Effect of inhibiting aldosterone production on human adrenocortical cells

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COI Disclosure: No financial relationships to disclose.

Background

ORIGINAL ARTICLE

The NEW ENGLAND JOURNAL of MEDICINE

Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension

Authors: Mason W. Freeman, M.D., Yuan-Di Halvorsen, Ph.D., William Marshall, M.D., Mackenzie Pater, Ph.D., Jon Isaacsohn, M.D., Catherine Pearce, D.H.Sc., Brian Murphy, M.D., M.P.H., Nicholas Alp, M.D., Ajay Srivastava, M.D., Deepak L. Bhatt, M.D., M.P.H., and Morris J. Brown, M.D., for the BrigHTN Investigators* Author Info & Affiliations

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Naunyn-Schmiedeberg's Archives of Pharmacology
https://doi.org/10.1007/s00210-025-03838-0

RESEARCH

Check for updates

Phase 1 studies of the safety, tolerability, pharmacokinetics, and pharmacodynamics of BI 690517 (vicadrostat), a novel aldosterone synthase inhibitor, in healthy male volunteers

Friedrich Schulze[1] · Jennifer Schaible[2] · Markus Goettel[1] · Yuko Tanaka[3] · Kathrin Hohl[2] · Armin Schultz[4] · In-Jin Jang[5]

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ORIGINAL ARTICLE

The NEW ENGLAND JOURNAL of MEDICINE

Lorundrostat Efficacy and Safety in Patients with Uncontrolled Hypertension

Authors: Luke J. Laffin, M.D., Branko Kopjar, M.D., Carrie Melgaard, M.S., Kathy Wolski, M.P.H., Jessica Ibbitson, M.S., Shivani Bhikam, Matthew R. Weir, M.D., Elizabeth O. Ofili, M.D., Reena Mehra, M.D., James M. Luther, M.D., Debbie L. Cohen, M.D., Ashish Sarraju, M.D., Michael J. Wilkinson, M.D., John M. Flack, M.D., David Rodman, M.D., and Steven E. Nissen, M.D., for the Advance-HTN Investigators* -9 Author Info & Affiliations

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eClinicalMedicine
Part of THE LANCET *Discovery Science*

Safety and efficacy of once-daily dexfadrostat phosphate in patients with primary aldosteronism: a randomised, parallel group, multicentre, phase 2 trial

Paolo Mulatero[a] · Gregoire Wuerzner[b] · Michael Groessl[c] · Elisa Sconfienza[a] · Aikaterini Damianaki[b] · Vittorio Forestiero[a] · Bruno Vogt[c] · Hans Brunner[d] · Teresa Gerlock[e] · Ronald Steele[e] · Christoph Schumacher[e] Show less

Affiliations & Notes · Article Info

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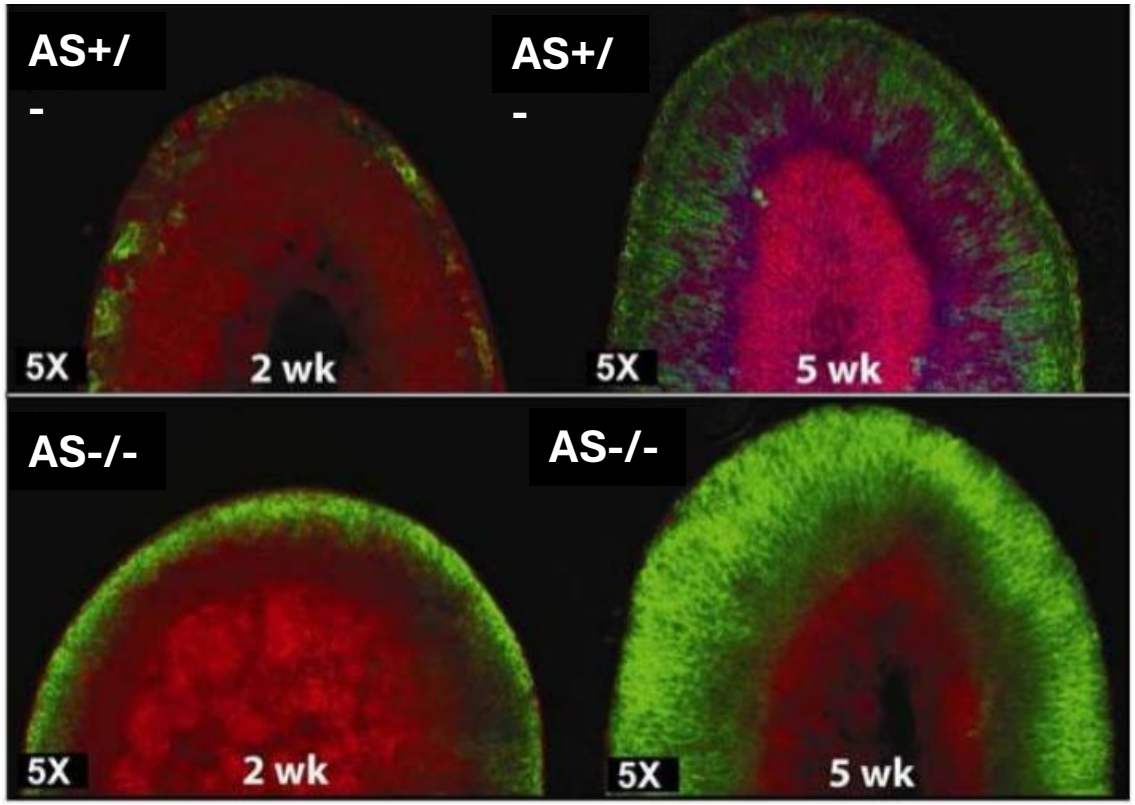
DOI: 10.1016/j.eclinm.2024.102576 Also available on ScienceDirect

AS knockout mice models

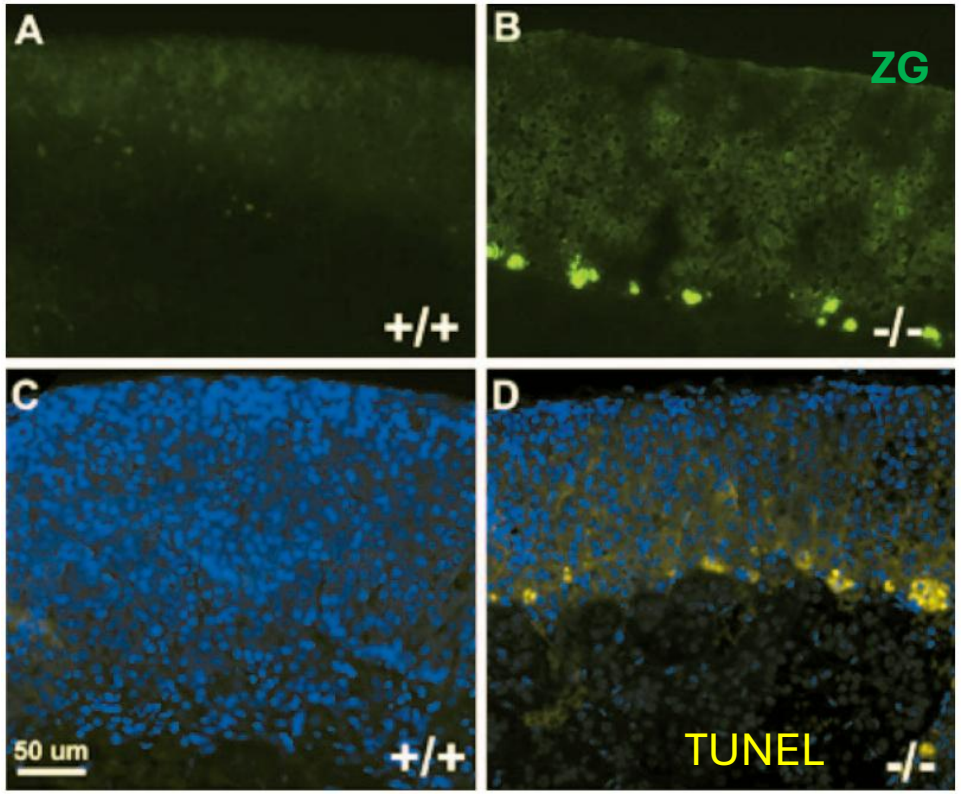
Adrenals from mice with heterozygous (AS+/−) and homozygous (AS−/−) knockout of aldosterone synthase (CYP11B2)



CYP11B2 deletion induces centripetal migration of outer zona glomerulosa (ZG; green) cells towards the inner layer of the adrenal cortex.

Freedman, B. D. et al. Adrenocortical zonation results from lineage conversion of differentiated zona glomerulosa cells. Dev. Cell 26, 666–673 (2013).

Adrenals of wild-type (+/+) and CYP11B2-null (-/-) mice at 3-6 months

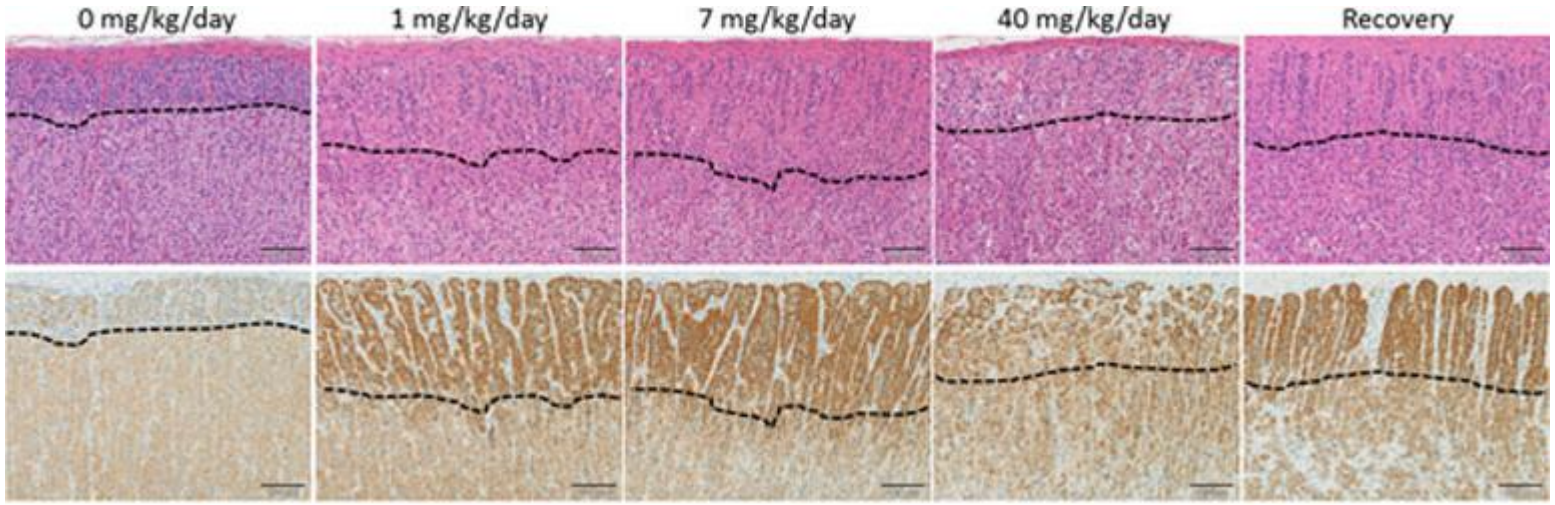


In AS−/− mice migrated ZG cells (green) expresses markers for apoptosis (yellow).

Lee, G. et al. Homeostatic responses in the adrenal cortex to the absence of aldosterone in mice. Endocrinology 146, 2650–2656 (2005).

AS inhibition in monkeys

4-week toxicology studies ASI in cynomolgus monkey. H&E, immunohistochemistry of CYP11B2 expression, apoptosis (TUNEL), and cell proliferation (Ki-67) of the adrenals.



Dose (mg/kg/day)	0	1	7	40	Recovery
CYP11B2	1	3	3	2	2
Transitional zone	P	A	A	A	A
Apoptosis	0	1	1	1	1
Proliferation	1	2	2	2	2

Both apoptosis and proliferation of ZG cells were increased suggesting increased cell cycle turnover. There was also an ASI-related expansion of the ZG, hypertrophy, and increased AS (CYP11B2) expression of ZG cells.

Bogman, K. et al. Preclinical and early clinical profile of a highly selective and potent oral inhibitor of aldosterone synthase (CYP11B2). Hypertension 69, 189–196 (2017).

Aims

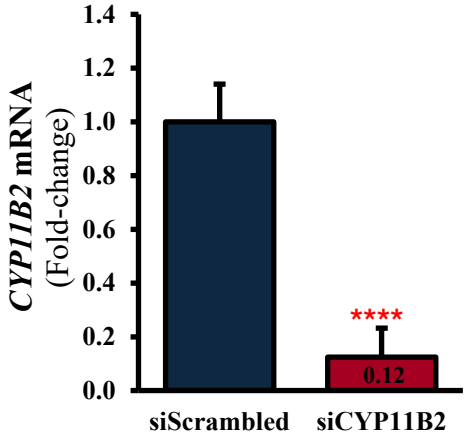
To examine the impact of CYP11B2 inhibition on human adrenal cell function

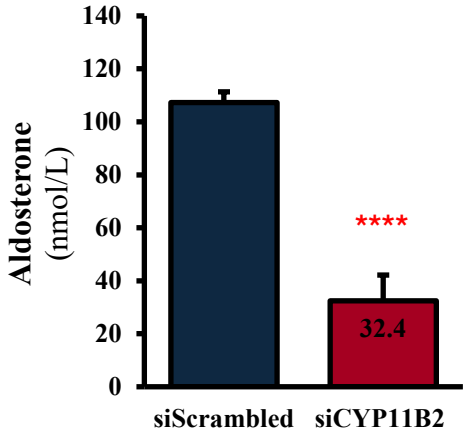
Methods

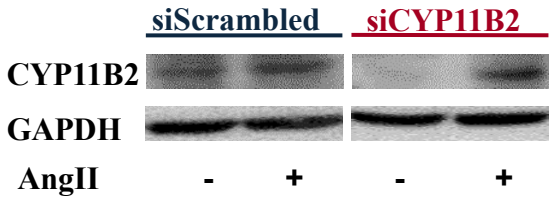
CYP11B2 was inhibited in HAC15 cells using siRNA (siCYP11B2) or Baxdrostat, a selective CYP11B2 inhibitor.

48 hours post-transfection/post-treatment, transcriptome analysis, hormone levels, Annexin V/SYTOX Apoptosis Assays, EZMTT and xCELLigence proliferation assay, and functional assays were performed.

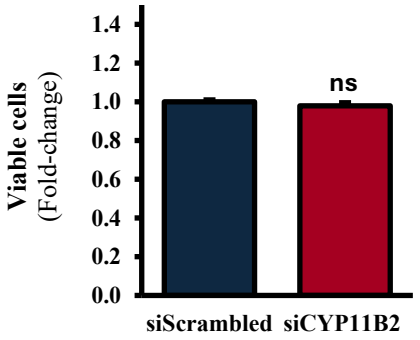
Results

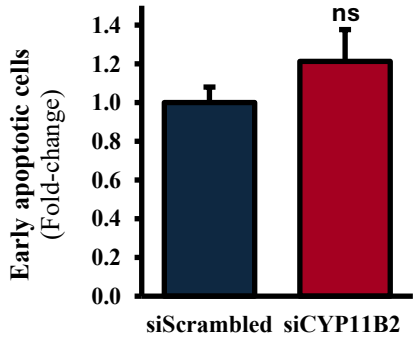


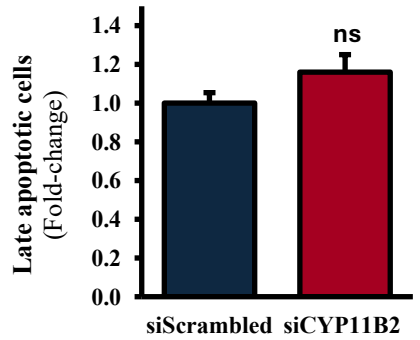




Annexin V/SYTOX Assay

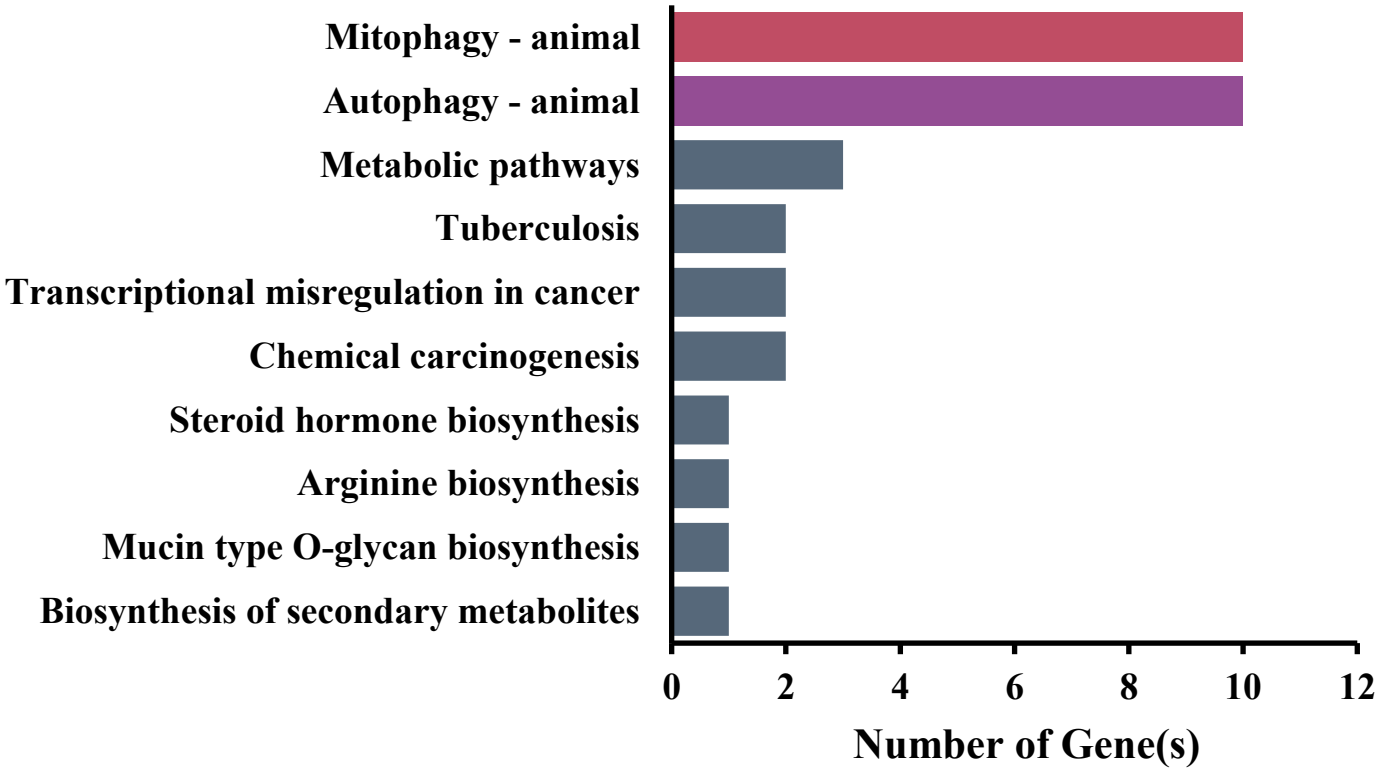




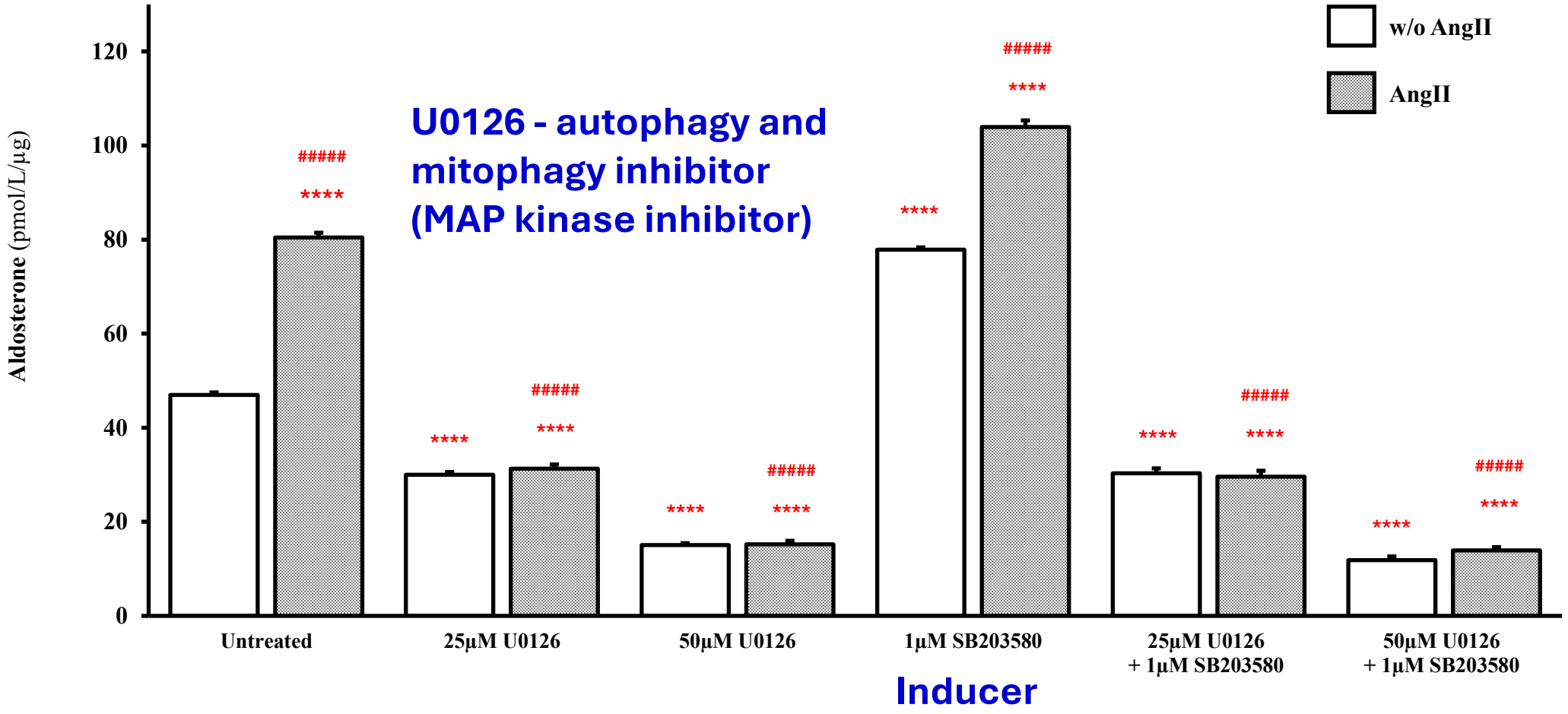


n=12

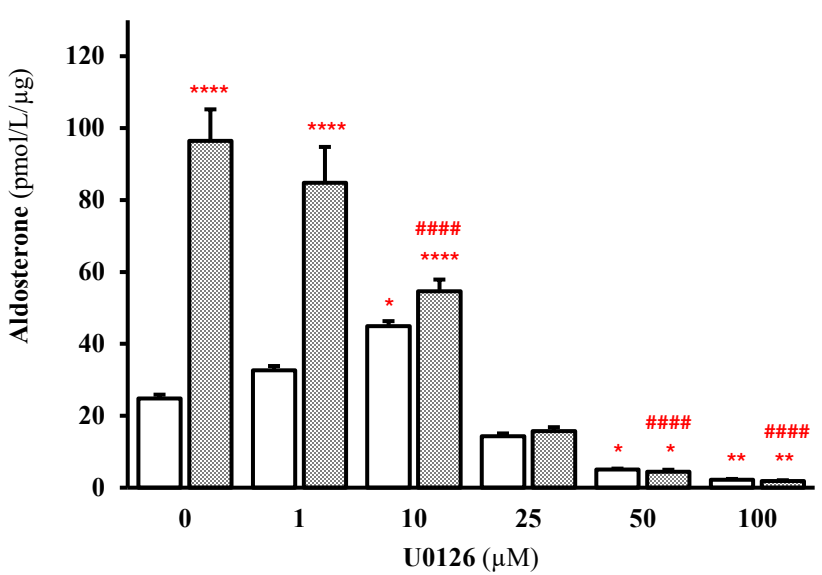
KEGG Pathways enriched in DEG

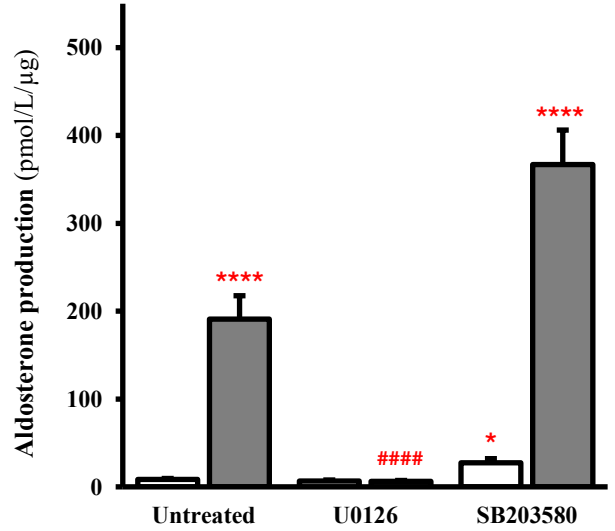


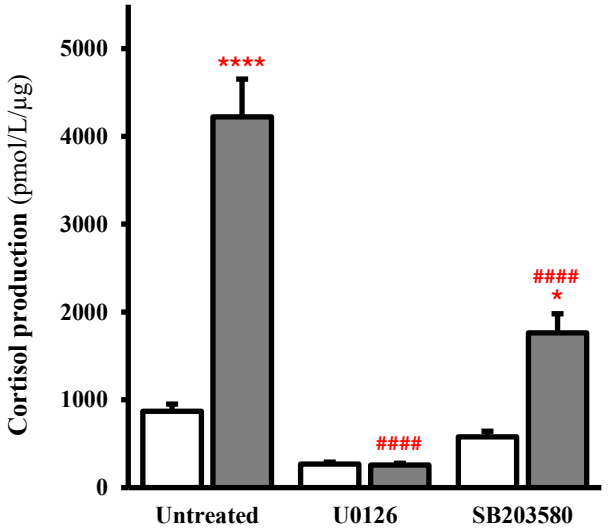
Results


w/o AngII
AngII
U0126 - autophagy and mitophagy inhibitor (MAP kinase inhibitor)
Aldosterone (pmol/L/µg)
120
100
80
60
40
20
0
#####
****
Untreated
25µM U0126
50µM U0126
1µM SB203580
25µM U0126 + 1µM SB203580
50µM U0126 + 1µM SB203580
Inducer

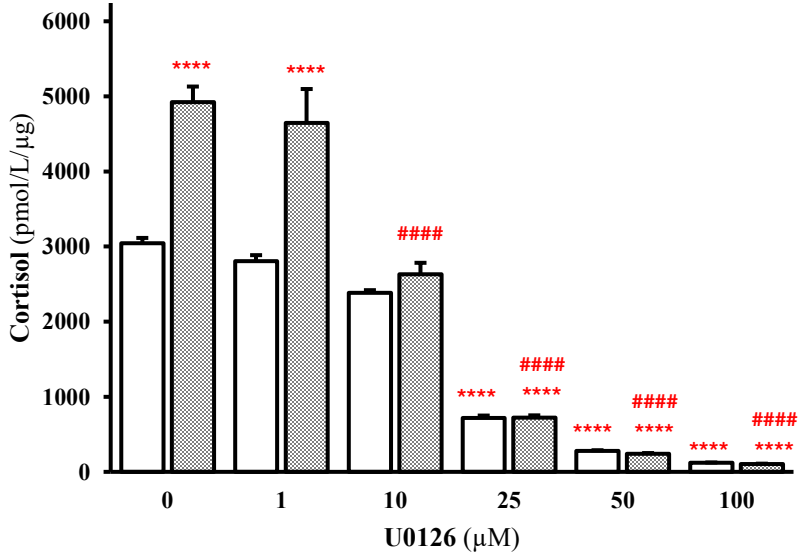
Results

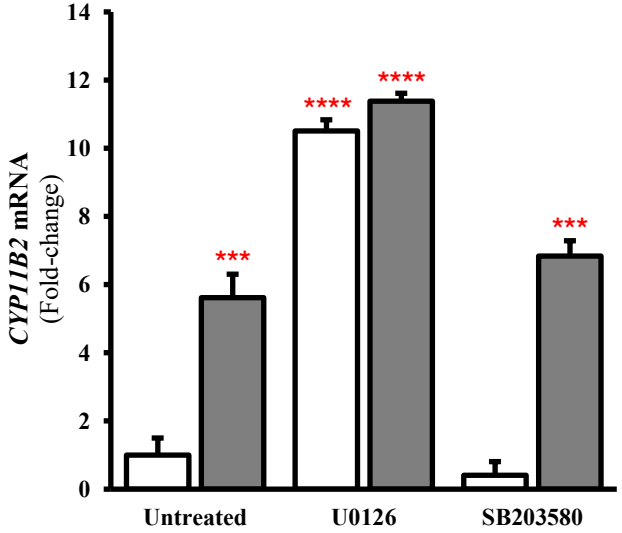

Aldosterone (pmol/L/µg)
U0126 (µM)
0
1
10
25
50
100

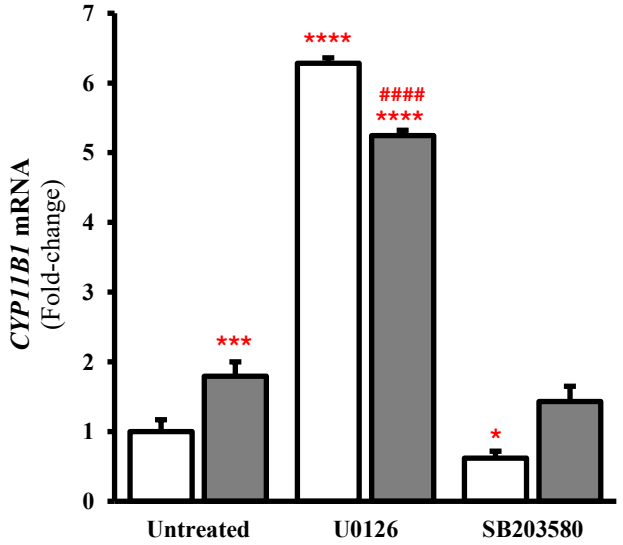

Aldosterone production (pmol/L/µg)
Untreated
U0126
SB203580


Cortisol production (pmol/L/µg)
Untreated
U0126
SB203580

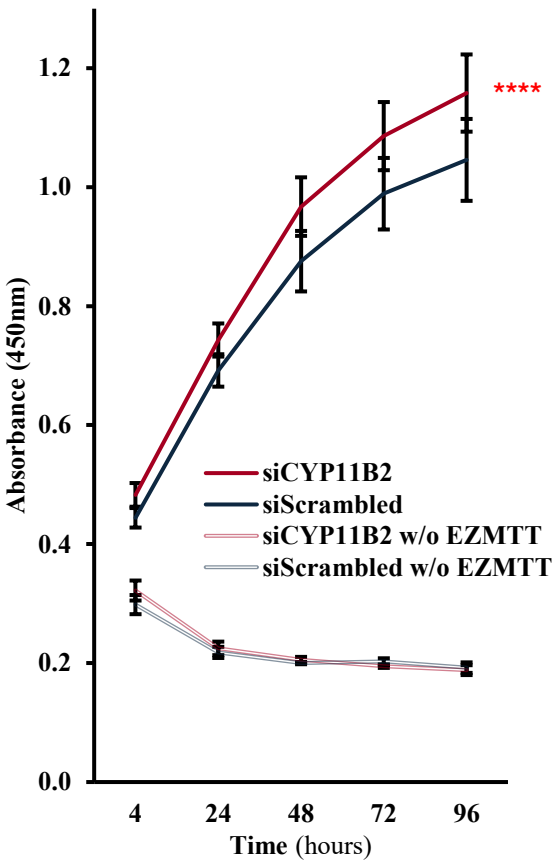

w/o AngII
AngII

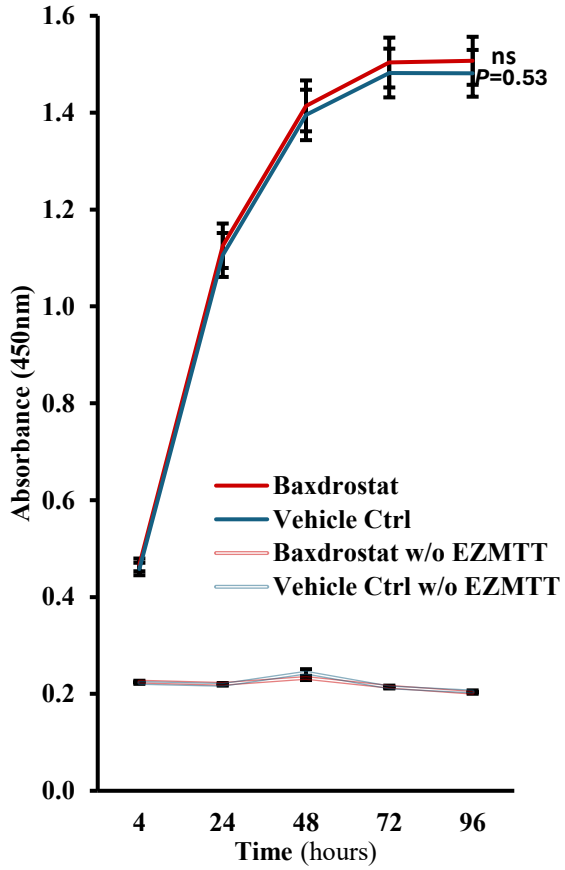

Cortisol (pmol/L/µg)
U0126 (µM)
0
1
10
25
50
100

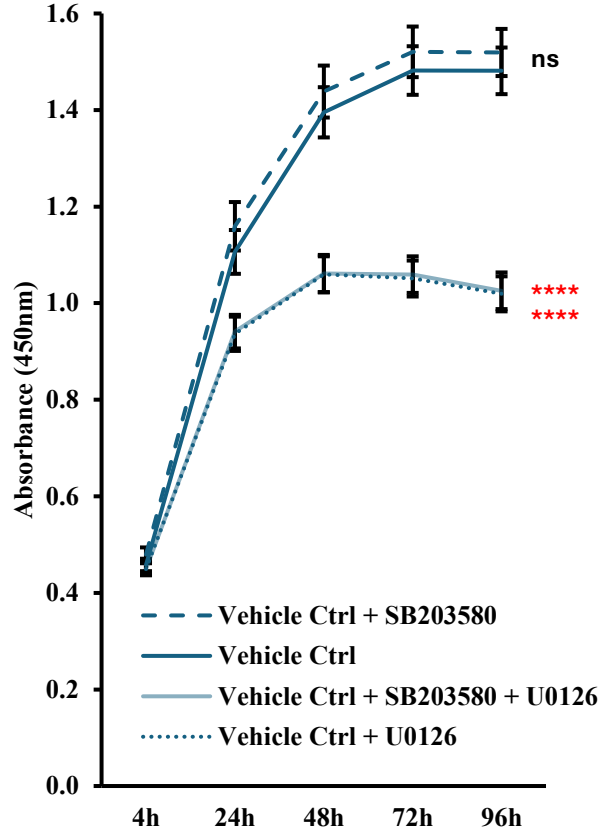

CYP11B2 mRNA
(Fold-change)
Untreated
U0126
SB203580


CYP11B1 mRNA
(Fold-change)
Untreated
U0126
SB203580

EZMTT Cell Proliferation Assay



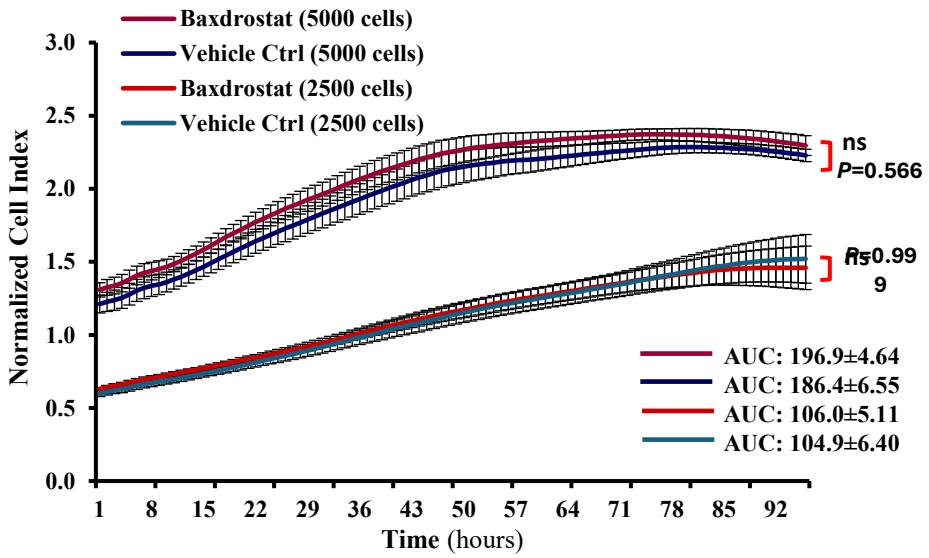


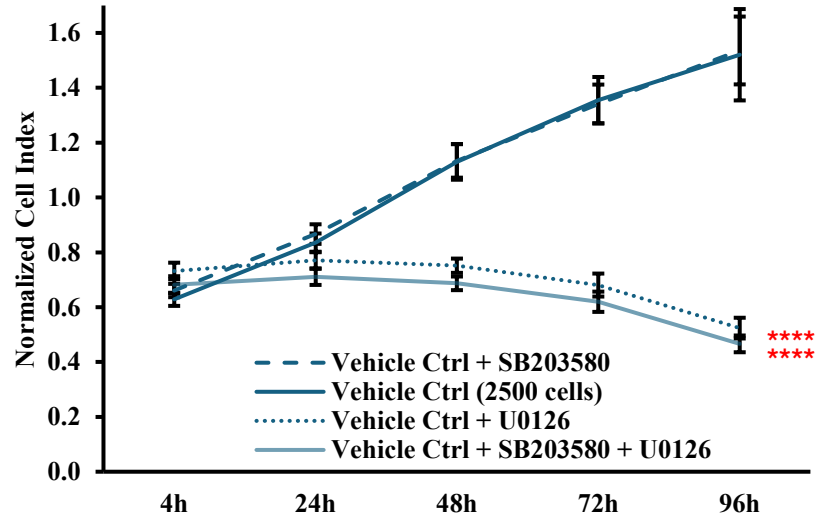


The EZMTT assay showed a 0.141±0.02 increased in absorbance in siCYP11B2 cells (96 hours), but not in Baxdrostat-treated cells.

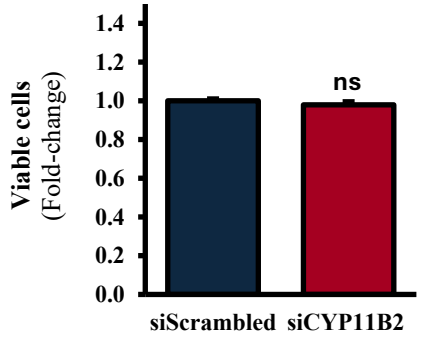
A substantial decrease (~30%) of absorbance was seen with U0126 treatment .

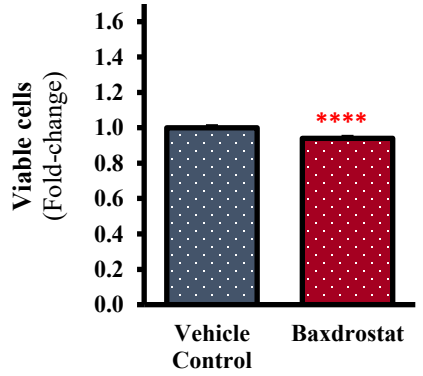
xCELLigence proliferation and apoptosis assay

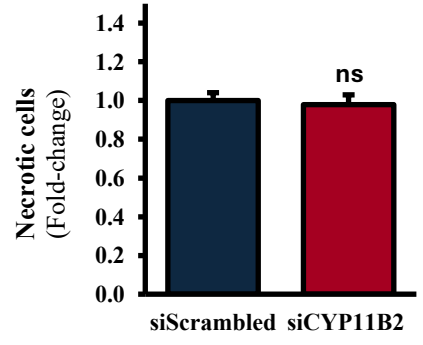


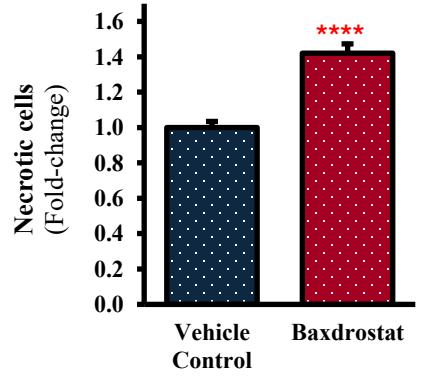


Annexin V/SYTOX Assay









Baxdrostat increased necrosis by 40%

Summary

- Mitophagy and autophagy was the most enriched pathways in the DEG of siCYP11B2 cell transcriptomes.
- U0126 (autophagy inhibitor) reduced aldosterone in a dose-responsive manner.
- SB203580 (autophagy inducer) increases basal and stimulated (Ang II) aldosterone production.
- The EZMTT assay showed an increased in absorbance in siCYP11B2 cells but not in Baxdrostat-treated cells.
- U0126 decreased absorbance of EZMTT by 41.2% (Reproduced in the xCELLigence assay).
- No consistent apoptosis changes were observed with siCYP11B2, though Baxdrostat treatment did significantly increased necrotic cells.

Conclusion

Aldosterone production capability modulates adrenal cell fate potentially through autophagy and/or mitophagy, with pharmacological inhibition of CYP11B2 potentially leading to the cells expressing CYP11B2 (ZG) cell death.

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