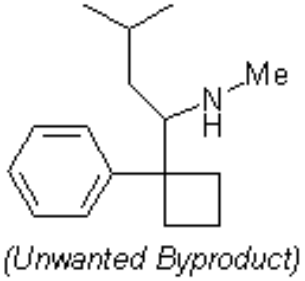


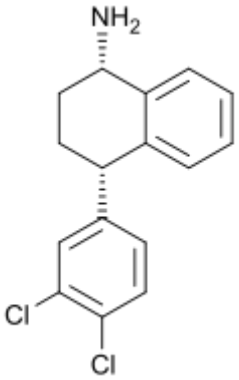
Fig 6 The modification process

(iii) Formulation development



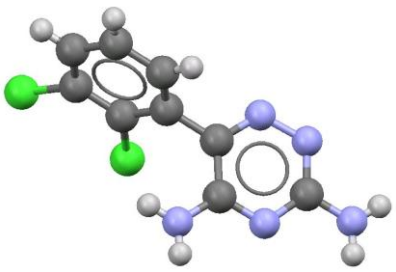
1. Fig 7 The unwanted byproduct

The **reducing agents of choice** for the last step of selectively reducing the carbonyl to the methyl group were sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al®) and borane dimethyl sulfide complex. The Red-Al® produces about 5% of an **unwanted byproduct** (shown above) whereas the borane dimethyl sulfide complex does not. Therefore, the **borane dimethyl sulfide complex** is suggested to be a better reducing agent for this synthesis.



2. Fig 8 Desmethylsertraline (DMS)

Furthermore, **Desmethylsertraline (DMS)** ,which is an **active metabolite** of Sibutramine was discovered to have potential in **treating sexual dysfunction (**性功能障礙**)** by Jerussi et al. in 2002. Throughout 2002, Mendel et al. filed a series of patients, claiming that Sibutramine was effective in treating addictive disorders (上癮性失調症狀) , pulmonary hypertension, cardiovascular disease, Chronic Fatigue Syndrome, hyperactivity disorders, menstrual dysfunction and orthostatic hypotension.



3. Fig 9 Molecular fragment

This is a very close analogue of Sibutramine, as found in the Cambridge Crystal Structure Database. It is shown with another **molecular fragment** which is **unidentified** at this time. It is possible that this is the **metabolism** of Sibutramine by the body - The other fragment may very well be part of a large enzyme or protein, or a model compound used to study the effect of the enzyme or protein. This model gives a better indication of how the Sibutramine molecule exists in real life.

(iv) Safety tests and human trials

Before being a diet drug in the market, tests and trials were important to be carried out.

There were **16 clinical trials** involving over 5000 patients have been carried out. In random and controlled trials, Sibutramine was more effective than a placebo(安慰劑) at promoting weight loss; by 3kg at 8 weeks, by 4- 9kg at 24 weeks and by 14 - 15kg at 1 year. While this demonstrates Sibutramine's effectiveness, it also shows that over a longer period of time **behavioral changes** becomes a more predominant factor in weight loss.

In addition, however, for the use as an antidepressant, neither its properties were fully evaluated nor any clinical trials were published. This may be due to poor results, however the fact that it has been verified as a serotonin uptake inhibitor means that, pharmacologically speaking at least, it is believed to be an effective antidepressant.

(v) Approval for marketing

Abbott Laboratories, S.A.

Fig 10 Logo of Abbott Laboratories

Fig 11-13 Different brand names of Sibutramine Meridia, Reductil and Sibutrex

The modern use of Simbutramine as an anorexiant started in 1997 when the FDA (Food and Drug Administration) in America approved the drug for use in treating clinically obese people. Simbutramine was originally launched and marketed by Knoll Pharmaceuticals and is now manufactured and marketed by Abbott Laboratories (美國雅培製藥有限公司).

Sibutramine was under different brand names in different countries such as Reductil, Meridia and Sibutrex. It was claimed that it has virtually no potential danger for misuse. It is likely that the compound's use as an anorectic is the sole reason is it classified as a controlled drug, as "overprescription" of anorectics (as a class) in the mid-20th century resulted in a number of cases of abuse or addiction. These cases show that overdose of the drugs may still have harmful effects to human body.

V. Additional information - Disapproval from the market:

In recent years, more and more news articles and letters are petitioning the US government for banning the use of Sibutramine. According to Worst Pills, Best Pills, which is a guide for consumers to choose appropriate drugs so as to avoid drug- induced death or illnesses, Sibutramine is classified as a **DO NOT USE** drug.

Though Sibutramine (Meridia) received marketing approval from the US's Food and Drug Adminstration (FAD) in 1997, its **potential risk** raised the concern of FDA Endocrinologic and Metabolic Drugs Advisory Committee since 1996. The committee voted five to four against recommending approval of Sibutramine. Their decision are based on the fact that the drug's significantly causing **blood pressure and increase heart rate**. These side effects make Sibutramine a dangerous drug for patients with high blood pressure, heart disease, blood vessel disease and other cardiac diseases.

The FDA medical officer who reviewed Sibutramine wrote that "sibutramine has an unsatisfactory risk-benefit ratio" (Coleman E. Sibutramine (Meridia). Medical Officer Review May 10, 1996; 162.) and therefore this reviewer recommends non-approval of the original submission. However, FDA against the advise of the advisory committee and marked Sibutramine (Meridia) as an officially approved drug.

Since then, Public Health, Worst Pills, Best Pills and many other organizations published articles and researches showing Sibutramine not recommendable and petitioning the FAD for removing Sibutramine from the market. Most of them are supported by statistics and scientific researches, proving the adverse effect of Sibutramine on human. Beside causing high blood pressure, and increasing heart rate, some of its side effects are listed below.

1.Birth defects

It was found that sibutramine may cause **fetal toxicity.** One of the reports proved that sibutramine may cause **cardiovascular birth defects** by 4 cases. These defects include bicuspid aortic valve with cardiac murmur, cardiomegaly (large heart), congenital anomaly, congenital heart disease and ventricular hypoplasia (**underdeveloped heart chamber**). In addition, there are reports showing that sibutramine may cause damage to central nervous system which may cause fatal in serious case.

2.Serotonin syndrome

Sibutramine **inhibits the reuptake of the brain transmitter serotonin**. Serotonin syndrome requires immediate medical attention and may include one or more of the following symptoms: excitement, restlessness, loss of consciousness, confusion, disorientation, anxiety, agitation, weakness, tremor, incoordination, shivering, sweating, vomiting and rapid heartbeat. All these directly **affect the normal life** of patient.

3.Memory problems

The World Health Organization (WHO) international database contains 33 reports of **amnesia** (健忘症) associated with sibutramine. In 25 cases, sibutramine was the only drug suspected of causing the amnesia.

VI. Conclusion:

After the researches throughout the project, we understand more about this diet drug. We know more about the fact about Sibutrumine and investigate both its development and side effects. Although Sibutrumine is an **approved and useful** medicine as antidepressant and anorexiant, it still has some **drawbacks** to the human body when overdose. Therefore, consumers are advised to use **alternative methods**, like **exercises, changing lifestyle and die**t other that Sibutramine when they are on diet since FAD takes no immediate response to the petition of Sibutramine up to now. People with cardiac diseases, pregnant women and patients under other medical treatments are highly recommended to **consult doctors** before taking this drug. We should understand that there are many alternative ways to keep fit, and choosing the one which is **healthy** and **would not cause any harm** to us is the key. Most importantly, we ought to bear in mind that outlook is not the major element in our lives, so we need not to always dream for a "beautiful" or "perfect" figure.

***Reference:**

1. Wikipedia (http://en.wikipedia.org/wiki/Sibutramine#Synthesis)
2. ICL (http://www.ch.ic.ac.uk/local/projects/rowlands/)
3. Americanchronicle (http://www.americanchronicle.com/articles/printFriendly/136251)
4. Yahoo! Knowledge (http://hk.knowledge.yahoo.com/question/question?qid=7006111501276)
5. Worst pills, Best pills (http://www.worstpills.org/)
6. Public citizens (http://www.citizen.org/Page.aspx?pid=183)