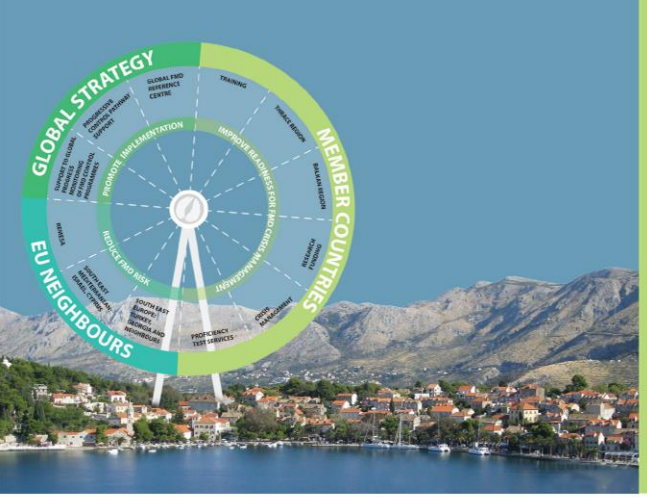

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european commission for the control of foot-and-mouth disease

A THIAZEPINO[4,5-*a*]BENZIMIDAZOLE DERIVATIVE INHIBITS THE IN VITRO REPLICATION OF EURASIAN SEROTYPES OF FOOT-AND-MOUTH DISEASE VIRUS

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CODA - CERVA

Emergency vaccination against FMD

- Council Directive 2003/85/EC

- Emergency FMD vaccines:
  - Induce protective, neutralizing antibodies 4 to 7 days post vaccination (“immunity gap”)
  - Serotype- and subtype-specific (7 FMDV serotypes, multiple subtypes)

Alternative strategies

- Interferons

(Dias et al, J Interferon Cytokine Res, 2011; Perez-Martin et al, J Virol, 2012)

- CpG oligonucleotides

(Kamstrup et al, Antiviral Res, 2006)

- Poly IC

(Dias et al, J Interferon Cytokine Res, 2012)

- RNA or DNA(-like) interference

(Chen et al, J Virol, 2006; Vagnozzi et al, J Virol, 2007; Kim et al, Antiviral Res, 2008)

- Small chemical molecules

(Furuta et al, Antiviral Res, 2009; Lefebvre et al, Transbound Emerg Dis, 2013; Rai et al, Antiviral Res, 2013; De Vleeschauwer et al, Transbound Emerg Dis, 2014)

- Combined therapy (Kim et al, Antiviral Res, 2012)

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SYNTHESIS AND STRUCTURAL FEATURES OF NEW CYCLOFUNCTIONALIZED BENZIMIDAZOLES

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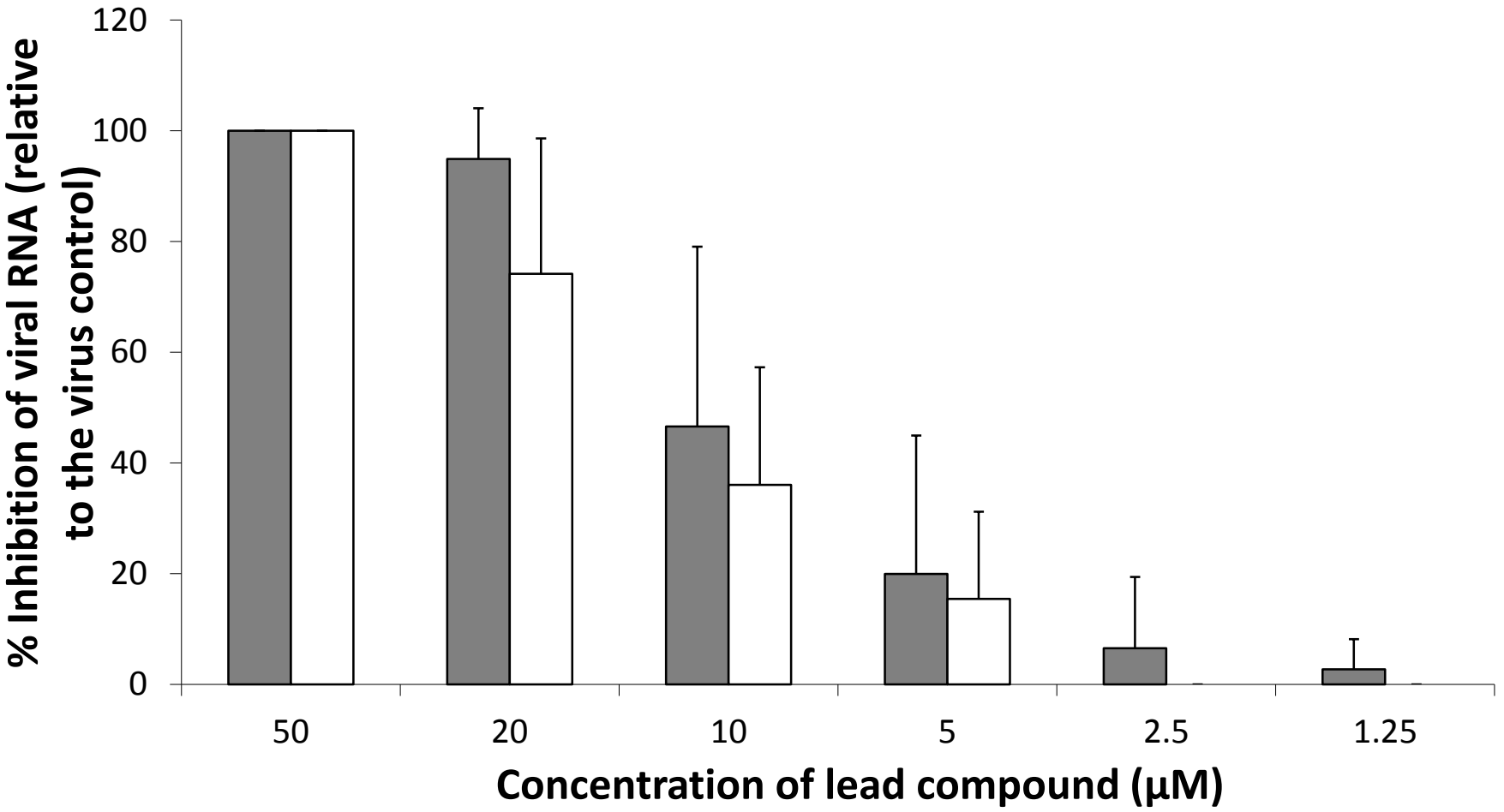
Abstract - The synthesis of new tricyclic derivatives having sulfur-containing six or seven-membered rings fused to the «a» edge of benzimidazole system, is reported. The stereochemical characteristics of thiazino- and thiazepinobenzimidazoles (**4-7**) are described and comparative NMR data are discussed. The synthetic approach to new benzo- or pyridothiazinobenzimidazole tetracyclic systems (**8**) is also reported.

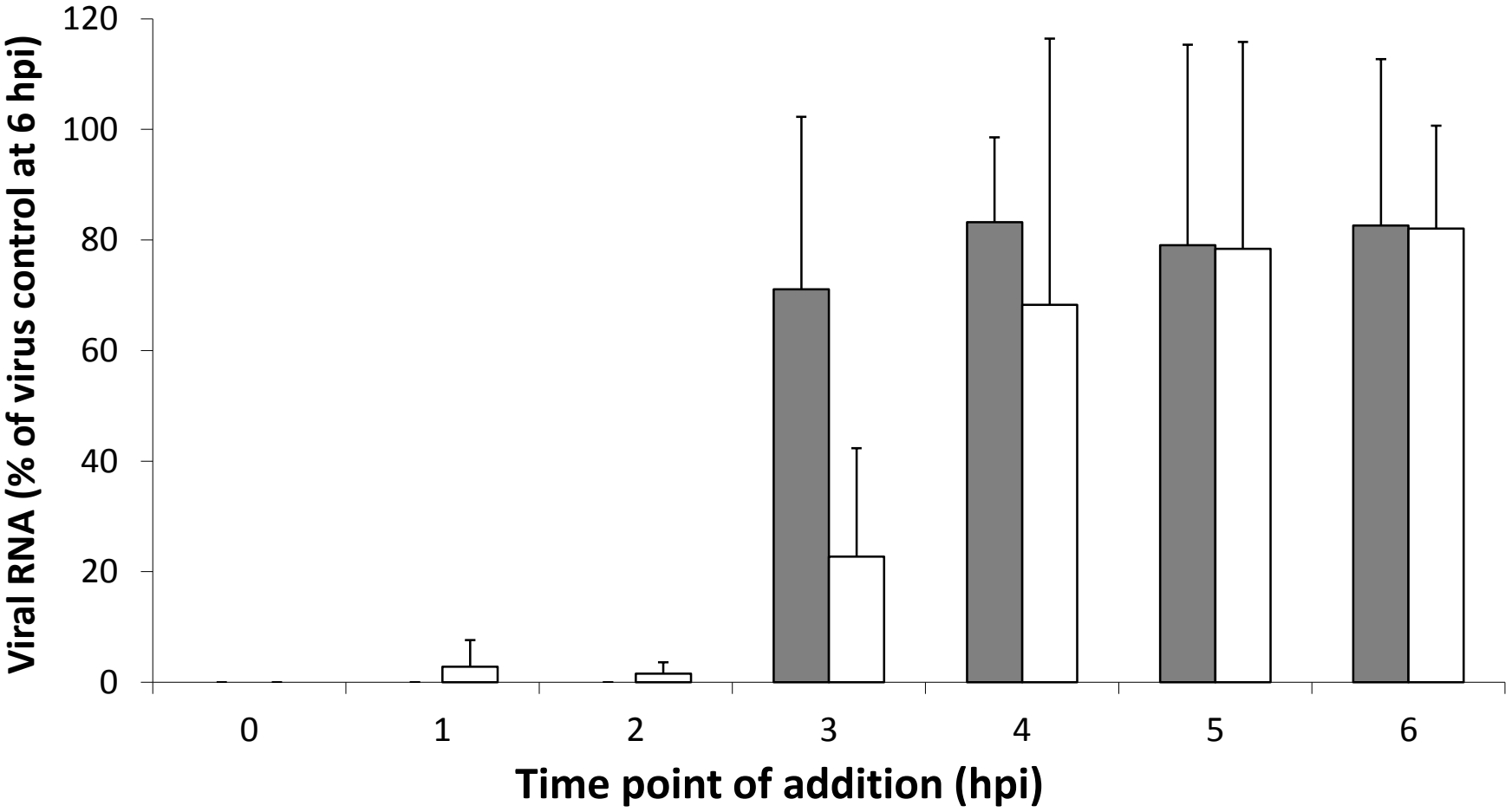
Reduction of CPE in SK-6 cells

Virus strain	EC_{50} (µM)	EC_{90} (µM)
FMDV O1/MAN/TUR/69	15.6 ± 8.6	44.2 ± 14.3
FMDV A22/IRQ/24/64	18.4 ± 8.2	41.1 ± 4.3
FMDV A/IRN/11/96	8.0 ± 1.5	28.5 ± 16.7
FMDV C1/Noville/SWI/65	39.7 ± 27.8	58.8 ± 32.9
FMDV Asia1/Shamir/ISR/89	51.4 ± 27.1	83.8 ± 39.6
FMDV Asia1/CAM/9/80	26.6 ± 5.8	51.2 ± 11.6
FMDV SAT1/ZIM/25/89	>100	>100
FMDV SAT2/ZIM/3/97	>100	>100
FMDV SAT3/ZIM/4/99	>100	>100
SVDV UKG/27/72	>100	>100

Dose-activity curve for FMDV RNA reduction



Effect of delayed addition on FMDV RNA levels



Conclusions

The present study further illustrates the potential of small molecule inhibitors to interfere with the replication cycle of FMDV

Further research and development are ongoing

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EN LEEFMILIEU

SEVENTH FRAMEWORK PROGRAMME

EPIZONE