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Traditional Chinese medicines and new drug development

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Abstract. The recent study of the traditional medicines in China has given us confidence that what was recorded in Chinese ancient medical literature through empirical observations is indeed still coincident with modern chemistry, pharmacology and medicine. An antimalarial drug, artemether, and an acetylcholinesterase inhibitor, huperzine A, are exemplified.

INTRODUCTION

Plants were mankind's first medicines. From ancient to modern history, traditional plant-based medicines have played an important role in health care. In spite of the great advances of modern scientific medicine, traditional medicine is still the primary form of healing methods readily available to the majority of the people in the developing countries. In fact many of today's popular drugs have their origins in traditional medicines, and even in the United States, over half of the prescriptions contain a plant-derived compound. Morphine, quinine, digitalin, ephedrine and reserpine, for example, were isolated from traditional medicinal plants, which were known to be efficacious in the treatment of certain diseases long before phytochemical and pharmacological investigations. For thousands of years, traditional medicine and remedies have been practiced and used in China. They have proved to be valuable and the essence of vast historical experience. The Chinese people believe that traditional medicine is consistent with their own culture and continues to play a crucial role in helping the Chinese nation flourish.

However, in the Western scientific community the study and use of ethnic or traditional drugs have been virtually ignored for decades. The new methods and techniques for new drug design and modern biotechnology were supposed to have led into the age of rational drug design, in which drugs would be formulated by means of scientific principles and computer aided design, doing away with the need to rely on natural sources. A number of pharmaceutical companies and research institutions now realize that synthetic drugs cannot always duplicate the curative effects of natural products, and new drug design methods and techniques cannot always provide the totally novel bioactive molecules which exist in nature. No matter how important and potential the rational drug design is for the future drug development, it has so far proved difficult to design novel molecules completely from scratch. Millions of years of plant evolution have led to the development of many secondary metabolites with various and unique chemical structures, that mankind has not even thought of.

TRADITIONAL CHINESE MEDICINES

The medicinal plants studied nowadays in China could be arranged under 4 categories (ref.1,2):

1. Traditional Chinese medicines,
2. Chinese folk medicines,
3. Western medicinal plants, and
4. Traditional compound prescriptions.

Traditional medicines mean that they have been prescribed by most of the traditional medical doctors all over the country and recorded in the ancient medical classics and pharmacopoeias. Folk medicines including those materials taken by the Chinese minorities are usually adopted by local witch doctors as well as some medical doctors. Generally, folk medicines are not nationwide popular, and are used mainly for the treatment of endemic diseases. They have not yet been described in Chinese medical classics.

The Western medicinal plants include all those plants which have been studies abroad already. The compound prescriptions refer to the ones containing several plants and other components. Most of them have been collected in ancient classics, but some are nostrums and still kept in secrecy by families. According to the traditional Chinese medical philosophy, a compound prescription often consists of 4 different functional groups, namely, the principal, adjuvant, auxiliary and conductant. The principal provides the principal curative effect, the adjuvant helps strengthen the principal effect, the auxiliary relieves secondary symptoms or decreases the toxicity of the principal, and the conductant directs the action of the principal to the target organ or site. Each group in a compound prescription may comprise more than one plant or other component.

In Chinese ancient medical literature, there are several famous medicinal classics. Among them the Compendium of Materia Medica is the most outstanding and comprehensive work, compiled and published in 52 volumes by Li Shizhen in 1590. It lists 1,892 medicinal substances including plants, insects, animals, minerals and so on. There are over one thousand illustrations and ten thousand prescriptions in this compendium with detailed descriptions of the appearance, properties, methods of collection, preparation and use of each substance. Modern drugs are classified by the chemical structures, pharmacological actions or therapeutic purposes but in terms of traditional Chinese medicine, the traditional drugs are categorized into 4 energies and 5 tastes. The 4 energies are: cold, hot, warm and cool. They are judged by the body's reaction to and the therapeutic effect of the drug. The 5 tastes are sour, bitter, sweet, salty and pungent. Energy and taste are interrelated. Different drugs may fall into the same energy category but taste differently or *vice versa*.

During the last 4 decades 104 drugs have been developed in China, 60 of them originated from medicinal plants (ref.3,4). In 1990, the new edition of Chinese Pharmacopoeia was published in 2 volumes. Volume one deals with 784 traditional Chinese drugs, and volume two contains 967 Western drugs. It is necessary to explain that the promotion of traditional medicine does not mean to advocate a return to the primary folk medicine. Traditional medicine mainly is a complement to, rather than a substitute for modern medicine. In China the idea of integrating traditional with modern medicine has met with opposition from a number of modern medical doctors, pharmacologists and medicinal chemists. They are engaged in an argument with traditionalists in several aspects.

In modern medicine in order to avoid drug interactions, the use of a single drug is preferred. Conversely, in traditional Chinese medicine a prescription usually contains several herbs, but were it simplified in certain way, the traditional doctors and pharmacists would argue that any modification of a prescription would violate the traditional medical theory, and therefore could alter the efficacy and toxicity (ref.5). Another aspect of the modern scientific approach to natural products is to chemically isolate, identify and pharmacologically screen the active principles from medicinal plants. A plant extract, for instance, might contain many components which then have to be laboriously separated to see which one is active in the screening assay. In addition, the natural substance often has to be modified to get safer and more effective analogs. When chemists and pharmacologists fail to get any active compounds, they will give up the project. However, the benefits of traditional Chinese remedies frequently result from the combination of various plants and ingredients. The efficacy of a prescription could be evaluated as the sum of additive, synergetic and antagonistic effects of all ingredients (ref.6). The traditionalists suppose that the search for pure active principles just reflects the analytical methodology of modern science, and traditional Chinese drugs may sometimes be effective only in combination, i.e. in the form of compound prescription.

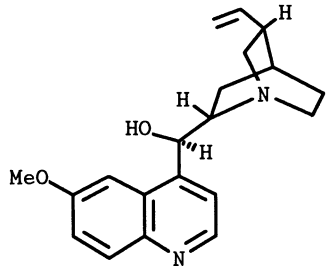
From the viewpoint of modern scientists, there are a few factors making them hesitate to study these compound prescriptions, for instance, difficulties in getting raw materials with the same quality, no standard processing for the pretreatment of the material, difficulties in establishing suitable screening models and monitoring the metabolism pathway of each component in a compound prescription, and a wide gap between ancient Chinese medicine and modern medicine in concepts and theories of diseases (ref.7).

In recent years there has been much work done in the area of traditional medicinal plants in China, and many good results or promising leads have been achieved. However, most of the research projects carried out are designed on the principles of modern medicine and chemistry, and applying the pharmacological models commonly used in Western countries. How to establish different screening models adapted for traditional Chinese medicine is one of the crucial problems. Obviously, there are big differences between the therapeutic effects of a compound prescription, those of an individual plant, and those of one active principle from a single plant. Whether the optimal effectiveness results from the combined action of known and unknown compounds originally occurring in plants, or whether there are additional new active principles resulting from preparation and formulation of a prescription is also a formidable challenge to be taken in the future.

The next part of this review will present two new drugs which were discovered and developed from Chinese traditional medicine in recent decades by the Shanghai Institute of Materia Medica.

ARTEMETHER: AN ANTIMALARIAL DRUG

It is well-known that the first natural product which gained worldwide acceptance as an antimalarial is quinine(1), an alkaloid isolated from cinchona bark. Another plant *Dichroa febrifuga* Lour which grows in China has been also used against fevers and malaria. However, its active principle, the alkaloid febrifugine(2), was found to be too toxic in humans. In view of the number of chloroquine-resistant strains of *Plasmodium falciparum* emerging everywhere, WHO reported a big increase in malaria cases in the tropics and estimated that 110 million people worldwide contracted malaria each year with 1-2 million deaths, the need for new antimalarials cannot be overlooked.



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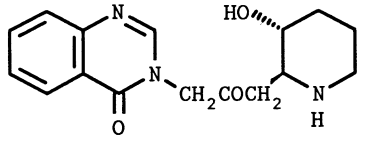

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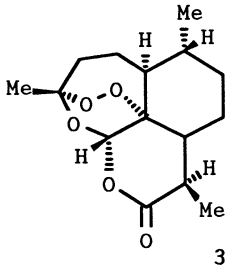

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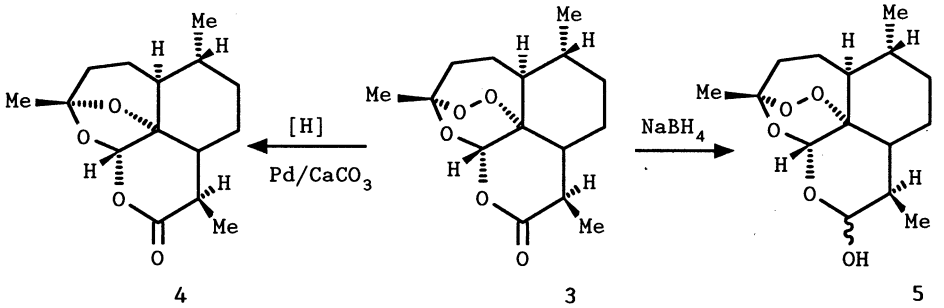
In China the herb *Artemisia annua* L. has been used as a cure for fever and malaria for many centuries. The early experiments on aqueous and ethanolic extracts of the herb failed to confirm its therapeutic effects. Later, extracts with ethyl ether at low temperature produced good results in both murine and simian malaria. Various solvents such as petroleum ether, ethyl ether, acetone and gasoline can be used as solvents for the extraction. In 1972, an antimalarial principle called artemisinin (qinghaosu,3) was isolated from the leaves of this herb. The yields of artemisinin from the dried herb vary between 0.01-0.6%, depending on the origin of the herb and the collecting season (ref.8,9). The structure of artemisinin and its configuration were determined unambiguously by spectral analysis and X-ray diffraction. It is a sesquiterpene lactone containing a peroxide and unlike most of other antimalarials it lacks a nitrogen ring system (ref.10,11). It is poorly soluble in water or oil, decomposes in protic solvents. The compound has been used successfully in over ten thousand malaria patients in China and other countries with both chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum* and *vivax*. Although it is fast-acting and effective against malaria that resists chloroquine, the problems encountered with recrudescence as well as poor solubility led to efforts to its chemical modification.

Chemically, the peroxy group in artemisinin (3) is essential. Catalytic hydrogenation of artemisinin affords deoxyartemisinin (4), an epoxide, which is devoid of antimalarial activity. However, when it is reduced with sodium borohydride, the lactone moiety of the molecule is converted into a lactol, dihydroartemisinin (5), in which the peroxide is preserved(Scheme 1). The lactol is an even stronger antimalarial. In crystalline form, the hydroxy of lactol is in the ß configuration, but a mixture of the α and ß epimers is formed in solution. The hydroxy group of the molecule provides the way for synthesizing various derivatives. Three types of derivatives of dihydroartemisinin have been studied intensively (ref.12,13).

Scheme 1. Reduction of artemisinin



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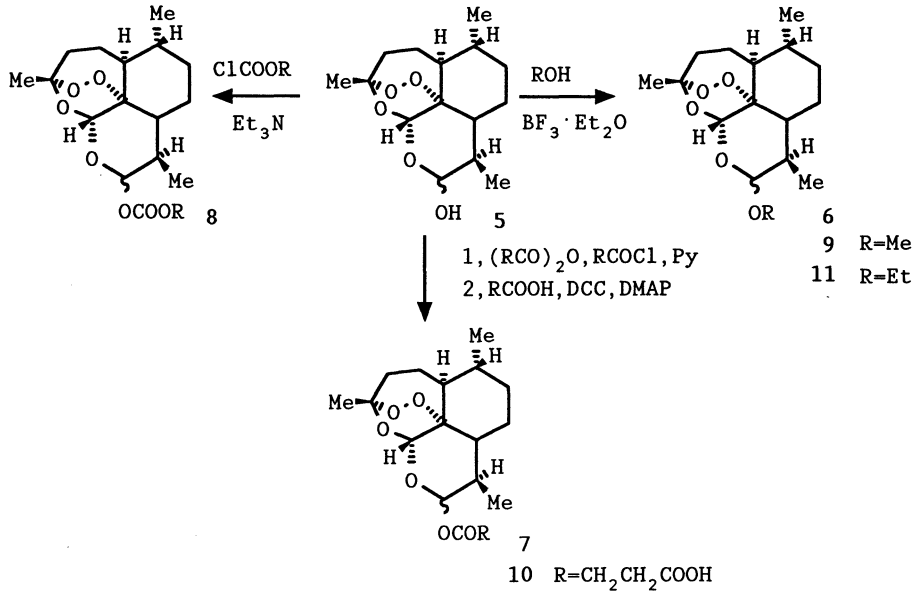
Scheme 2. Synthesis of artemisinin derivatives



The ether (6) was made by treating dihydroartemesinin (5) with alcohol in the presence of boron trifluoride etherate. The ester (7) was obtained when (5) was treated either with an anhydride or an acyl chloride in pyridine or with a carboxylic acid and DCC. The carbonate (8) was prepared by the reaction of (5) with chloroformate, triethylamine and DMAP. All derivatives thus obtained are a mixture of the α- and ß-epimers, which are more soluble in oil and could be separated by chromatography (Scheme 2). In acidic media the ß-epimers are formed predominantly, and in basic media the α-epimers are mainly yielded. Over 300 derivatives of dihydroartemisinin (5) were prepared and screened (ref.14). Among them, 20 derivatives are over 10 times as potent as artemisinin based upon their overall antimalarial efficacies. In general, carbonates (8) are the most potent ones in *in vivo* tests but they have not been tested clinically.

The mixed epimers of artemether (9, α:ß= 1:3) show higher antimalarial activity in animal tests and clinical trials. Compared with artemisinin and other derivatives, artemether is superior in many aspects, such as higher antimalarial efficacy against rodent malaria, better solubility in oil, chemical stability, and simpler preparative procedure. Therefore, comprehensive studies have been made on its pharmacodynamics, toxicology, drug metabolism and clinical trials(ref.15). Clinically, it shows an excellent therapeutic effect against falciparum malaria, including the chloroquine- or multi-resistant malaria, and was found to save severe cerebral malaria. The schizonticidal action of artemether is much more potent than quinine and other antimalarials currently used. Another derivative, the monoester of succinate (10) is able to form a water-soluble salt. The sodium salt of (10), sodium artesunate can be taken intravenously. It acts rapidly in restoring to consciousness comatose patients with cerebral malaria (ref. 16). Artemether and sodium artesunate have been approved by the Chinese authorities as new antimalarials. Arteether (11) first prepared by Shanghai Institute of Materia Medica in 1980 has been further developed by the Walter Reed Army Institute of Research in Washington (ref.17). WHO has financed the development of arteether.

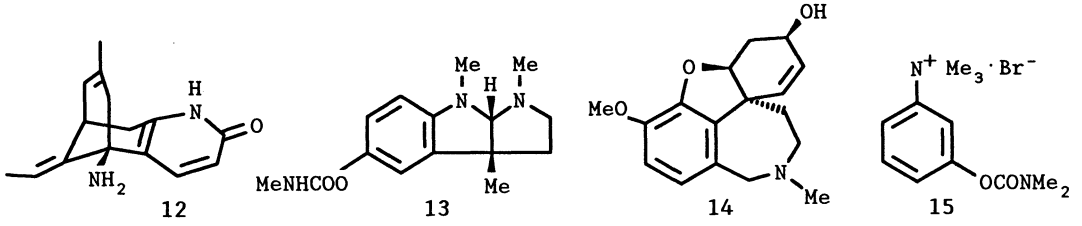
Chemically being nonalkaloidal, artemisinin and its derivatives belong to a totally novel class of antimalarials. The discovery and development of the artemisinin group mark a notable success in malarial chemotherapy in being active against multi-resistant organisms and much safer than others.

HUPERZINE A: AN AChE INHIBITOR

The second molecule to be discussed is huperzine A (12), an alkaloid isolated from *Huperzia serrata* (Thunb) Trev., a clubmoss indigenous to China, by researchers at the Shanghai Institute of Materia Medica and Zhejiang Academy of Medical Science in 1982 (ref.18). Another alkaloid selagine isolated from *Lycopodium selago* L. is identical with huperzine A. Reinvestigation of the selagine structure has revealed the earlier structural assignment to be incorrect (ref.19). For centuries in some districts of China, people have brewed tea from the leaves of this plant and served it to elderly people to alleviate memory problems.

It is estimated that Alzheimer's disease (AD) affects 5-15% of the population over age 65. The

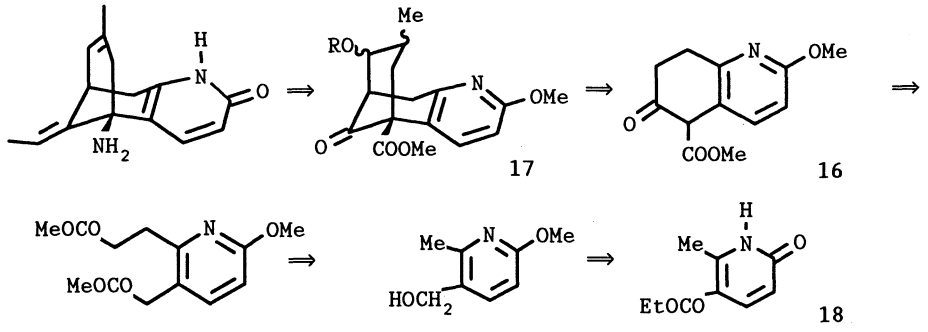
number of victims is increasing steadily as the average age of the population rises. The disease is characterized by a gradual and progressive mental deterioration. The earliest and most prominent symptom is memory impairment. At present, there exists no effective treatment. There is considerable evidence that the memory deficits observed in AD patients are due to impairment of cholinergic neurotransmission in the central nervous system. The well-known naturally occurring acetylcholinesterase (AChE) inhibitors physostigmine (13) and galanthamine (14) have already shown utility as possible agents in the treatment of AD.



Huperzine A is a potent inhibitor of AChE in rat erythrocytes and pig caudate as well as a weaker inhibitor of butyrylcholinesterase in rat and human serum (ref.20). The rank order of anti-AChE activity is huperzine A > physostigmine > neostigmine (15). Huperzine A has been shown to be useful in treating myasthenia gravis in humans. In rats huperzine A facilitates learning and retrieval in a Y-maze (ref.21). Scopolamine and atropine antagonize these effects. In a study of 100 patients (46-82 years old) suffering from memory impairment including 17 AD patients, memory was improved 1-4 h after a single intramuscular injection of 30 μg of huperzine A with few and mild side effects. The effect was sustained for about 8 h (ref.22). Huperzine A can produce a long-term inhibition of AChE in brain and an increase in the acetylcholine levels up to 40%. As a novel AChE inhibitor, it shows interesting cholinomimetic properties, and its effects satisfy more closely the established criteria for an ideal AChE inhibitor for the treatment of AD than physostigmine (ref.23).

Because of the difficulty in obtaining a large quantity of huperzine A from plants and the necessity of molecule modification for the search for new agents which might possess high activity, longer action duration, less toxicity, and could be prepared by a simpler and efficient approach as compared with huperzine A itself, an intensive project has been carried out at Shanghai Institute of Materia Medica since 1984. The total synthesis of racemic huperzine A was achieved in 1985.

Scheme 3. Retrosynthetic analysis of huperzine A

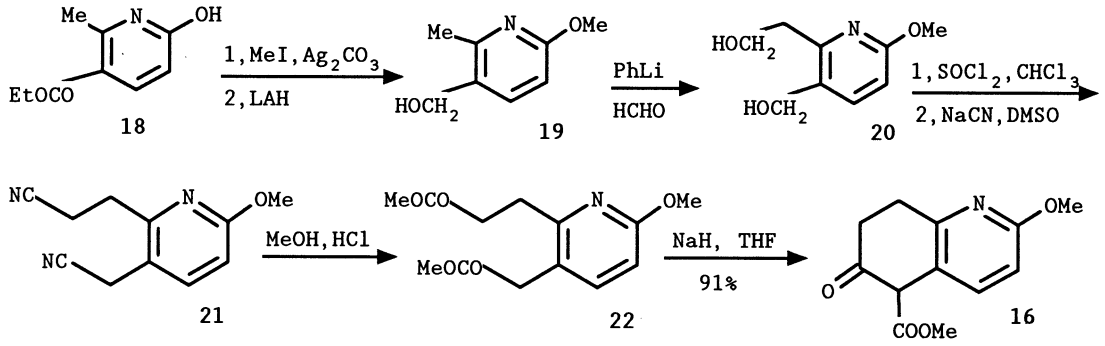


The retrosynthetic analysis of huperzine A is shown in Scheme 3. The key intermediate is methyl 2-methoxy-6-oxo-5,6,7,8-tetrahydroquinoline-5-carboxylate (16), in which the carbomethoxy group can be utilized dually as an activating group for the construction of the bridged ring via Michael-Aldol addition as well as a precursor for introduction of the amino group by Curtius rearrangement. The subsequent reactions to reach the target molecule are dehydration of the aldol product (17) and Wittig reaction to form the exocyclic olefin.

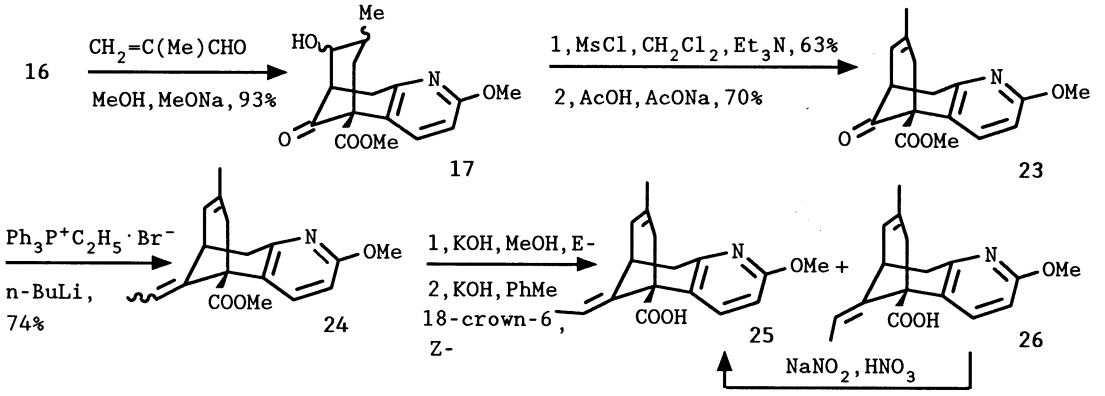
The synthetic approach started from ethyl 2-methyl-6-hydroxy-nicotinate (18), which was first prepared by Ramirez et al. (ref.24) via dehydrogenation of a substituted dihydropyridone over palladium black. By employing 30% palladium on activated carbon, the yield of (18) was increased from 40% to 70%. Selective 0-methylation of (18) with methyl iodide and silver carbonate followed by reduction with LAH, afforded compound (19). Compound (19) reacted with 2 equivalents of phenyl lithium followed by reaction with gaseous formaldehyde, yielding compound (20). The diol (20) was converted with thionyl chloride in chloroform into the chloride, which was then treated with sodium cyanide in DMSO. The cyanide (21) thus formed was subjected to methanolysis in the presence of hydrogen

chloride to obtain diester (22). An intramolecular base-catalyzed cyclization of (22) with sodium hydride in anhydrous THF afforded the key intermediate (16) in an excellent yield (91%). The overall yield of (16) was 39% via 7 steps of reaction (Scheme 4).

Scheme 4. Preparation of key intermediate 16

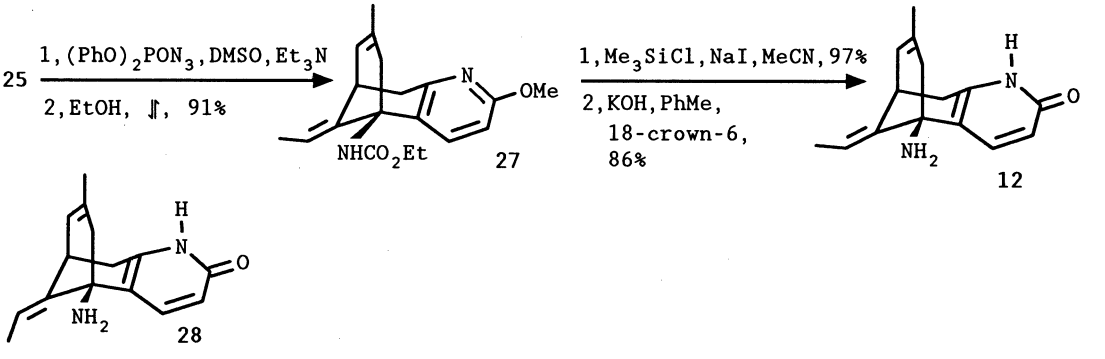


Scheme 5. Synthesis of acids 25 and 26



The bridged ring in compound (17) was easily constructed by the addition of ß-ketoester (16) and methacrolein catalyzed with sodium methoxide in methanol. Product (17) is a mixture of 8 isomers. The subsequent dehydration via mesylation was accomplished with sodium acetate in acetic acid to give the expected olefin (23). Wittig reaction of (23) and ethyltriphenylphosphonium bromide afforded (24), a mixture of Z-and E-isomers in a ratio of 19:1. They could be readily separated by hydrolysis under different conditions. The E-isomer could be hydrolyzed into acid (25) with potassium hydroxide in methanol under reflux, but the Z-isomer was only hydrolyzed into acid (26) with potassium hydroxide in toluene in the presence of crown ether. The major isomer acid (26) was recycled by isomerization

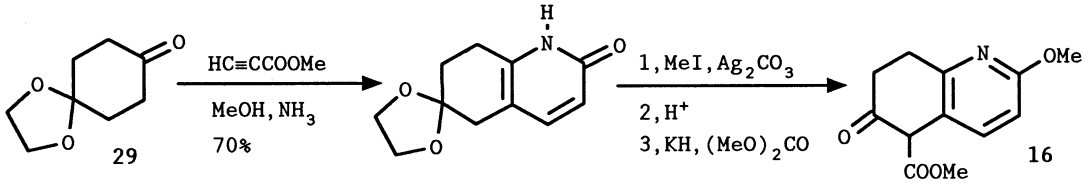
Scheme 6. Completion of the synthesis of huperzine A



with sodium nitrite in nitric acid, giving acid (25) in a 75% yield (Scheme 5). Acid (25) was first converted into azide with diphenylphosphoryl azide, followed by Curtius rearrangement in ethanol to afford urethane (27). The final two steps for the preparation of the target molecule were the conversion of the 2-methoxypyridine ring into a 2-pyridone ring and the deprotection of the amino group. Treatment of the urethane (27) with trimethylsilyl chloride and sodium iodide in acetonitrile gave the 2-pyridone derivative. Removal of the carbethoxy group from the 2-pyridone derivative by hydrolysis with potassium hydroxide in the presence of 18-crown-6, afforded the recemic huperzine A (12,Scheme 6). All the spectral data of the synthetic sample including IR, HNMR, MS are identical with those of the authentic natural product (ref.25). Concurrently, Z-huperzine A (28) was obtained from acid (26) (ref.26).

Independently, the Kozikowski group at the University of Pittsburgh accomplished the synthesis of huperzine A by using 1,4 -cyclohexanedione monoethylene ketal (29) as the starting material (ref. 27). They have developed an efficient route to the key intermediate (16) (Scheme 7) (ref.28). The remaining steps of this route including the construction of the bridged ring, the formation of two double bonds, and the conversion of the carbomethoxy into an amino group are very similar to the approach mentioned above.

Scheme 7. Preparation of intermediate 16



It is noteworthy that huperzine A possesses structural features comparable to those of acetylcholine (ACh). In the molecule of huperzine A there is an amino nitrogen atom which will attract a proton *in vivo* to form a positively charged center, it is as distant from the carbonyl of the amide group as the quaternary nitrogen atom is from the ester carbonyl group in ACh. In Fig.1 a computer-generated superposition of huperzine A with ACh is demonstrated (ref.29). It is apparent from the superposition of the two molecules that a reasonable similarity of structure can be found between the nitrogen atom, carbonyl, and oxygen atom in ACh with the corresponding amino nitrogen, carbonyl and nitrogen atom of the pyridone ring in huperzine A. Therefore, several types of the simplified analogs of huperzine A were designed and prepared (ref.30). All of them possess structurally the pharmacophoric moiety of both ACh and huperzine A molecules.

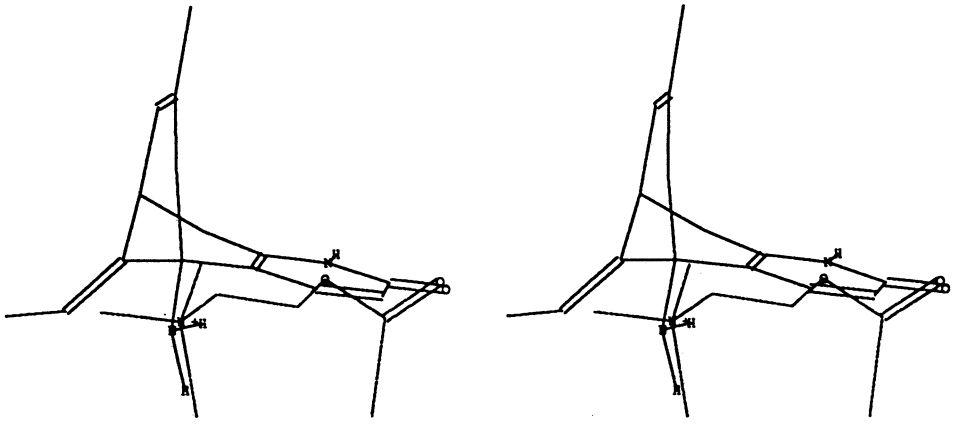
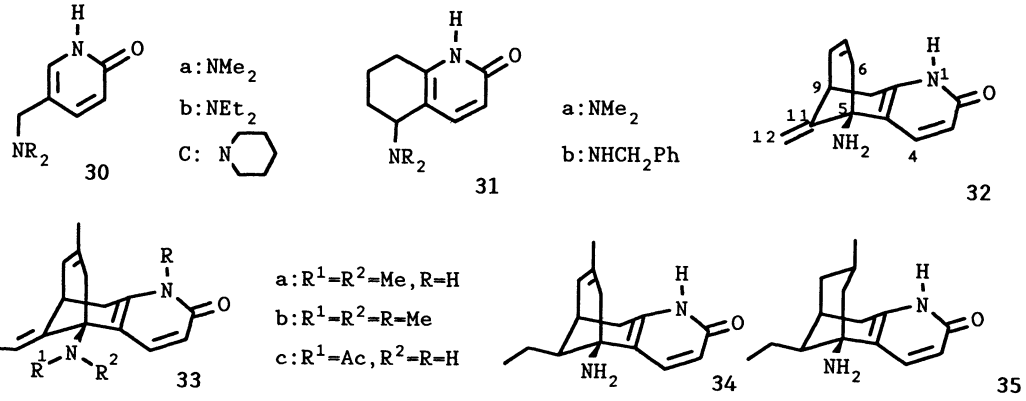


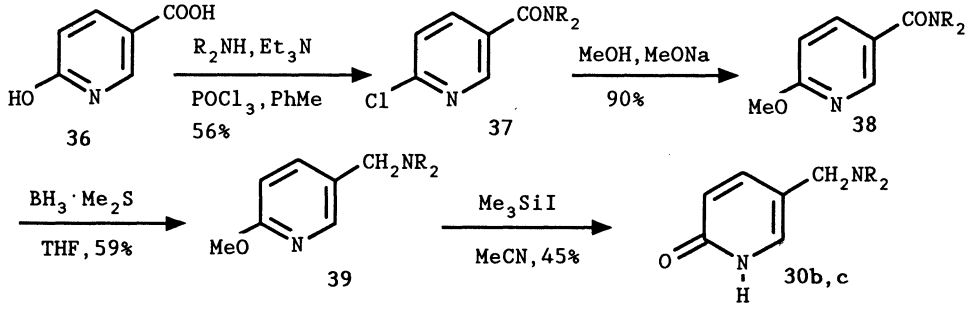
Fig.1 Stereo view of the superposition of huperzine A and ACh (MacroModel)

5-N,N-Dialkylaminomethyl-2(1H)-pyridones (**30a,b,c**) are the simplest analogs of huperzine A, in which the essential portion of the structure of both huperzine A and ACh is retained, and conformationally they are more flexible than the rigid huperzine A. Compound (**31a**) and (**31b**) are fused ring pyridones, the analogs without the bridged ring and exo double bond of huperzine A. Compound (**32**) would provide a measure of the contribution of the two methyl groups in huperzine A to the AChE inhibitory activity. Using natural huperzine A as the starting material, a dozen of the optically active derivatives (**33a,b,c;34;35**)were prepared too (ref.18).

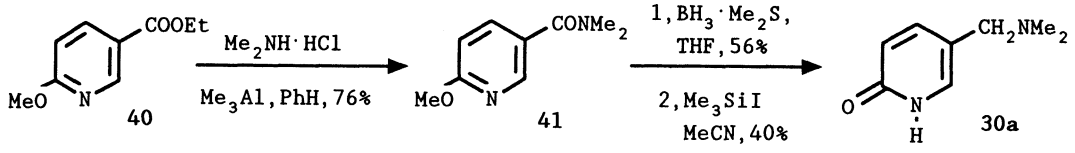


Compounds (**30b**) and (**30c**) were prepared from 6-hydroxynicotinic acid (Scheme 8), which reacted with phosphorus oxychloride and diethylamine or piperidine in toluene to obtain the corresponding N,N-disubstituted-6-chloronicotinamides (**37**). Compounds (**37**) were treated with sodium methoxide in methanol, followed by the reduction of (**38**) with borane-methyl sulfide complex in THF, yielding 5-N,N-disubstituted aminomethyl-2-methoxypyridines(**39**). The product (**30b**) and (**30c**) were formed by demethylation of (**39**) with iodotrimethylsilane in acetonitrile. Compound (**30a**) was obtained from ethyl 6-methoxynicotinate (**40**) via a sequence of reactions involving the formation of amide (**41**) with dimethylamine hydrochloride pretreated with trimethylaluminum in benzene (ref.31), reduction of (**41**) with borane-methyl sulfide complex, and final deprotection (Scheme 9).

Scheme 8. Preparation of analogs 30b and 30c



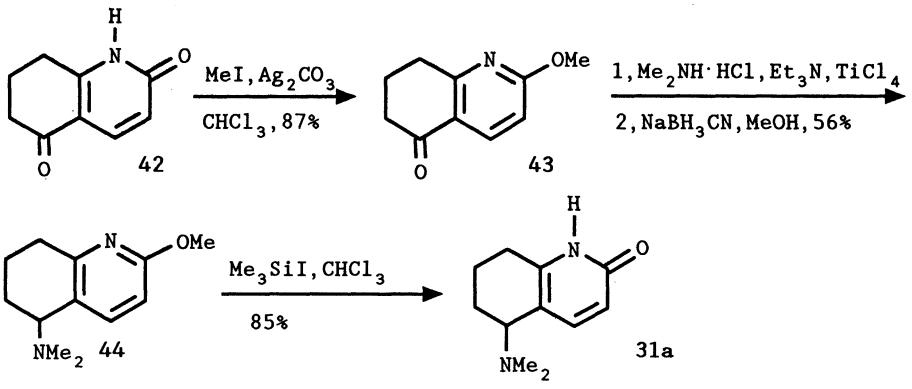
Scheme 9. Preparation of analog 30a



To prepare analog (**31a**), 2,5-dioxo-hexahydroquinoline (**42**) was first protected with methyl iodide and silver carbonate to form the 2-methoxy derivative (**43**), which was subjected to a reductive amination utilizing titanium tetrachloride-sodium cyanoborohydride and dimethylamine hydrochloride in the presence of triethylamine in one pot,yielding compound (**44**) (ref.32). Demethylation of (**44**) gave compound (**31a**) (Scheme 10). The synthesis of compound (**31b**) was carried out according to the above-mentioned procedure, using benzylamine instead of its hydrochloride. Demethylation occurred simultaneously during reductive amination, giving directly the analog (**31b**).

Compound (32) was synthesized by reactions identical to those presented in Scheme 5, using acrolein and methyltriphenylphosphonium bromide instead of methacrolein and ethyltriphenylphosphonium bromide respectively. Compounds (33), (34) and (35) which possess the whole carbon skeleton of huperzine A were derived from natural huperzine A through N-methylation, N-acetylation or hydrogenation of the double bond.

Scheme 10. Preparation of analog 31a



All the analogs and derivatives were tested for their inhibitory activity of AChE isolated from rat erythrocyte membrane. The PI_{50} of these compounds are listed in Table 1 (ref.33). Neither the structurally simplified compounds nor the derivatives from natural huperzine A have the anti-AChE potency of huperzine A. Among them dihydrohuperzine A (**34**) shows the highest activity but its potency is 10 times less than huperzine A.

TABLE 1 Inhibitory activity of huperzine A and its analogs on rat erythrocyte membrane AChE

Compound	PI_{50}* (M)	Compound	PI_{50} (M)
(-)-Hup A	7.1	33b	3.5
30a	no Activity	33c	< 2.5
30b	no Activity	34	6.2
30c	no Activity	35	5.6
31a	no Activity	Physostigmine	6.7
31b	no Activity	Neostigmine	6.7
32	3.55	Galanthamine	5.7
33a	3.8		

* Negative logarithm of the molar concentration causing 50% inhibition.

In the United States, the Kozikowski and Hanin groups have also reported the preparation of a variety of huperzine A analogs and their extent of AChE inhibition. None of the analogs has yet achieved the potency of the parent compound (ref.27,34). So it would appear from the chemical and biological data reported to date that the essential structural features for high anti-AChE activity in the molecule of huperzine A should include an amino group, a pyridone ring, a bridged ring, and an exocyclic and endocyclic double bond.

CONCLUSION

The recent study of the traditional medicinal plants in China has given us confidence that what was recorded in Chinese ancient medical and pharmaceutical literature through empirical observations is indeed still coincident with the concepts of modern chemistry, pharmacology, and medicine. Artemisinin and huperzine A are two examples to illustrate the role of the traditional Chinese medicines in new drug development. The task of discarding the dross and selecting the essence in traditional Chinese medicines may require scientific research lasting for several generations.

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