68. Potent agelastatin derivatives as modulators

(MIT)

Asset Overview

Product Type	Small Molecule
Disease Area	Oncology
Indication	Cancer
Current Stage	Lead Optimization
Target	Cancer metastasis
MoA	AgA and AgE block metastasis by abrogating Tiam1-osteopontin
Brief Description	• This technology is a panel of agelastatin A (AgA) and agelastatin E (AgE) derivatives with anti-metastatic properties. AgA and AgE block metastasis by abrogating Tiam1-osteopontin induced epithelial to mesenchymal transition (EMT), which is a key step in the metastasis of many cancers. • These inventors demonstrated that AgA and AgE derivatives are highly effective in preventing breast cancer migration in in vivo assays at concentrations far below levels that are cytotoxic. In mouse breast cancer xenotransplantation studies AgA and AgE have no effect on primary tumor growth; however, strikingly, they block nearly all metastatic spread. • Importantly, osteopontin has a pro-metastatic role in many other cancer types, suggesting that AgA/E may be generalizable anti-metastasis drugs for other cancer indications. The pre-clinical data all indicate that AgA and AgE are promising anti-metastasis drug candidates
Intellectual Property	US20200062771A1
Publication	Synthesis and Evaluation of Agelastatin Derivatives as Potent Modulators for Cancer Invasion and Metastasis. J Org Chem. (2017)
Inventors	Mohammad Movassaghi, Alyssa H. Antropow, Rachel J. Buchsbaum, Kun Xu Xu

Highlights

- Anti-metastasis drug candidates
- Promising *in vitro* and *in vivo* pre-clinical data indicating effective metastasis inhibition
- No toxicity at effective doses *in vitro* or *in vivo*
- Potentially generalizable to other cancer types in addition to breast cancer

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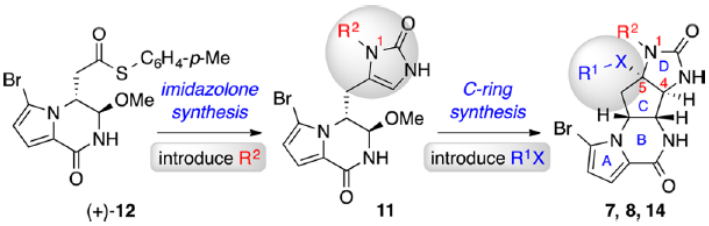
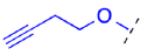
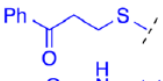
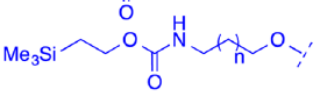
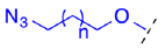
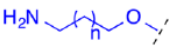
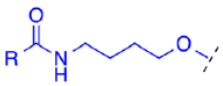
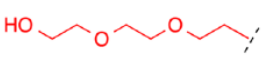
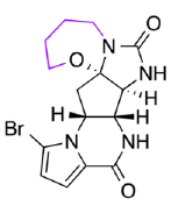
Key Data

N1- and C5-substituted Agelastatin derivatives prepared



entry	substituent	agelastatin derivative
agelastatin E derivatives	R^2 = Me	
	R^1X–	
1		**7a**
2		**7b**
3		**7c**
4 5		**7i**, n = 1 **7d**, n = 2
6 7		**7e**, n = 1 **7f**, n = 2
8 9		**7g**, n = 1 **7h**, n = 2
10 11		**7j**, R = Me **7k**, R = Ph
agelastatin A derivatives	R^1X = OH	
	R^2–	
12 13		**8a**, n = 1 **8b**, n = 3
14		**8c**
15		**8d**
16		**8e**, $R^1X = N_3$
agelastatin derivative		
17		**14**

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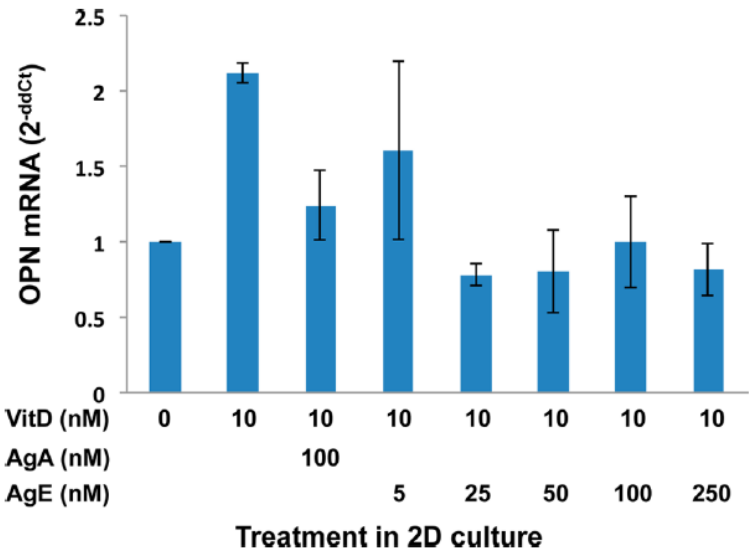
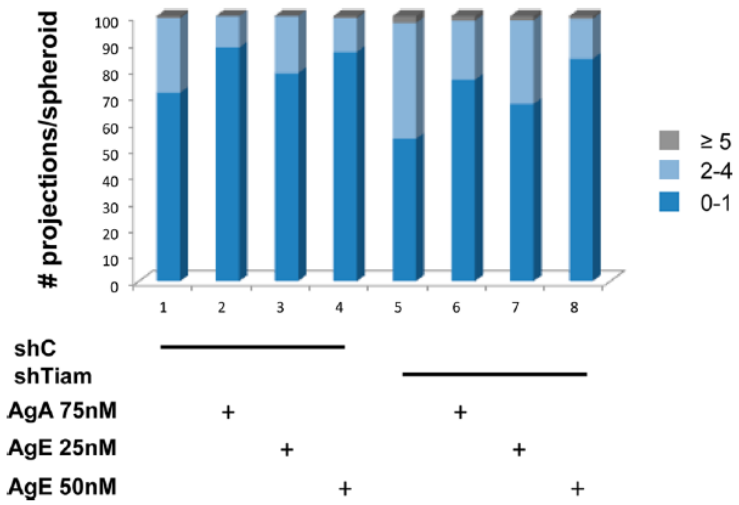
AgE blocks stimulated transcription of osteopontin in fibroblasts



VitD = vitamin D

Effect of AgA (1) and AgE (5) on breast cancer cell invasion in cocultures with mammary fibroblasts



Number of projections per spheroid for SUM1315 breast cancer cells and indicated mammary fibroblasts in 3D mixed cell spheroid coculture is shown as percent of total spheroids. shC = control silencing retroviral hairpin vector. shTiam = Tiam1 silencing hairpin vector.

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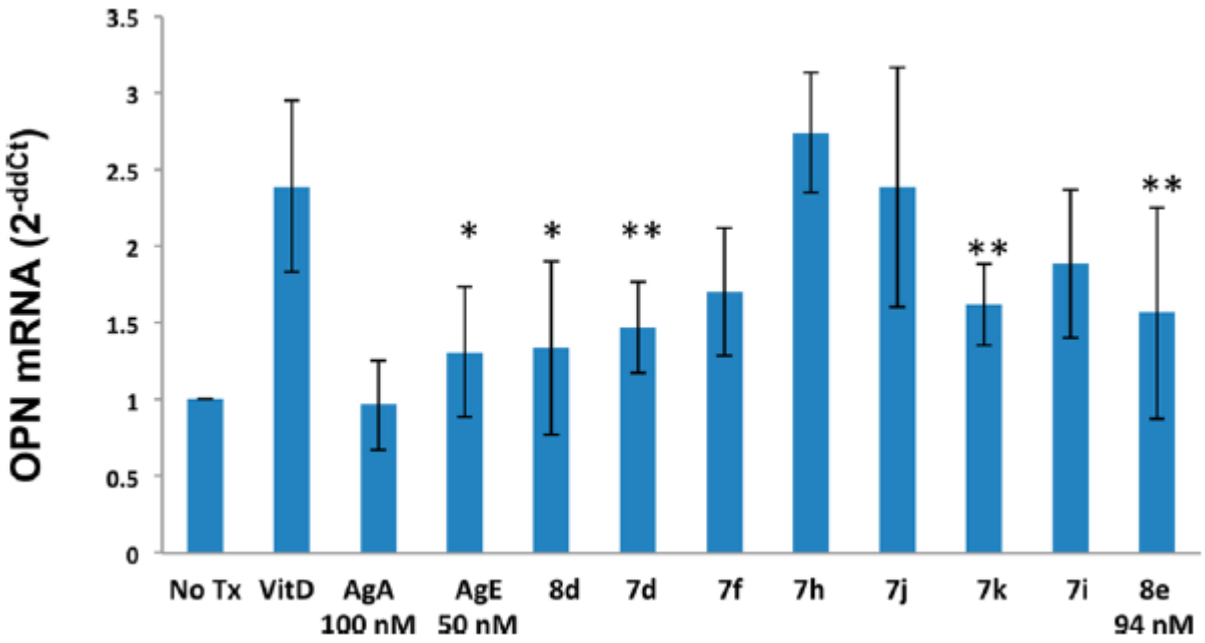
Key Data

Varying effects of agelastatin derivatives in blocking stimulated fibroblast expression of osteopontin



All agelastatin derivatives were tested at 100 nM concentration unless noted otherwise. *Statistical equivalence with AgA (1) at 100 nM concentration; **Equivalence with AgE (5) at 50 nM concentration, but not AgA (1) at 100 nM concentration by t test. No Tx = baseline control with values normalized to transcription of a housekeeping gene.