Introduction

Interest in squaramides has grown drastically over the last few years. One of the reasons is that squaramides can be used in many different ways in important fields such as organic chemistry, medicine, and chemical biology.

First of all, the rigidity of their cyclobutadiene-dione rings, the restricted rotation around the C–N bonds, and the possibility of having both acidic hydrogens and basic functionalities in a single molecule make them effective bifunctional organocatalysts for asymmetric reactions. Furthermore, they act as ion detectors, forming hydrogen bonds with the corresponding anion or cation. The interaction with anions through hydrogen bonding also brought them to the attention of studies regarding transmembrane anion transport.

In addition, squaramides have shown antimalarial, antibacterial, and anticancer activity.

Abstracts

(A) Organocatalysts
Soós and co-workers recently reported the asymmetric conjugate addition of different acetylacetates to nitrostyrenes with high yields and enantioselectivities using immobilized squaramides. The most appealing aspect of this work is that the reactions were carried out successfully in batch and flow reactors, bringing this catalyst closer to industrial applications.

(B) Anion Sensors
Taylor and co-workers reported the use of a N,N′-diarylsquaramide as a colorimetric sensor for anions such as fluoride and tosylate. The squaramide showed different colors depending on the anion present in a DMSO solution. This behavior seems to be in agreement with an enhanced acidity in comparison with ureas.

Preparation

Squaramides are usually synthesized under mild conditions in high yields, and both symmetric and asymmetric squaramides are accessible (Scheme 1).
(C) Cation Sensors
Costa and co-workers developed a squaramide-based sensor for selective detection of Cu²⁺.12 When this compound chelates with Cu²⁺, a zwitterionic colored radical species is formed rapidly, allowing the visual detection of Cu²⁺. Interestingly, this compound can be used in water for the detection of Cu²⁺, displaying good selectivity for this cation over other metallic cations.

(D) Transmembrane Anion Transporters
Gale and co-workers reported the use of squaramides as anion transporters across lipid bilayers, obtaining better results than their urea and thiourea analogues.13 This research opens a door for the use of squaramide-based drugs in the treatment of diseases caused by malfunctioning ion channels.

(E) Antimalarial Agents
Santos and co-workers synthesized squaramide aza vinyl sulfones that were shown to have antimalarial activities.6 These compounds could be used as medicines in the complex fight against malaria, an illness that infects millions of people every year and develops resistance to the drugs used in its treatment.13

(F) Linkers for Biomolecules
Luk and co-workers reported the use of squaramides as axis linkers.14 These reactions make squaramides suitable for modifying existing biomolecules, adding parts containing peptides to their structures. This peptide coupling is carried out using water as the solvent, which might make the use of this type of compound suitable for in vivo studies.

References