ABSTRACT

The search for new crystals with novel supramolecular networks is an important area due to their practical applications. Carboxylate molecular crystals have been of interest due to the presence of hydrogen bonding, which plays an indispensable role in chemical and crystal engineering, as well as in supramolecular chemistry. Acid–base adducts possess hydrogen bonds which increase the thermal and mechanical stability of the crystal. Many new carboxylate molecular crystals have been found on the supramolecular chemistry and have wide applications in biological systems and non-linear optics. 2, 2'-Thiodiacetic acid (Tda), oxydiacetic acid (Oda) and iminodiacetic acid (Ida) are the versatile ligands that have been widely explored, employing its multidentate and chelating coordination abilities with many metals; however, molecular crystals of thiodiacetic acid, oxydiacetic acid and iminodiacetic acid with aliphatic and aromatic diamines including ethylenediamine and o-phenylenediamine have not been reported.

In the present study, the five molecular salts, namely ethylenediaminium 2,2'-thiodiacetate, $[(Tda)^{2-}(en)^{2+}]$, denoted Tdaen, 2-aminoanilinium-2-(carboxymethylsulfanyl)acetate $[(Tda)^{-}(o\text{-}phen)^{+}]$, denoted Tdaophen, ethylenediaminium oxydiacetate hydrate $[(Oda)^{2-}(en)^{2+}].H_2O$, denoted Odaen, 2-aminoanilinium-2-(carboxymethoxy) acetate $[(Oda)^{-}(o\text{-}phen)^{+}]$, denoted Odaophen, ethylenediaminium iminodiacetate, $[(Ida)^{-}.0.5(en)^{+}]$, denoted Idaen and Ida zwitterion were synthesized and characterized by single crystal X-ray diffraction, ATR, UV-Visible absorption and Transmittance, ^{1}H and ^{13}C NMR spectroscopic measurements. The thermal stability of the crystals was carried out by simultaneous Thermogravimetric-differential thermal analysis (TG-DTA). The *in-vivo* anti-convulsant activity of the four molecular salts Tdaen, Tdaophen, Odaen and Odaophen were investigated. The histopathological studies and clinical parameters were also analyzed. Iminodiacetic acid with o-phenylenediamine form zwitterions instead of molecular crystals. An attempt is made to synthesis molecular

crystals of iminodiacetic acid and o-phenylenediamine and *in-vivo* anti-convulsant activity of iminodiacetic acid molecular crystals will be performed in future.

The characterization techniques and pharmacological studies exhibit the following results.

The single crystals of ethylenediaminium 2, 2'-thiodiacetate (Tdaen) and 2-aminoanilinium-2-(carboxymethylsulfanyl)acetate (Tdaophen) were grown by slow evaporation solution growth technique. Single crystal X-ray structure determination revealed that 2, 2'-thiodiacetic acid was deprotonated to form divalent anions with ethylenediamine and monovalent anions with o-phenylenediamine. The divalent Tda^{2-} anions form one-dimensional (1D) linear supramolecular chain and monovalent Tda^{-} anions form one-dimensional (1D) zigzag supramolecular chain. These one-dimensional (1D) chains can be extended to form two different three-dimensional (3D) chains by the interaction of diamine cations. The Hirshfeld surfaces and two-dimensional (2D) fingerprint plots of Tdaen and Tdaophen revealed that O….H/H….O and H….H interactions are well dominated. The structures of diamines influence the intermolecular contacts in Tdaen and Tdaophen molecular crystals. The results of spectroscopic characterizations confirmed the formation of charge transfer complexes of thiodiacetic acid with ethylenediamine and o-phenylenediamine. The thermal stability of the crystals has been confirmed by simultaneous TG-DTA studies. The results revealed that both the crystals are stable up to 120°C.

The single crystals of ethylenediaminium oxydiacetate (Odaen) and 2-aminoanilinium-2-(carboxymethoxy)acetate (Odaophen) were grown by slow evaporation solution growth technique and characterization analysis was discussed. Single crystal X-ray structure determination of these salts revealed that oxydiacetic acid was deprotonated to form divalent anions with ethylenediamine and monovalent anions with o-phenylenediamine. The divalent Oda^{2-} anions and water molecules form

supramolecular chains in a zigzag manner where the two chains overlapped to form one-dimensional (1D) chains. The Oda^- anions form one-dimensional (1D) linear supramolecular chains. These one-dimensional (1D) chains were extended to form two different two-dimensional (2D) chains by the interaction of diamine cations. The Hirshfeld surfaces and 2D fingerprint plots of Odaen and Odaophen revealed that O….H/H….O and H….H interactions are mostly dominated interactions. The spectroscopic characterizations confirmed the formation of molecular salts of oxydiacetic acid with ethylenediamine and o-phenylenediamine. The thermal stability of the crystals has been confirmed by simultaneous TG-DTA studies. The results revealed that Odaen and Odaophen were stable up to 100°C and 150°C.

The single crystals of ethylenediaminium iminodiacetate (Idaen) and iminodiacetic acid zwitterion were grown by slow evaporation solution growth technique and various characterization analyses were discussed. Single crystal X-ray structure determination revealed that iminodiacetic acid was deprotonated to form monovalent anions with ethylenediamine. In Idaen, both intermolecular and intramolecular proton transfer occurred. The monovalent Ida^- anions form one-dimensional (1D) zigzag supramolecular chains. These 1D chains were extended to form two different two-dimensional (2D) chains by the interaction of 0.5 en^+ cations. Instead of the molecular salt, iminodiacetic acid form zwitterions with o-phenylenediamine. Ida zwitterions form 1D ladder-type supramolecular network. The Hirshfeld surfaces and 2D fingerprint plots of Idaen and Ida zwitterion revealed that O….H/H….O and H….H interactions are mostly dominated interactions. The spectroscopic characterizations confirmed the formation of molecular salt and zwitterion of iminodiacetic acid with ethylenediamine and o-phenylenediamine. The thermal stability of the crystals has been confirmed by simultaneous TG-DTA studies. The results revealed that Idaen and Ida zwitterions were stable up to 239°C.

The crystal data of the molecular crystals were compared and analyzed in detail.

In the present study, we have evaluated *in-vivo* Anti-convulsant activity against Maximal Electroshock model (MES) and subcutaneous pentylenetetrazol model (scPTZ) model and Neurotoxicity for Tdaen, Tdaophen, Odaen and Odaophen compounds at a two dosages 100 mg/kg and 300 mg/kg. All the compounds are free from neurotoxicity. The compound Odaophen was active against both the MES and scPTZ model at a dosage of 300 mg/kg. The compound Odaen was inactive against both the MES and scPTZ model at a dosage of 100 and 300 mg/kg. Tdaen and Tdaophen show lesser activity than Odaophen and standard drug Sodium valproate. The clinical parameters and histopathological studies revealed that the consumption of Odaophen compound did not alter the structure and function of the liver and brain. The compounds Tdaen and Tdaophen exhibit abnormal results in clinical parameters and histopathological studies. The results of biological studies revealed that the compound Odaophen show better anticonvulsant activity and lesser side effects than other compounds.

The summary of the present investigations and suggestions for future research activities are described.