September 2025

RACE ONCOLOGY

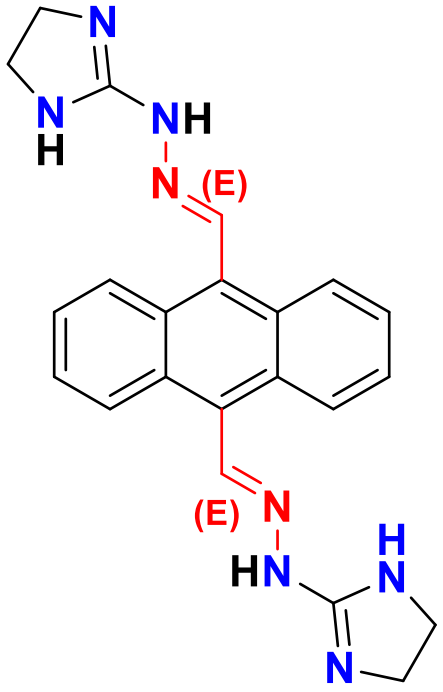
AT THE HEART OF CANCER CARE

Dr Daniel Tillett – CEO
Prof Michael Kelso – VP of Research
Dr Pete Smith – Exec Chair

Isomer IP Webinar

Overview

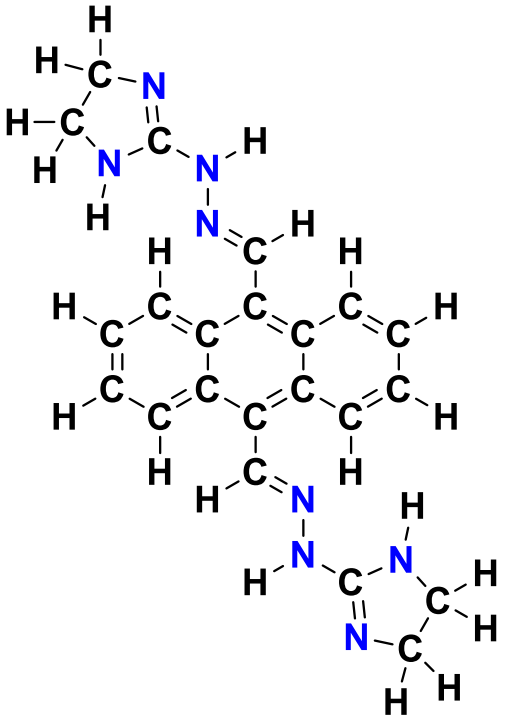
- Bisantrene found to consist of three photoisomers with different biological and anticancer activities, which rapidly interconvert upon exposure to visible light.
- Race has created a range of manufacturing and physical processes to only infuse the pure active (E,E)-bisantrene isomer into patients.
- Three patent applications filed.
- Granting of a composition of matter patent would protect (E,E)-bisantrene for 20 years.
- **Composition of matter patents the most valuable IP in the pharma industry as they cover the chemical structure of the active drug in any formulation or dosage form.**



(E,E)-Bisantrene

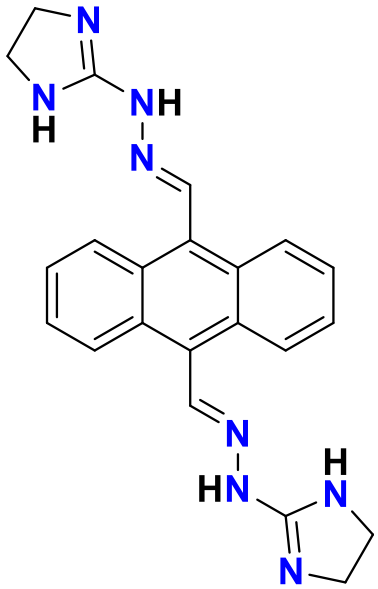
Chemistry & Discovery

Bisantrene – Chemical Structure



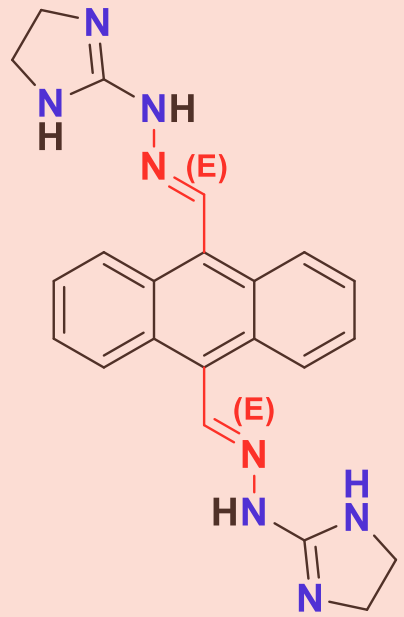
Bisantrene Chemical Structure

All atoms and bonds showing

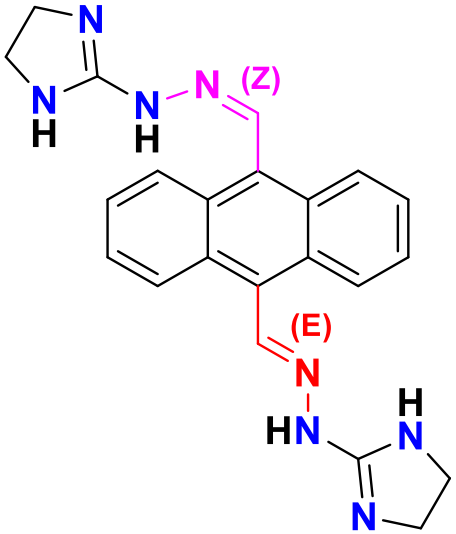


Chemist's Representation

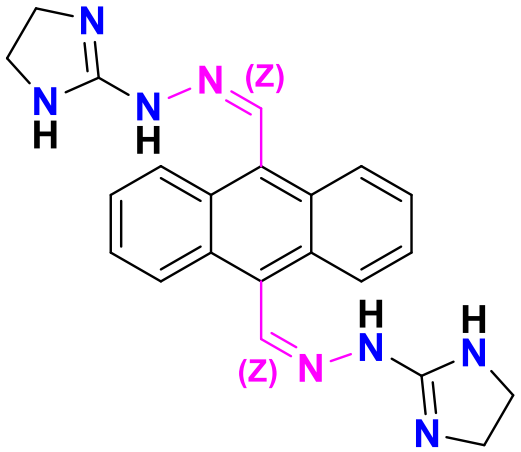
Bisantrene – Possible Isomers



(E,E)-Bisantrene



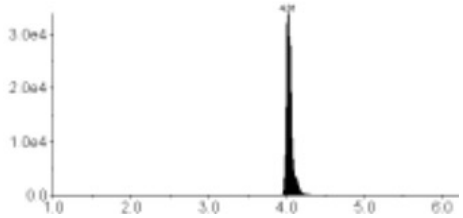
(E,Z)-Bisantrene



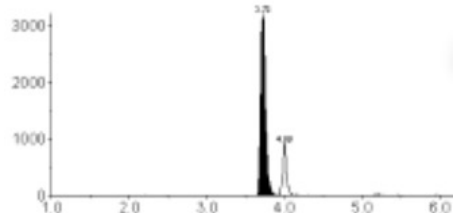
(Z,Z)-Bisantrene

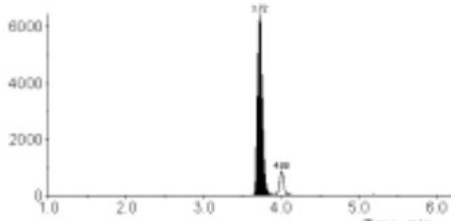
Bisantrene Isomerism – First observations

- Results from a toxicology study in animals
  - Measured bisantrene in the blood by liquid chromatography/mass spectrometry (LCMS)



Bisantrene = 1 peak
(expected)



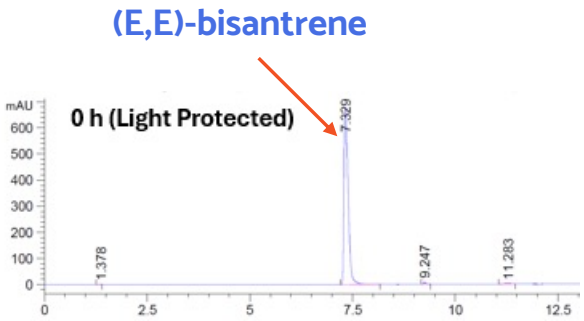


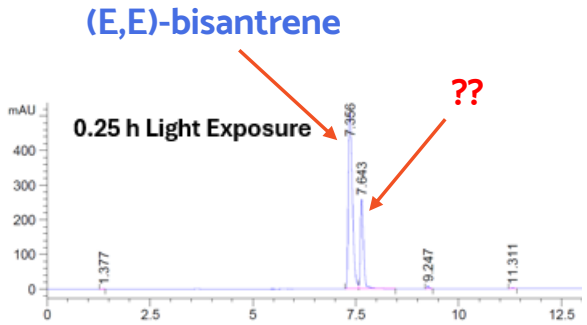
Variable appearance of a second peak with
same molecular weight as bisantrene (isomer?)

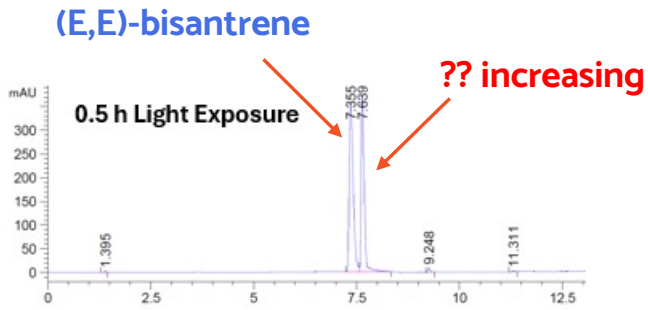
Hypothesis: Metabolism? No.
What about variable exposure to light?

Detective Work (Race Team)

- Dissolve pure (E,E)-bisantrene in water, expose it to light and monitor by HPLC





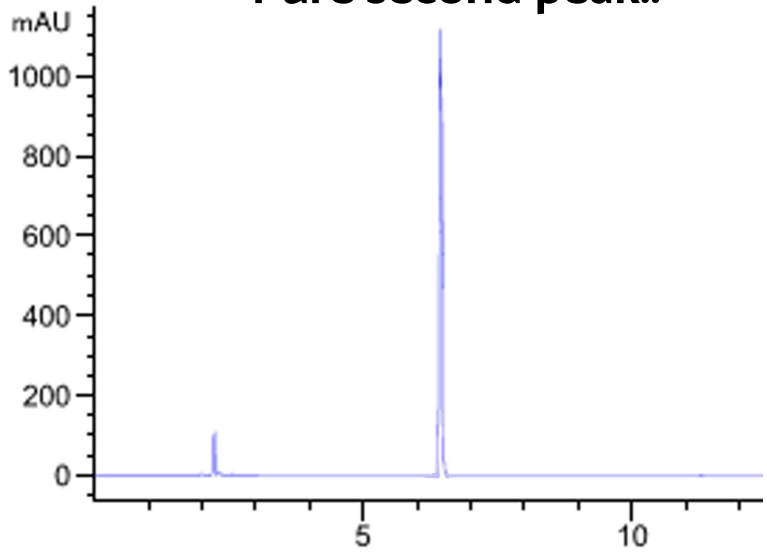


- **Observation:** Visible ambient light triggers rapid formation of the ?? second peak.

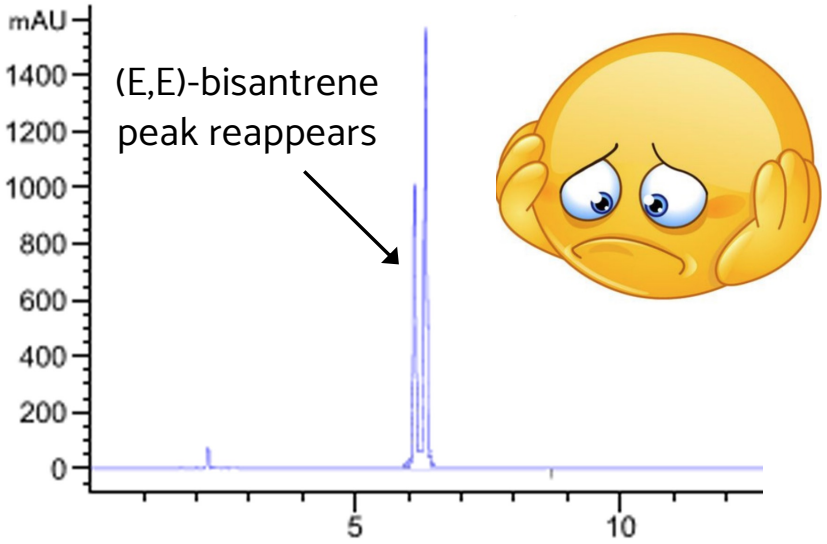
Detective Work – What is the Second Peak?

- To identify the second peak need to isolate a pure sample

Pure second peak!!

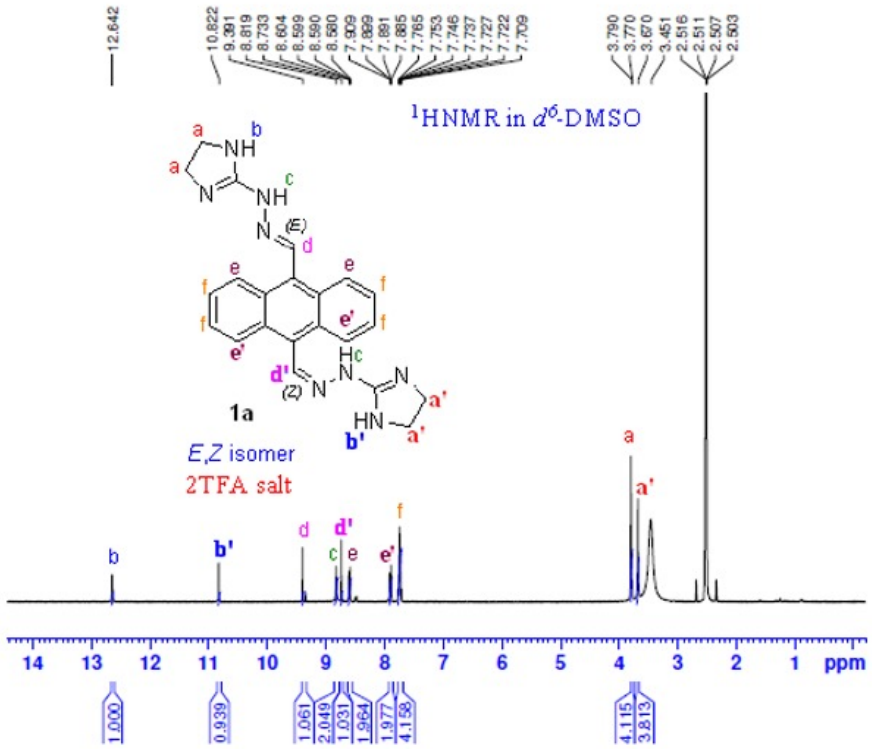


RAPID

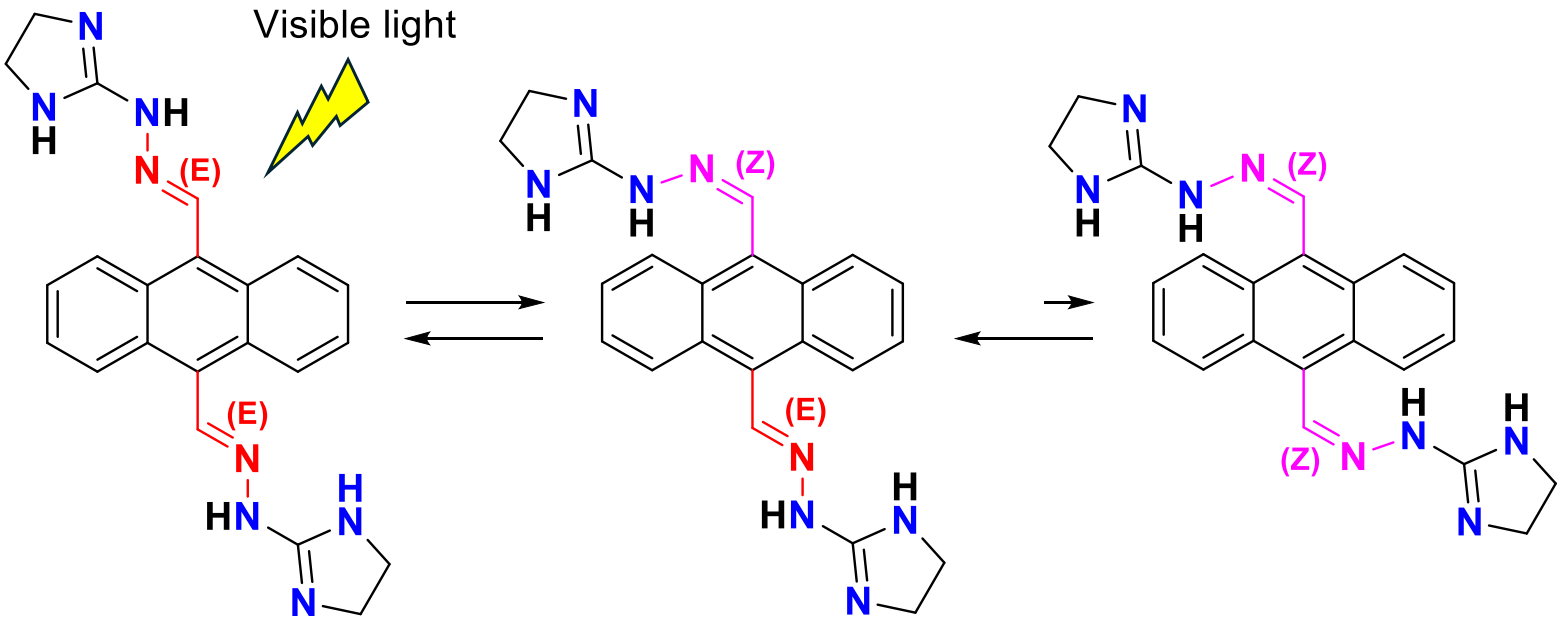


Detective Work – Voila! It's (E,Z)-bisantrene

^{1}H Nuclear Magnetic Resonance (NMR) analysis unambiguously proved the second peak is (E,Z)-bisantrene



Bisantrene – Photoisomerism



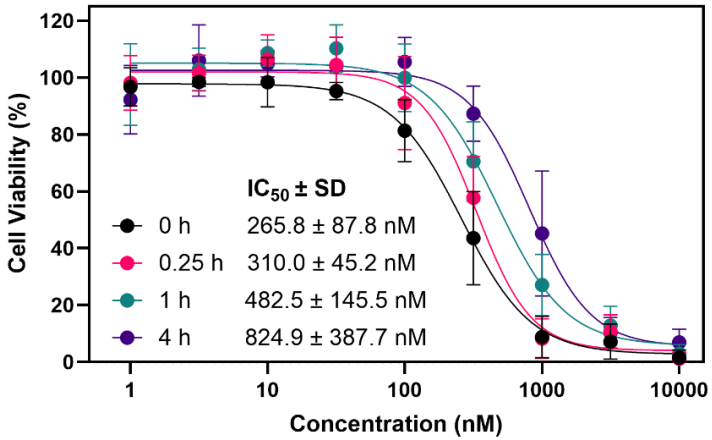
(E,E)-Bisantrene (E,Z)-Bisantrene (Z,Z)-Bisantrene

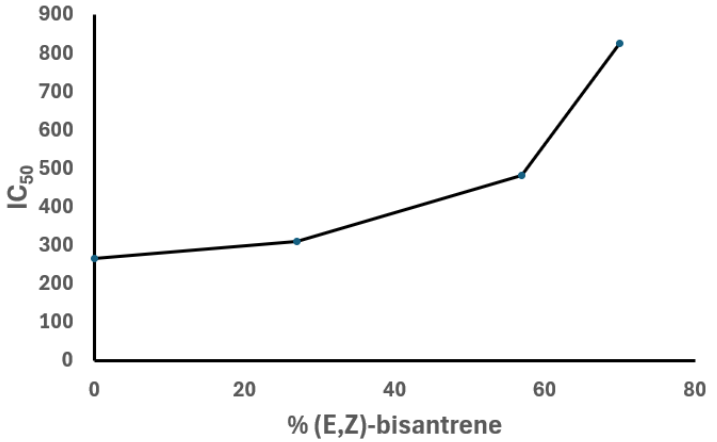
(E,Z)-Bisantrene has low anticancer activity

- Expose pure (E,E)-bisantrene solution to light for different amounts of time to make different isomer mixtures
- Test the different isomer mixtures for ability to kill MDA-MB-231 breast cancer cells

0 h	100% (E,E), 0% (E,Z)
0.25 h	73% (E,E), 27% (E,Z)
1 h	43% (E,E), 57% (E,Z)
4 h	~30% (E,E), ~70% (E,Z)

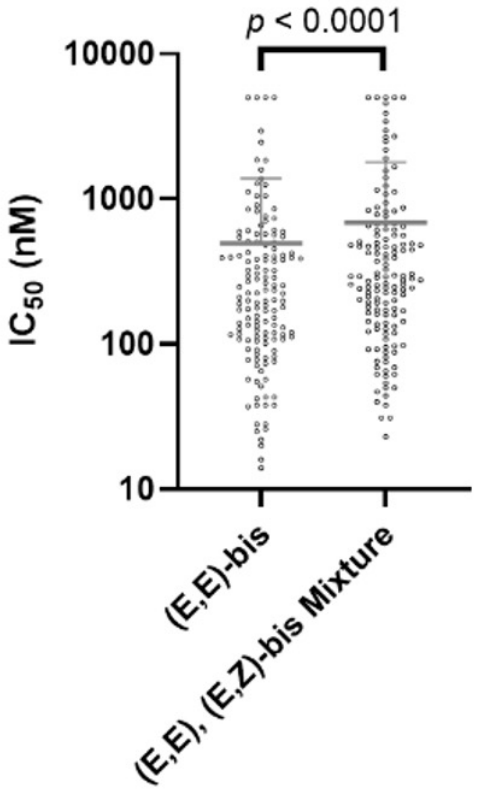
Cytotoxicity Testing





(E,Z)-bisantrene has low anticancer activity

- Measure how well an (E,E), (E,Z)-bisantrene mixture kills 143 individual cancer cell lines from 23 different tissue types compared to pure (E,E)-bisantrene



(E,E)-bisantrene: 100% (E,E), 0% (E,Z)

(E,E), (E,Z)-bisantrene mixture: 58% (E,E), 42% (E,Z)


Patents & Value

Composition of Matter IP

- Composition of matter patent claims protect the chemical structure of the active drug
- Strongest IP possible in the pharmaceutical industry
- Composition of Matter IP drives significant value uplift for any drug. Why?
  - No generic competition until end of Composition of Matter patent
  - Possibility of additional 5-year patent extension
  - Can't be worked around by changing the formulation
- Patent life critical
  - Longer the better - increases net present value of drug

What is Required for a Patent?

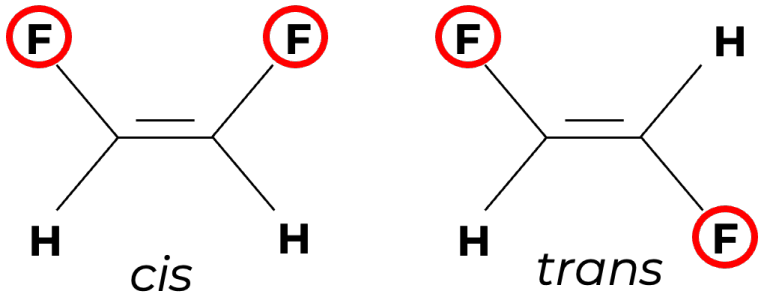
Novelty	Non-Obviousness	Utility
✓	✓	✓
Bisantrene photoisomerism not previously reported	Only discovered through careful scientific observations and follow-up R&D	Only (E,E)-isomer active

Race Oncology has filed three isomer patents:

(i) Isomeric Forms of Bisantrene
(ii) Pharmaceutical Compositions Suitable for Intravenous Administration
(iii) Process for Manufacturing High Purity (E,E)-Bisantrene

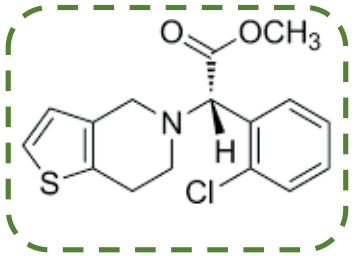
Isomer Mixture Drugs

- European Medicines Agency (EMA) no longer approving drugs consisting of isomer mixtures – none since 2016
- FDA demands you provide strong evidence for why your API is not a single isomer
- Why single-isomer drugs are better than mixtures?
  - Reduced dosing requirements
  - Reduced toxicity and side effects
  - Reduced drug-drug interactions
  - Simpler, better-defined pharmacodynamics and pharmacokinetics
- Examples



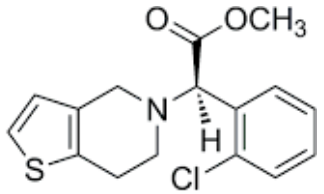
Plavix® (Clopidogrel)

- Antithrombotic and antiplatelet drug
- Original patent (1983) was an isomers mixture
- Later patent (1988) only claimed (S)-isomer
- Approved by FDA as a pure (S)-isomer
- Over its 1988 patent life, Plavix® generated US$42.8B in revenue



Pharmacologically active isomer

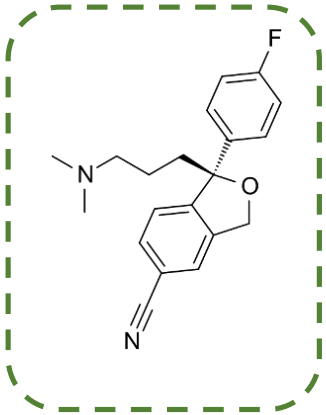
***(S)*-Clopidogrel**



***(R)*-Clopidogrel**

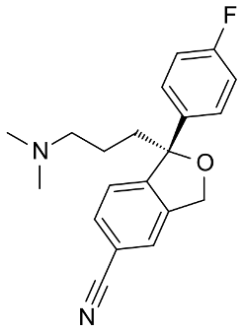
Lexapro® (Escitalopram)

- Used for the treatment of depression
- Citalopram was approved in 1998 as isomer mixture
- (S)-isomer later found to be 100 times more potent than the (R)-isomer and patented
- (S)-Citalopram (Escitalopram) was approved in 2002
- Over its patent life, Lexapro generated US$13.8B in revenue



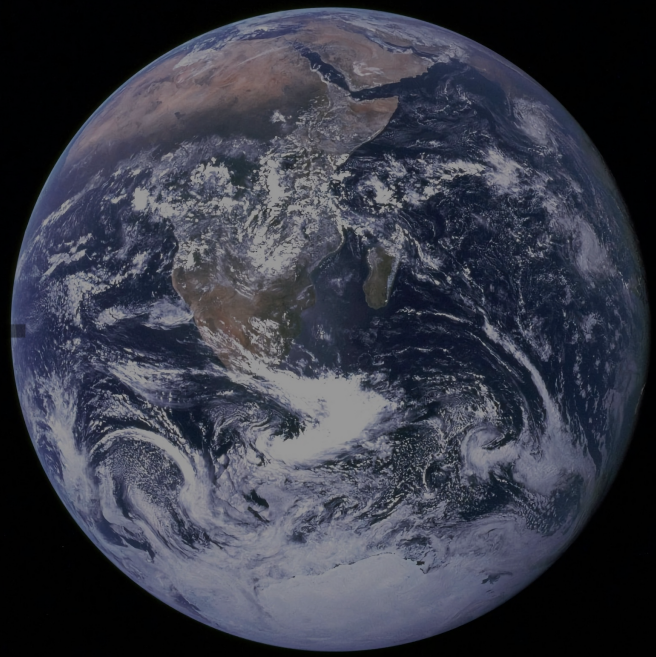
Potent Isomer

***(S)*-Citalopram**



***(R)*-Citalopram**

Commercial significance



RC220

- From a partnering point of view, composition of matter patent claims are very valuable
  - Ensure that no other formulation can enter the market even if clinical studies are conducted
  - Any other (E,E)-bisantrene containing formulation would infringe Race patents
  - Other bisantrene formulation would be unapprovable or be captured by our IP
- Provides a unique position of having a broadly active cancer drug with solid IP protection if granted
- Adds to the building safety data with RC220
  - Efficacy and cardioprotection data to follow from RAC-010 study

RC110 in acute myeloid leukemia (r/rAML)

Phase II trials of (E,E)-bisantrene RC110 in r/r AML

- RC110 as a mono agent: **40% overall response rate.**[1]
- RC110 in combination with purine nucleoside antimetabolites: **40% overall response rate.**[2]
- RC110 is an effective salvage agent in late-stage, very heavily pre-treated r/r AML patients.

1. Canaani J, Danylesko I, Shemtov N, et al. *Eur J Haematol.* 2021;106(2):260-266
2. Danylesko I, Shimoni A, Avigdor A, et al. *Br J Haematol.* 2025;00:1-10

Composition of matter patent would provide strong IP protection of the RC110 formulation

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ORIGINAL PAPER

Haematological Malignancy – Clinical

Bisantrene in combination with fludarabine and clofarabine as salvage therapy for adult patients with refractory or relapsed acute myeloid leukaemia (AML)—An open-label, phase I/II study

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Funding information
Race Oncology

Summary

Bisantrene (Bis), an anthracene derivative with topoisomerase-II inhibitory activity and low cardiotoxicity, may enhance its efficacy when combined with nucleoside analogues such as clofarabine (Clo) and fludarabine (Flu) in preclinical acute myeloid leukaemia (AML) studies. We conducted a phase I/II open-label study (NCT04989335) to evaluate the safety and efficacy of Bis/Clo/Flu in relapsed/refractory AML. Twenty-one patients (median age: 47 years, 55% female) received Flu (30 mg/m^2), Clo (30 mg/m^2) and Bis (250 mg/m^2) intravenously for 4 days. Sixteen had relapsed post-allogeneic stem cell transplantation, and six had extramedullary disease (EMD). Liver toxicity occurred in 10 patients but resolved. No significant cardiac toxicity was observed. Efficacy was assessable in 15 patients, while in six patients, it could not be evaluated due to early non-relapse mortality occurring within 30 days of treatment initiation, before the first post-treatment assessment. Six of the 15 patients responded: five achieved complete remission, and one with EMD achieved a partial remission, yielding a 40% response rate. Responses were transient, but six patients, including four undergoing second allo-HSCTs, proceeded to allo-HSCT within 1–3 months post-treatment. The Bis/Clo/Flu regimen demonstrated a tolerable safety profile and potential as a bridging therapy in high-risk, heavily pre-treated AML.

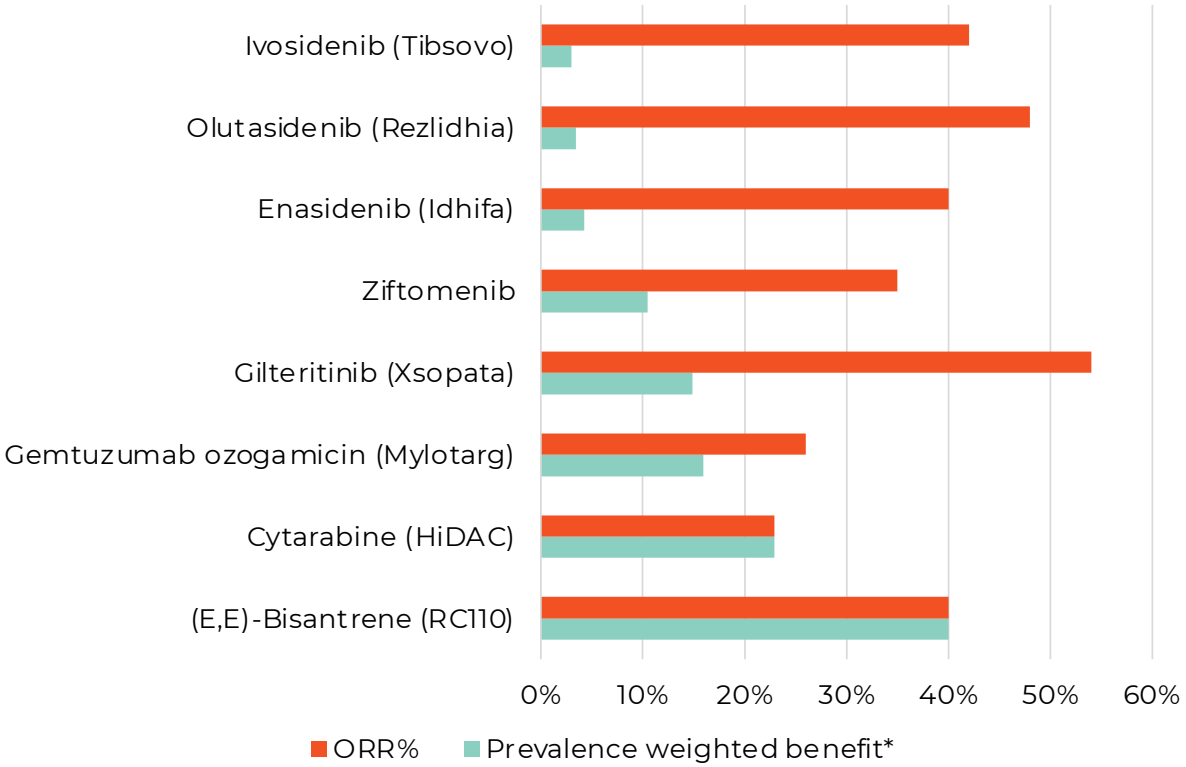
KEYWORDS
acute myeloid leukaemia, chemotherapy: refractory/relapsed

INTRODUCTION

Anthracyclines in combination with cytarabine (ara-C) have comprised standard-of-care induction chemotherapy in acute myeloid leukaemia (AML). Although 60% of patients achieve complete remission (CR), the majority relapse within 1–2 years. As such, outcomes remain poor, with overall 5-year survival around 30% and in elderly AML patients even worse.[1] Primary refractory and relapsed (R/R) disease remains a common clinical scenario with poor outcomes.[2] The anti-neoplastic activity of anthracyclines, mediated through topoisomerase II inhibition, was first recognized in the early 1970s, though their use is limited by cardiotoxicity.[3–5] The anthracene derivative bisantrene (Bis) has broad anthracycline-like anti-tumour activity[6] with reduced cardiotoxicity.[7] In the 1980s, it showed up to 50% response rates as salvage therapy in AML.[8] Preclinical data show that Bis activates macrophages,[9] inhibits telomerase[10] and targets fat

Data presented in part at the ASH 2023 meeting, San Diego, California (Blood. 2023;142 (Supplement 1):4292).

Performance of Second Line Mono Agents in AML



RC110 offers the highest prevalence weighted benefit as a mono agent therapy for r/r AML patients

RC110 could readily enter a registrational Phase 3 trial in r/r AML†

References on file.

ORR, overall response rate. * Prevalence weighted benefit for ORR accounts for patient eligibility based on the prevalence of targeted gene mutations/rearrangements (eg, *IDH1*, *IDH2*, *FLT3*, *NPM1*, *KMT2*Ar) or overexpressed proteins (eg, CD33+) in r/r AML.

† The cost of such a trial exceeds current resources and would likely require financial support from a pharma partner.

Potential to Partner RC110

- RC110 has been very effective in recent studies in AML
- Bisantrene was not protected by strong intellectual property
  - Only orphan drug designation - 7 years of exclusivity
  - Once orphan protection period expired generic RC110 competing with RC220
  - Limited the interest in future development of this formulation
- Composition of Matter IP covering (E,E)-bisantrene would provide strong protection of RC110
- Provides a potential path to a Phase 3 trial in AML
  - Both RC110 and RC220 can be marketed via careful positioning
  - Beyond the resources of Race and larger opportunity with RC220 (cardioprotection)
- RC110 may now be of interest to potential pharma partners with a focus in hematology or orphan diseases

Conclusion

- Bisantrene can exist in three isomeric forms - (E,E), (E,Z) and (Z,Z)
  - Photoisomerisation not known prior to Race's discovery
- Only (E,E)-bisantrene (RCDS1) shown to have potent anticancer activity
- Race is using pure (E,E)-bisantrene in its RC110 and RC220 formulations
  - RAC-010 protocol includes protecting the drug from light
- Three patent applications filed on isomers, including one with composition of matter (CoM) claims
- Patent counsel advice is these patents meet the three requirements for allowance
  - Non-obviousness
  - Novelty
  - Utility
- Expedited review process for rapid assessment
- CoM claims are the strongest IP protection and if granted will add significantly to value any future licensing or partnering transactions

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AT THE HEART OF CANCER CARE

Questions

Race Oncology

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