Novel anticoagulant rodenticides devoid of causing rodenticide-resistance -

A potential solution to an increasing and worldwide problem

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Background:

- Rodent associated annual agricultural loss exceeds 10% to 25 % of the annual world food production.
- Rodents serve as carriers of severe human diseases and epidemic plagues with case fatalies up to > 90% (e.g. Ebola etc.).
- To limit rodent associated damages pest control is sought from periodic rodenticide campaigns.
- However, an increasing number of rodent tribes have developed resistance to current first and second generation coumarin- and indandione based rodenticides (Fig 1) (in some areas up to 60% tribes are resistant.

Objectives:

- To design a new class of rodenticides devoid of known resistance mechanisms
- To maintain timely delayed toxixity in order to overcome rodents inherent social behavioral defense mechanisms
- To maintain anticoagulation as prime mode of toxicity

Mode of action of 1st and 2nd generation rodenticides:

- Coumarin and indandione- type (first and second generation) rodenticides act as Vitamin K antagonists
- They act indirectly by blockade of ß-carboxylation of coagulation factors II, VII, IX , X and Prot. C & Prot. S (Fig.1)
- Non carboxylated coagulation factor (PIVKAs) are devoid of coagulant activities resulting in the (almost) complete abrogation of blood coagulability leading to a fatal coagulation defect .

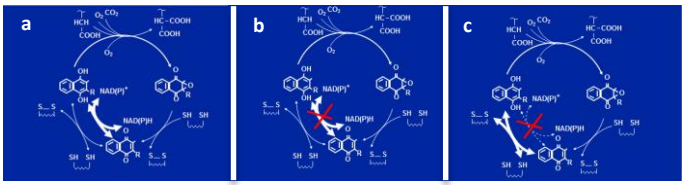

Fig. 1 a: Mode of action of Vitamin K: ß-Carboxylation; 1b : Mode of action of Vitamin K antagonists; 1b Mechanism of action of coumarin resistance

- Fatal bleeds occur in substantial timely distance to the rodenticide ingestion. By this delay and rodents finally succumb from fatal bleeds.
- By delayed mode of action rodents protective social behavior is tricked, an essential feature of such anticoagulant based rodenticdes

New (third generation) type of rodenticides:

- **We identified five families of novel rodenticides covered by our recently submitted patent [1], which are basically derivatives of:**

1. Benzimidazolcarbonylpyridylaminopropionate (Fig .2a)
2. Hydroxycarbaminidoylphenylmethylcarbamylaztidinaminoazetate (Fig.2b)
3. Methyloxohydrobenzolisobenzfurancarbamat (Fig. 2c)
4. Cyclopropyloxoethylthienopyridinacetat (Fig. 2d) or
5. Cyclopropylaminotriazolopyrimidincyclopentan. (Fig 2e)

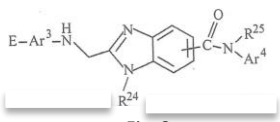
Fig. 3a

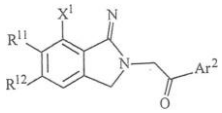
Fig. 3b

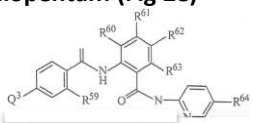
Fig. 3c

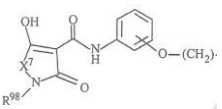
Fig. 3d

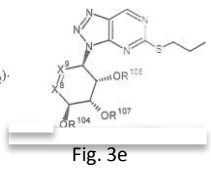
Fig. 3e

- They are based on small synthetic molecules that are readily ***orally available*** and can be synthesised at reasonable costs.
- They are of the ***non vitamin K inhibitor type of rodenticides***
- They are created through the repurposing of known oral anticoagulants used for therapeutic purposes in human medicine
- Due to extensive preclinical investigations for human therapeutic use, major preclinical data (pK, $t_{1/2}$ in rodents, LD50/LD90, MED, etc.) are already known.
- Their anticoagulant mechanism of action is basing on ***direct inhibition of specific coagulation factors, -inhibitors or essential receptor proteins.***
- There are ***no known or conceivable mechanism of resistance*** existing

Summary and Conclusions:

We describe five families of novel anticoagulant type rodenticides that exert their activity by direct molecular interactions with specific coagulation proteins (factors) and that are completely devoid of any existing and/or foreseeable resistance -mechanism. These novel anticoagulant-type of rodenticides may create the solution to the increasing worldwide problem of rodenticide resistance.

References: [1] Gulba, DC, Patent application DE 10 2014 108 210.9 (2014).