



Neutral Pharmaceuticals

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Field

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Drug development is an expensive and time-consuming process. It generally involves combing vast libraries of drug candidates, identifying those with a desired pharmacologic activity and testing their biological profiles relating to solubility, absorption, toxicity, bioavailability, stability, etc. This invention offers a streamlined method of both designing and assembling new pharmaceuticals and improving upon drugs already in existence. It is based on the concept that pharmacologic agents can be complexed with auxiliary ligands and transition metal cations of known desirable characteristics in order to improve their pharmacologic properties and profiles. Rather than cataloging drug analogs and testing the biological profile of each one, our method takes already identified active pharmacologic agents and adjusts their composition using metals and auxiliary ligands with known behavior-altering profiles to create safer, more efficacious compounds.

TECHNOLOGY

This invention consists of an elegant and economical method of designing and assembling drugs, addressing the problems of drug solubility, absorption, encapsulation and toxicity. The design consists of an active medicinal functionality (AMF) and one or more chemical-behavior-altering components: a transitional metal functionality (TMF), an auxiliary ligand functionality (ALF), or both. This creates an AMF-ALF-TMF complex. The TMF is a transition metal cation that can bind one or more active pharmaceutical moieties and an auxiliary ligand, such that the total molecular charge is neutral. The transition metal cations include numerous metals that have known low toxicity in humans, such as Manganese (Mn), Iron (Fe), Zinc (Zn) and Copper (Cu). The active medicinal functionality is simply any pharmaceutical molecule or ion containing one or more moieties to which the other functionalities may bind. And the auxiliary ligand functionality may be a solvent, another pharmaceutical molecule, a GRAS ("Generally Regarded As Safe by the U.S. FDA), or an approved food additive. The judicious choice of an auxiliary ligand affords the ability to significantly alter solubility and lipophilicity, both key parameters in absorption, distribution, metabolism, excretion and toxicity.

The use of transition metals in drug development has already led to the development of copper complex NSAIDS, with enhanced anti-inflammatory activity and reduced gastro-intestinal toxicity as compared to the uncomplexed NSAID. Nonetheless, the intrinsic properties of a metal can also negatively affect the physical properties of a pharmaceutical. This invention includes the use of an auxiliary ligand, which coupled with a metal moiety can further modify and refine the pharmacodynamic properties of a drug complex.

As examples of this technology, aspirin and copper (II) were paired with a series of auxiliary ligands: DMF, 3-bromopyridine, quinoline, pyridine, isonicotinamide, niconinamide and 3-phenilpyridine to form a series of mixed-ligand copper (II) coordination species. These complexes displayed a range of partition coefficients and solubility ratios, suggesting that mixed-ligand

coordination species can address the issues of solubility and lipophilicity without altering the parent drug compound via organic transformations. We found some degree of predictability in the observed lipophilicity and solubilities of the compounds on the basis of the partition coefficients of the ancillary ligand. The contribution of the drug ligand partition coefficient to the solubility data and the contribution that the size of the ligands plays on solubility and complex stability are currently under investigation.

Again, solubility and lipophilicity are key to determining a given drug's efficacy and toxicity. This invention offers a way to fine-tune and tailor these parameters without significantly altering the desirable chemical characteristics of a drug compound.

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