Anti-cancer activity of novel selective glucocorticoid receptor agonist 13S-G2 *in vitro* on the model of blood cancer

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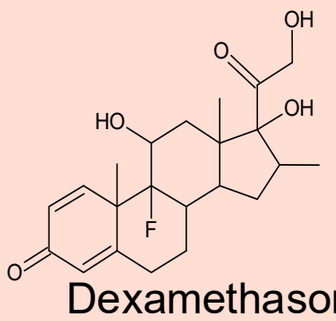
1. INTRODUCTION

The therapeutic effects of glucocorticoids (GCs) are realized via glucocorticoid receptor (GR) activation by DNA-independent transrepression (TR), while their side effects are associated with transactivation (TA). Side effects could be reduced by developing selective glucocorticoid receptor agonists (SEGRAs), acting via TR activation. In this work we studied biological activity of potential SEGRA, **2-(hexylamino)-1-(4-nitrophenyl)ethanol (13S-G2)**, in leukemia and lymphoma cells *in vitro.*

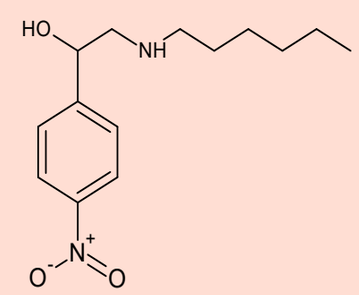
2. METHODOLOGY

Cell viability of chronic myeloid leukemia (CML) K562 and B-cell lymphoma Granta-519 cells was measured using **MTT assay**. TA and TR induction were studied by **quantitative PCR (qPCR)** of marker TR and TA genes. Additionally, TR was assessed by NF-κB activity using a **luciferase reporter assay**. The affinity of 13S-G2 was studied *in silico* by **molecular docking** (Molegro Virtual Docker), and *in vitro* via a **competitive radioligand binding assay**.

COMPOUNDS



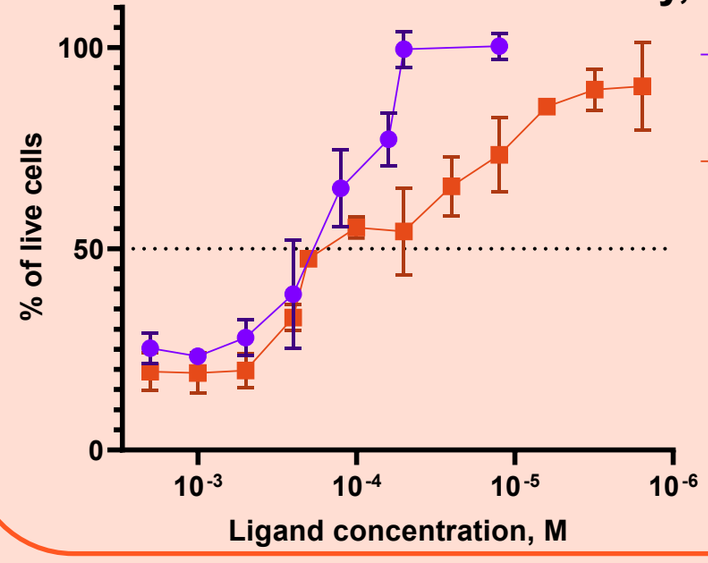
Dexamethasone (Dex)



13S-G2

3. RESULTS

Cell Viability, 24 h

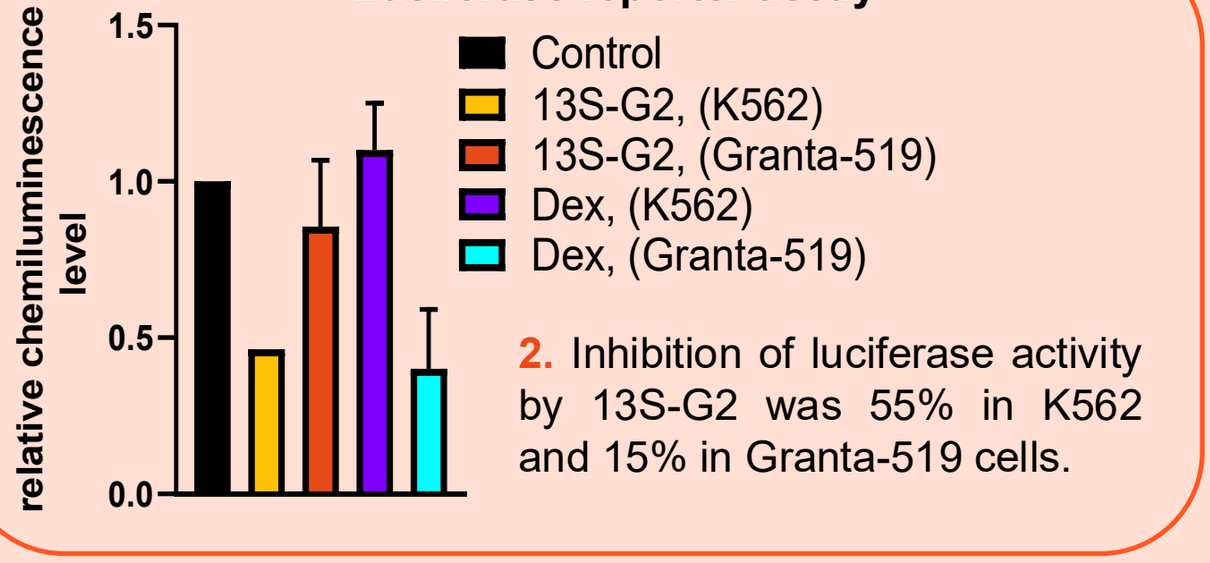


IC_{50}= 184±95 μM K562

IC_{50}= 26.8±1.2 μM Granta-519

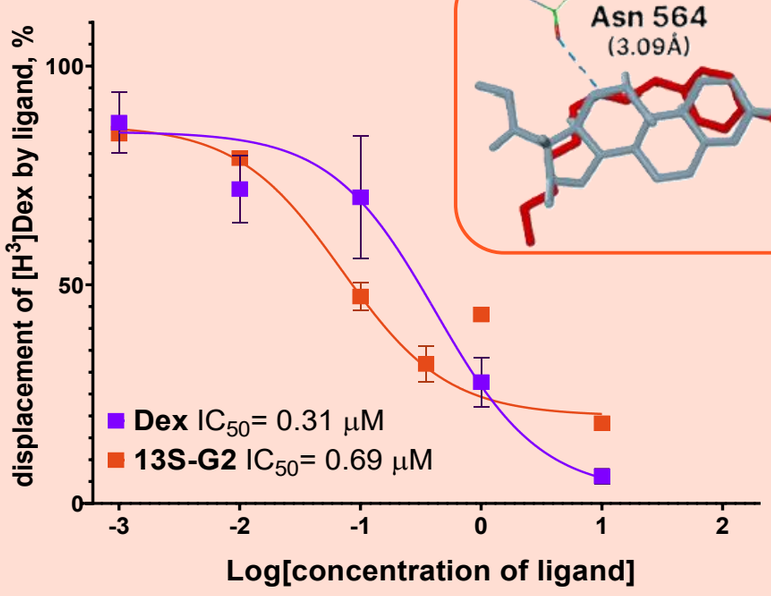
1. Granta-519 cells were more sensitive to treatment with 13S-G2 than K562 cells.

Luciferase reporter assay



2. Inhibition of luciferase activity by 13S-G2 was 55% in K562 and 15% in Granta-519 cells.

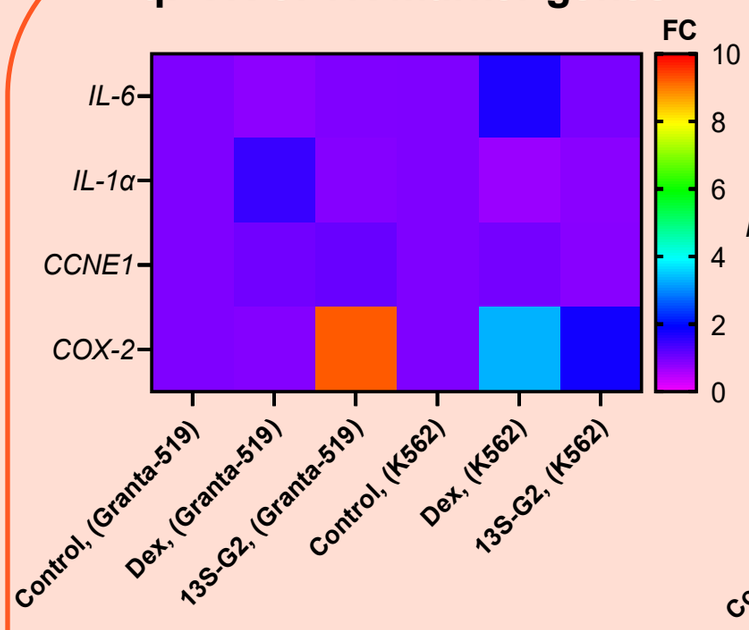
Radioligand binding assay, K562 cells



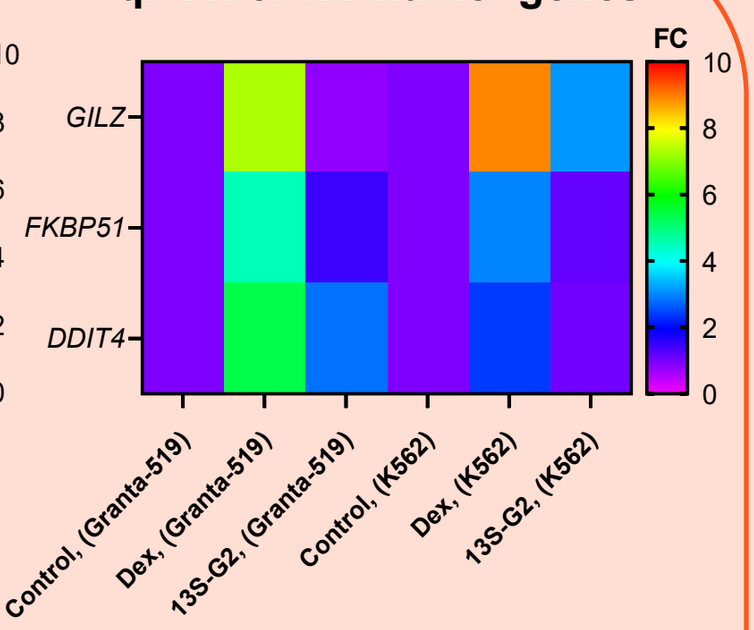
3. The 13S-G2 is a concurrent ligand of GR.

4. 13S-G2 occupied a sterically advantageous location at the GR binding site formed by Arg611, Asn564, and Gln642.

qPCR of TR marker genes



qPCR of TA marker genes



5. Compound 13S-G2 suppressed the expression of TR marker genes (*COX2, IL-1α, IL-6, CCNE1*), in most cases by 1.5-2.0-fold. The absence of TA induction was proved for 13S-G2 also by qPCR analysis of (*GILZ, FKBP51, DDIT4*) genes.

4.CONCLUSION

The novel compound **13S-G2** demonstrates promising SEGRA effect: TR-driven anti-cancer activity in hematological malignancies with the absence of TA induction and low potential for side effect development.

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