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PROPOSALS REGARDING CHLORPROMAZINE AND RELATED COMPOUNDS ACTIVITIES[1]

GUSTAVO LOYOLA-GUZMÁN[2]

The way by wich Chlorpromazine (Chlz) and related compounds exert their pharmacological activity on Central Nervous System as well as their unlike side effects, are not well known, even though numerous reports on their effects have been produced (**1-2**).

On the other hand it is important to know how the properties of these compounds are related with their molecular structure in order to obtain new drugs with enhanced physiological activity and less undesirable side effects.

Chlz, presents two well defined zones on its molecular structure (fig 1), a) an alkyl chain lead by an ammonium group at physiological pH(**3**) and b) a phenotiazine ring.

The pharmacological and undesirable effects are quite probably related with these two characteristic zones.

First, we propose that the alkyl chain led by the ammonium group as well as a portion of the phenotiazine central ring (projected zone in fig 1A), are recognised by neurotransmitter receptors of dopamine, adrenaline, acetylcholine, histamine and serotonine.

We have named this molecular zone as "**K**ey **T**ail **A**mmonium **H**ead" or "**KTAH**", because it resembles as a Skeleton Key led by an Ammonium Group. We recognised a similar KTAH zone on adrenaline, acetylcholine, histamine and serotonine molecules (see projected zones at fig 1) that we assume that normally are bound at their specific neurotransmitter receptors.

The above is on line with the principal pharmacological action of Chlz as a psychotropic molecule acting on dopaminergic receptors (**4-5**), and with its adrenergic, cholinergic, histaminic and serotonirergic blocking activity.

The existence of KTAH zones, is in agreement with the theoretical work of Goddard and his co-workers (**6**). They predicted that D2 dopamine receptors bound dopamine because they form 1) tight salt bridge with amine group designated as Ammonium Head, 2) hydrogen-bond with meta and para hydroxy groups of catechol ring both bound

to carbons signed by us as "positions 6 and 7" in Chlorpromazine's KTAH (fig 1-A and B), and 3) a mostly hydrophobic pocket for dopamine.

Moreover, Chlorpromazine's KTAH could be bound by other biochemical structures involved in anabolic or catabolic reactions of histamine and neurotransmitters named above. This could be the case in serum cholinesterase inhibition by chlorpromazine in humans (**7**).

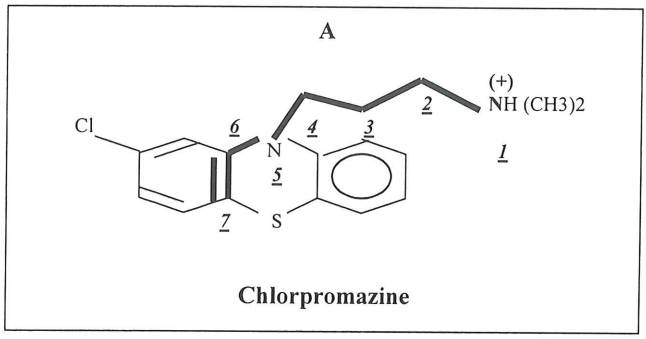
Additionally, our proposal can explain the related activity of other chemicals that include the KeyTail's Ammonium Head on its molecular structures. Some examples are 7-hydroxy-dipropylaminotetralin(7-hydroxy-DPAT), apomorphine, bromocriptine (dopamine agonist), Diphenhydramine (antihistaminic), Nicotine and Muscarine (colinergic receptors), Galantamine (on colinergic receptors and acetylcholinesterase enzyme), Physostigmine (acethylcoline inhibitor), Pramipexole (dopamine agonist), Imipramine (antidepressive) .... etc.

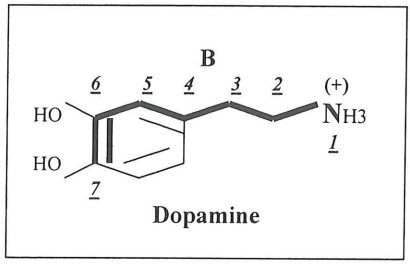
Second, we propose that Chlz (projected zone in fig 1-A'), could be bound to adenine or flavine (fig 1-I), (di)nucleotide binding sites of biochemical active structures that normally bind Adenine or Flavine.

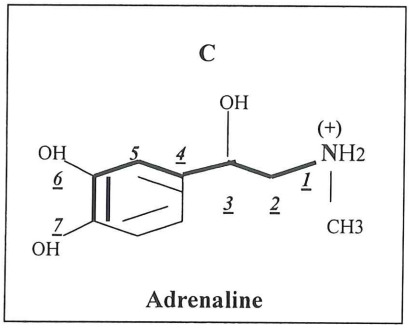
We postulate this, because phenotiazine moiety is a "tricyclic unsaturated system" similar to others tricyclics that have been recognized as to be bound at nucleotide binding sites. In effect, Leonard et al (**8**) and Biellman et al (**9**), correspondingly stablished that stretched-out benzopurine analogues and anthraquinone (fig 1-G) Cibacron Blue, are unambiguos examples of compounds having a moiety with coplanar character composed of three aromatic rings capable of being recognized by enzymes utilizing adenin(di)nucleotides. Furthemore, Orellano et al(**10**) based on kinetic results, postulated that acridine (fig 1-H) moiety, another tricyclic unsaturated system, may be recognized as adenine(di)nucleotide by some enzymes.

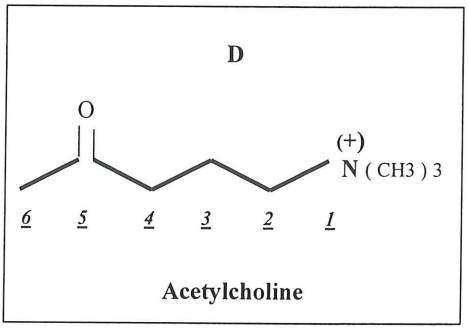
On line with our second proposal, many reports have evidenced or suggested the chlorpromazine "interference" on routes involving adenin or flavine(di)nucleotide dependent enzymes (**11-16**).

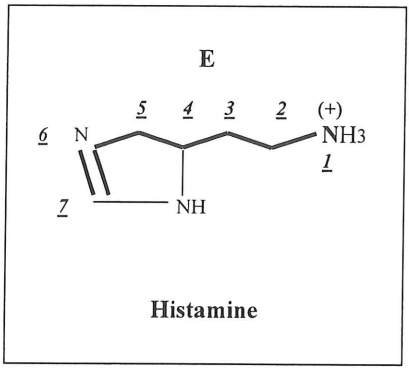
Finally, our proposals open the question about a common origin for KTAH binding zones present at neurotransmitters and histamine receptors contributing also to the design of new effective drugs with less undesirable effects.











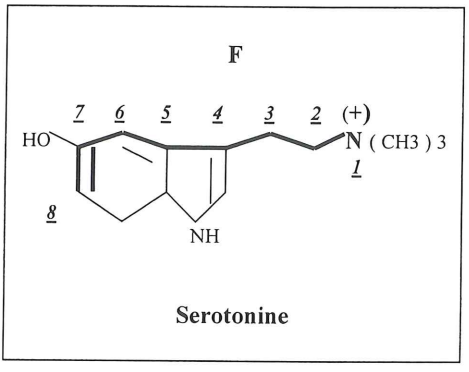
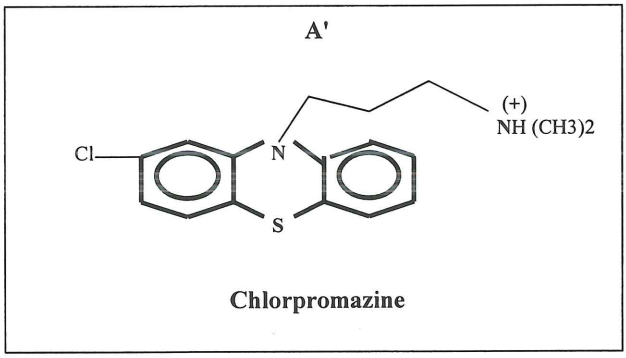
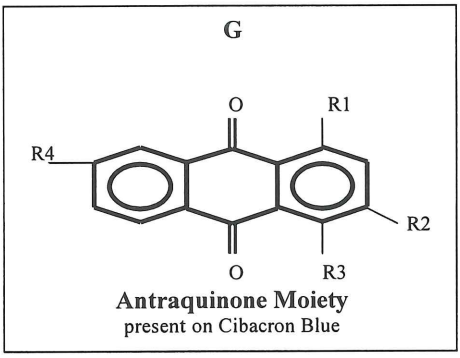
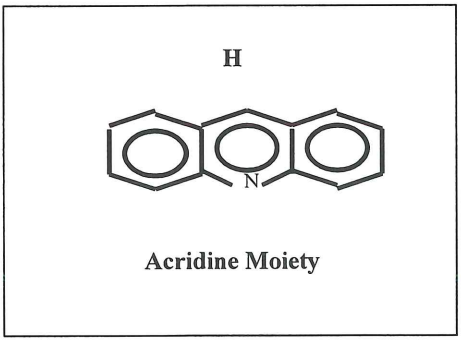


FIGURA 1. *Molecular structures (A-I)*







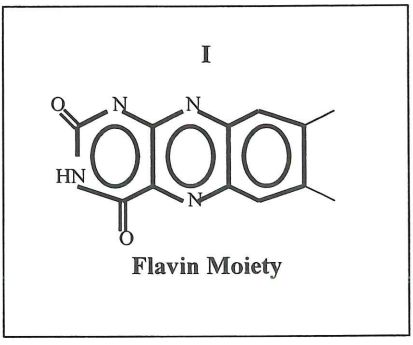


FIGURA 2. *Molecular structures (A-I)*

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