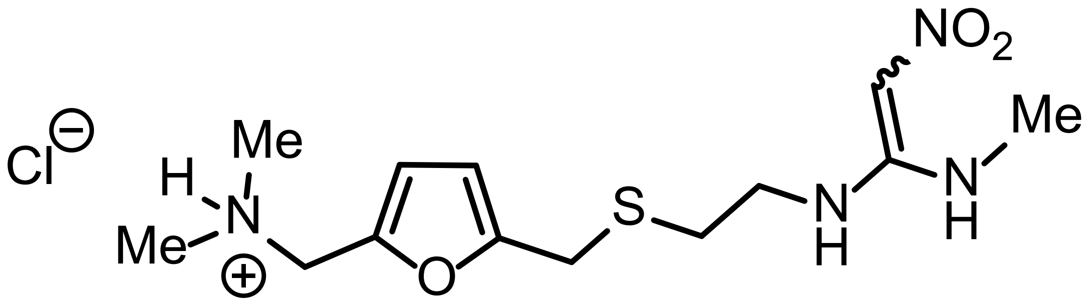
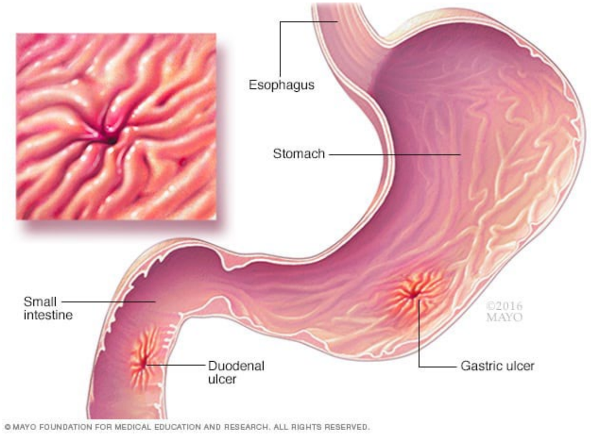
The Rise and Fall of Ranitidine Hydrochloride



Carter Cunningham
Denmark Group Meeting
February 25th, 2025

Peptic Ulcer Disease (PUD): Not Just Mild Irritation

What is PUD?



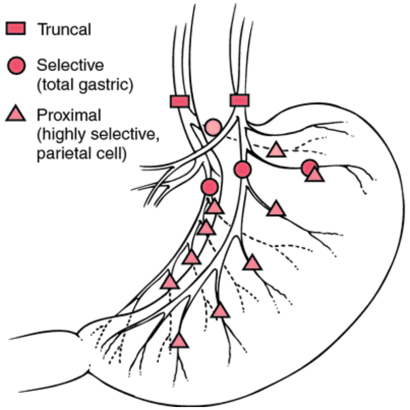
- Condition that causes ulcers (open sores) to develop in the stomach lining
- Once ulcers develop, stomach acid causes prolonged irritation

How is PUD caused?

- Originally thought to arise from stress and lifestyle habits, leading to over-secretion of stomach acid
- Later discovered by Warren and Marshall (1982) to primarily be caused from *Helicobacter pylori*

Treatment options prior to antibiotics?

- Antacids provided temporary relief, but primary treatment of chronic PUD was surgery (gastric vagotomy) providing up to 80% decrease in acid secretion



- ***Large demand for a non-invasive therapy of PUD***

Warren, J. R.; Marshall, B. *Lancet* **1983,** *1,* 1273.

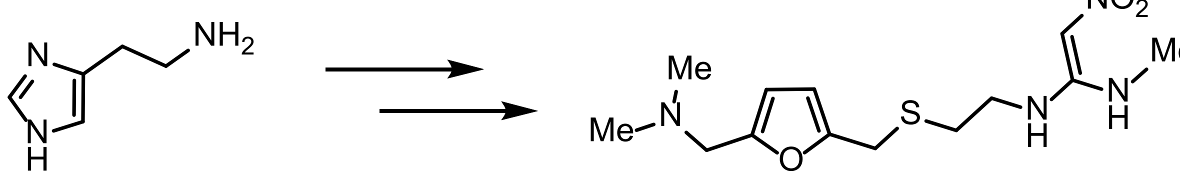
Schirmer, B. D.; *Ann. Surg.* **1989**, 209 (2), 131.

Presentation Overview

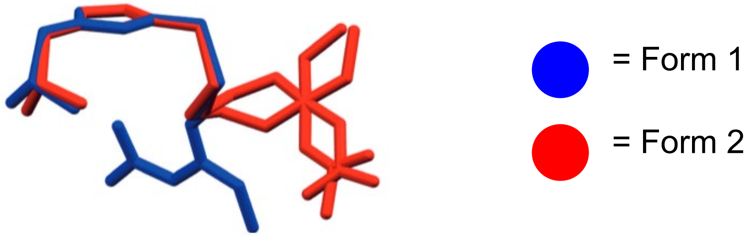
Discovery of H_2-Receptors and Their First Marketed Antagonists, Cimetidine and Ranitidine

From:

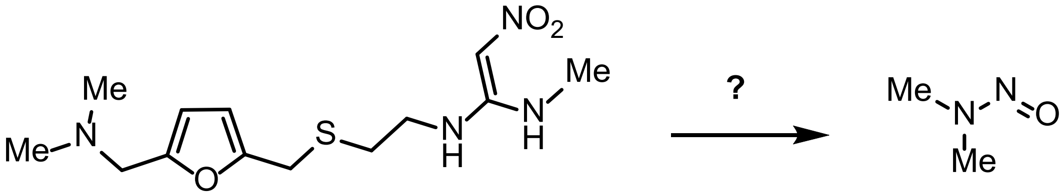
To:



Sudden Development of a New Polymorphic Form of Ranitidine



Concerns of *N*-Nitrosodimethylamine (NDMA) Formation From Ranitidine



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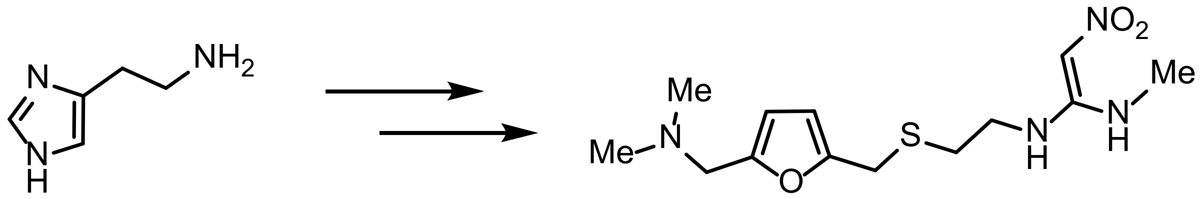

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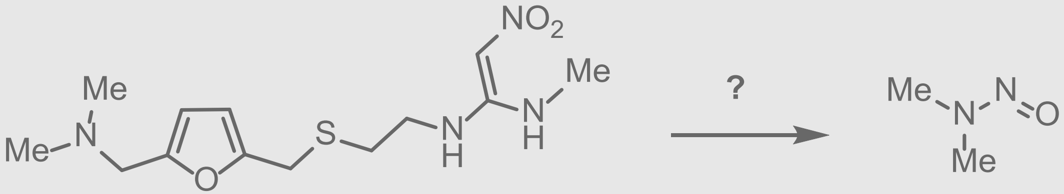
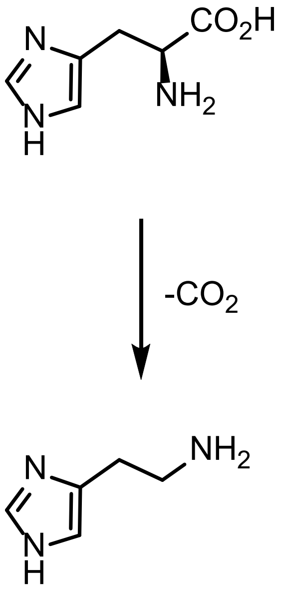


Background of Histamine Research

1907

First synthesis of histamine by Adolf Windaus

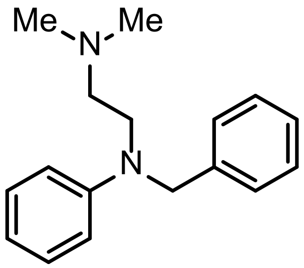


1910

Description of physiological responses to histamine by Sir Henry Dale (i.e., blood pressure lowering, gastric acid secretion, etc.)

1937 - 1942

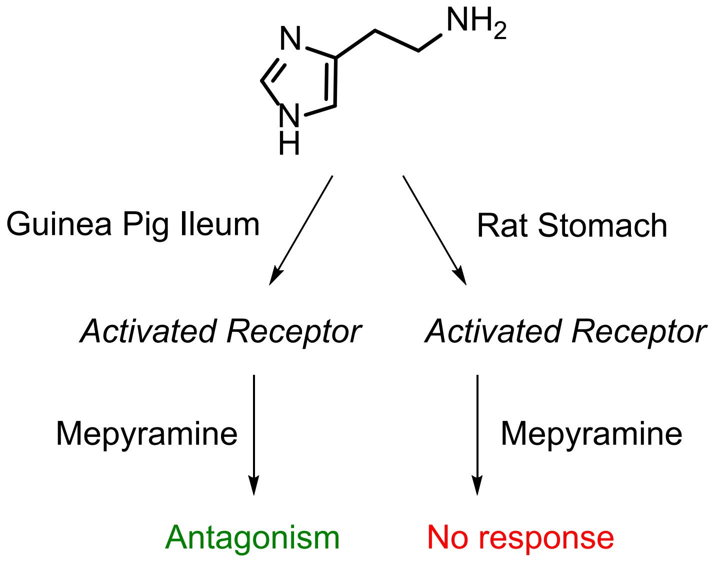
Synthesis of first antihistamine (thymoxyethyl-diethylamine) and marketing of first antihistamine (Antergan)



Antergan

1966

Ash and Schild defined the receptors that were sensitive to the antihistamine mepyramine as H_1 receptors



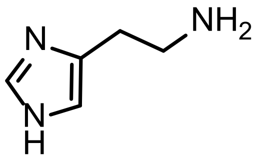
Identification of A New Histamine Receptor and Its Agonist: Cimetidine

First Successful Development of H_2-Receptor Antagonists:

- **1964** - Sir James Black leaves ICI Pharmaceuticals after his work on β-blockers for treating heart disease and joins Smith, Kline and French Laboratories
    - Gathered a team of researchers: Micheal Parsons (pharmacologist), William Duncan (biochemist), Graham Durant (chemist), John Emmett (chemist), and Robin Gannelin (chemist)

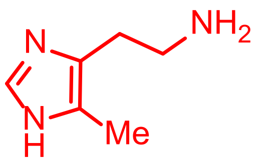
***Single goal**: Given the structure of histamine, find a new class of molecule that would selectively inhibit gastric acid secretion by competitive binding to the speculated H_2-receptors*

Initial Evaluation:



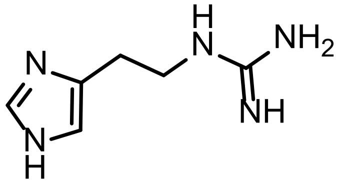
Over 200 novel analogues, ***but no success***

First Insight:



Stimulated acid secretion with no other histamine responses, ***proving existence of H_2-receptors***

An Overlooked Lead:



SK&F 71448

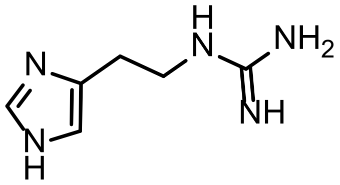
Evaluation ran at submaximal histamine stimulation failed to show partial antagonist activity. Rerunning evaluation **2 years later** showed antagonistic activity.

Li, Jie Jack, 'Beginning of an Era The First Blockbuster Drug, Tagamet', *Blockbuster Drugs: The Rise and Fall of the Pharmaceutical Industry*

Molinder, H. K. M. *J. Clin. Gastroenterol.* **1994**, 19 *(3)*, 248.

Modifications of SK&F 71448 to the Final Drug: Cimetidine

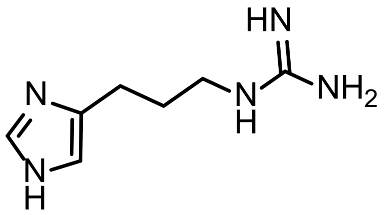
SK&F 71448



Partial agonist with low antagonism. SAR showed guanidine alone was not an antagonist

Homologation →

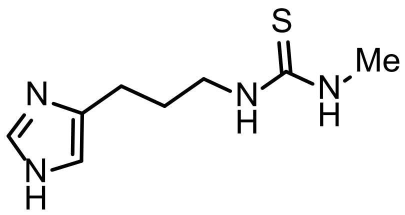
SK&F 91486



More active antagonist, still an agonist

N to S Conversion →

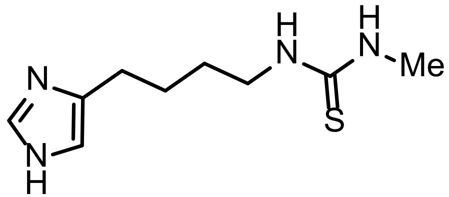
SK&F 91581



Removal of Lewis basic functionality shuts off agonism

↓ Homologation

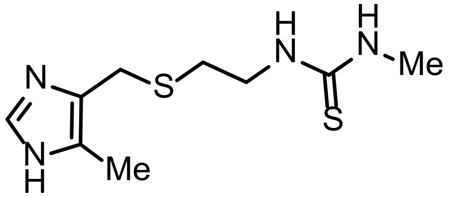
Burimamide (1972)



No agonism with improved antagonism but low bioavailability

← CH_2 to Sulfur and Methylation

Metiamide (1974)

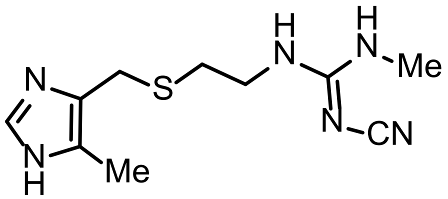


EWG (S) decreases the pK_a and increase equilibrium concentration of active imidazole tautomer in conjunction w/ EDG (Me)

Failed clinical trials due to small occurrence of granulocytopenia

← Replacement of Thiourea w/ Cyanoguanidine

Cimetidine (1976)



High antagonist activity, passed clinical trials, released in the UK in 1976, earned over $1 billion in the 1986 fiscal year

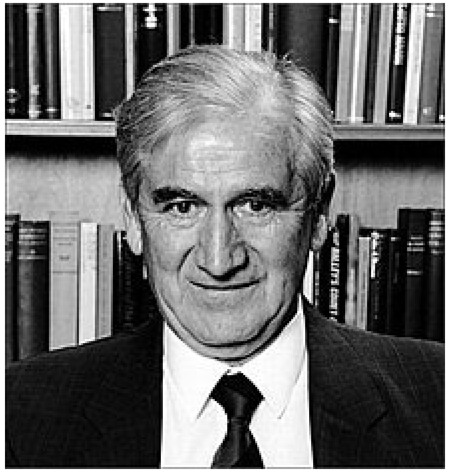
Brimblecombe, R.W.; *et. al. Gastroenterology* **1978**, *74*, 339.

Black, J. W.; *et. al. Nature* **1972**, *236*, 385.

Black, J. W.; *et. al. Nature* **1974**, *248*, 65.

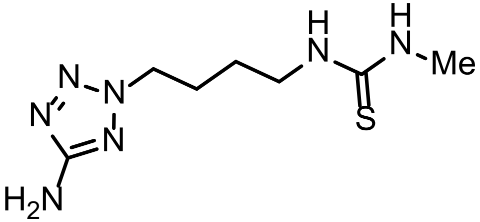
Allen and Hanburys (Glaxo) Enters the Scene

Discovery of Selective H_2-Receptor Antagonists Spurs Competition:



- **1961** - Sir David Jack (an ex-deputy researcher at SK&F) is hired as research director at Allen and Hanburys (A&H) (a subsidiary of Glaxo)
    - Throughout the 60's, A&H had a dwindling Peptic Ulcer Group investigating the activity of thioamides for inhibition of gastrin production
- **1972** - Jack attends a lecture by Sir James Black at Hatfield Polytechnic Institute that revealed the H_2-receptor antagonism of burimamide
    - Upon returning, he suspended all other projects in the Peptic Ulcer Group and hired Roy Brittain (pharmacologist) and Barry Price (chemist) to lead the team's new focus towards H_2-receptor antagonists using burimamide as a design platform

First Hit:

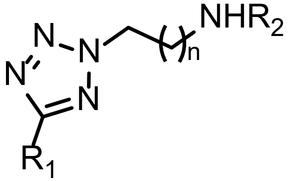


AH15475

"Experience in tetrazole chemistry encouraged incorporation of burimamide features into these tetrazoles"
-John Bradshaw

Gave equipotent activity to burimamide

Structural Modifications:



R_1 = H, Me, Ph, OMe, CF_3, etc.
R_2 = $C(=S)NHCH_3$, $C(=NH)NH_2$, $C(=NCN)NHCH_3$, SO_2Me, etc.

n = 2 - 4

No improvement in activity relative to AH15475, and by 1976 the number of chemists was reduced to three

Cimetidine was heading to market, and the Peptic Ulcer Group project was considering abandoning the target

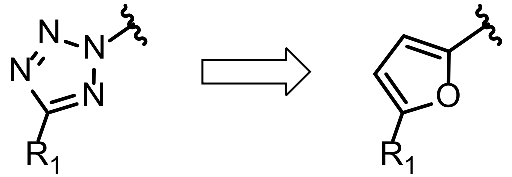
Li, Jie Jack, 'Beginning of an Era The First Blockbuster Drug, Tagamet', *Blockbuster Drugs: The Rise and Fall of the Pharmaceutical Industry* Ganellin, R. In '*Analogue-Based Drug Discovery*'

An Unexpected Development at A&H

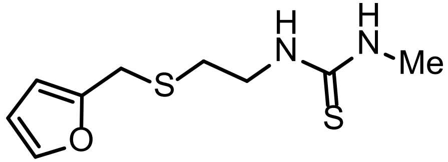
What was learned at A&H from their burimamide analogue survey?

1) The ring portion need not be significantly basic (pK_a of amino tetrazole = ~1)
2) The side chain need not be directly linked via the carbon atom of the heterocycle

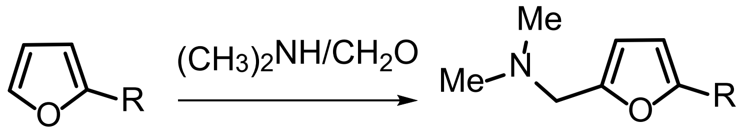
From insight #1, senior chemist John Clitherow suggested incorporation of a furan ring:



> *"The 2-isomer was chosen as 2-furfuryl mercaptan was readily available"*



Showed antagonistic activity but was poorly soluble and gave variable results

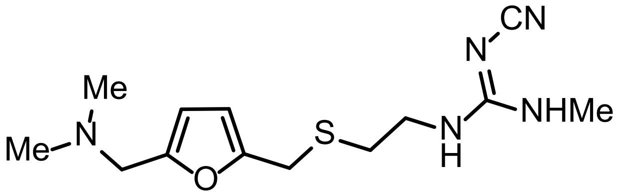


AH18665

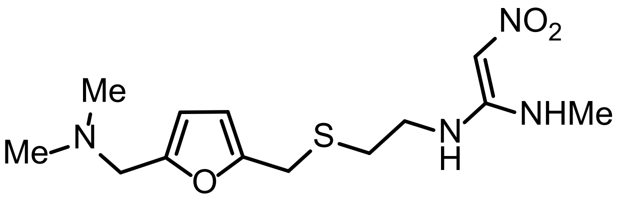
pKa = ~8.5

AH18665 gave antagonistic activity comparable to metiamide

R = $CH_2S(CH_2)_2NHC(=S)NHCH_3$



AH18801



AH19065 (**Ranitidine**)

Proactive removal of thiourea for expected granulocytopenia seen in metiamide. Poor crystallinity for production.

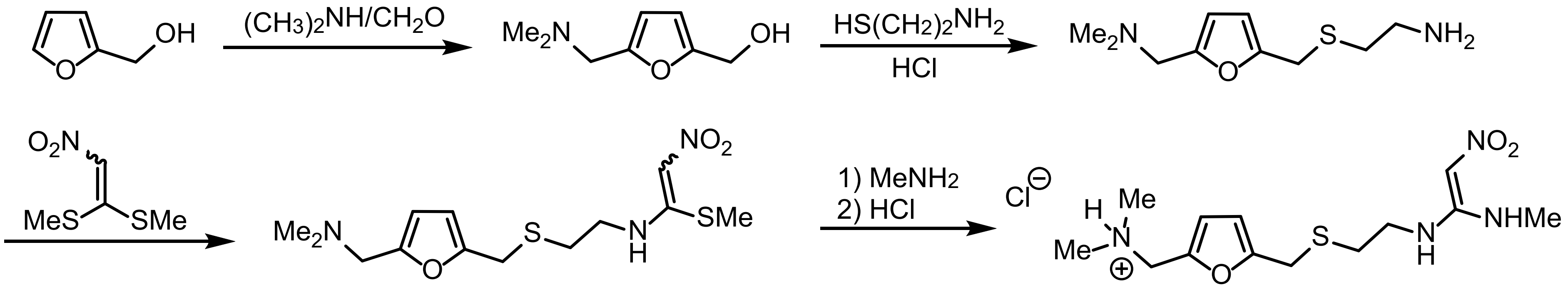
Nitrovinyl group had shown high crystallinity in previously tetrazole substrates but now gave a red oil with ~8x greater activity.

Li, Jie Jack, 'Beginning of an Era The First Blockbuster Drug, Tagamet', *Blockbuster Drugs: The Rise and Fall of the Pharmaceutical Industry*

Bradshaw J. In '*Chronicles of Drug Discovery*'

The Development Prior to Release of Ranitidine

The development chemistry department gave the final route and detailed crystallization conditions of the HCl salt of ranitidine:



Ranitidine was patented in the US in 1978 w/ crystallization conditions as follows:

EXAMPLE 32

N-[2-[[[5-(Dimethylamino)methyl-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine hydrochloride

N-[2-[[[5-(Dimethylamino)methyl-2-furanyl]methyl]-thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine (50 g, 0.16 mole) was dissolved in industrial methylated spirit 74° o.p. (200 ml) containing 0.16 of an equivalent of hydrogen chloride. Ethyl acetate (200 ml) was added slowly to the solution. The hydrochloride crystallised and was filtered off, washed with a mixture of industrial methylated spirit 74° o.p. (50 ml) and ethyl acetate (50 ml) and was dried at 50°. The product (50 g) was obtained as an off-white solid m.p. 133°–134°.

Process development up to multi-kilogram scale of Ranitidine HCl was performed over 4 years using the patented process

The batch prepared on April 15th, 1980 failed quality control IR analysis with a new peak at 1045 cm^{-1} suggesting a new polymorphic form

Bucar, D. J.; *et. al. Angew. Chem. Int. Ed.* **2015**, *54*, 6972.   Bradshaw J. In '*Chronicles of Drug Discovery*' Lednicer D.   J. Price, J. W. Clitherow, J. Bradshaw, US 4128658A, **1978**.

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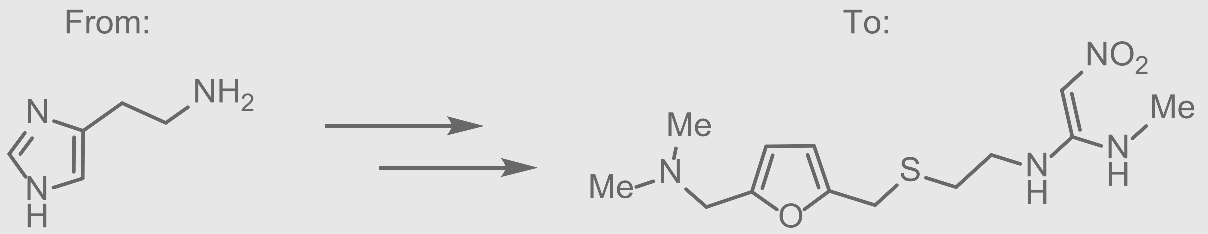
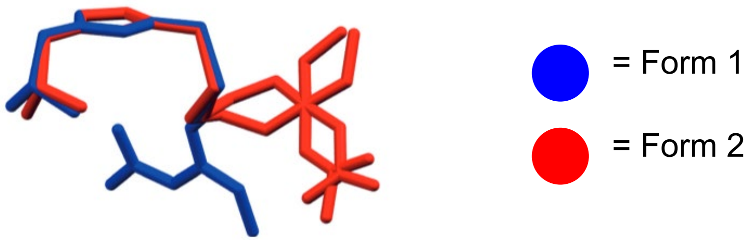
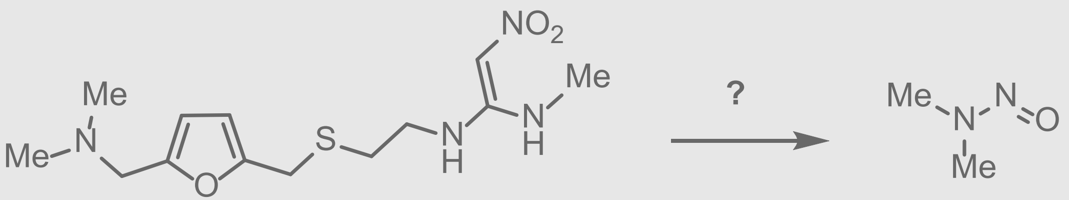


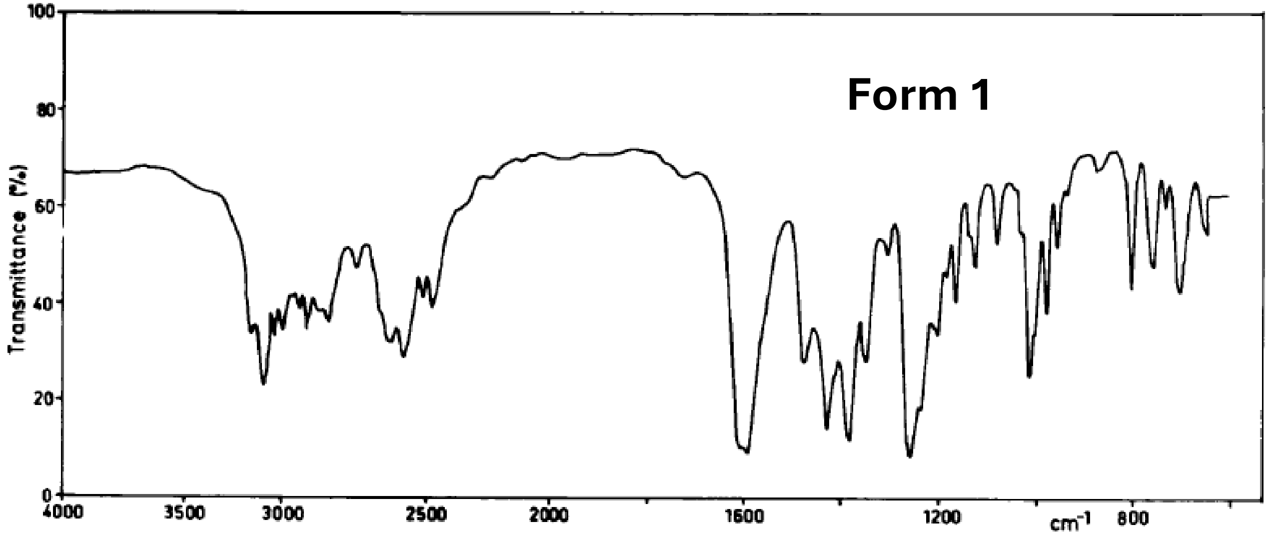
Sudden Development of a New Polymorphic Form of Ranitidine

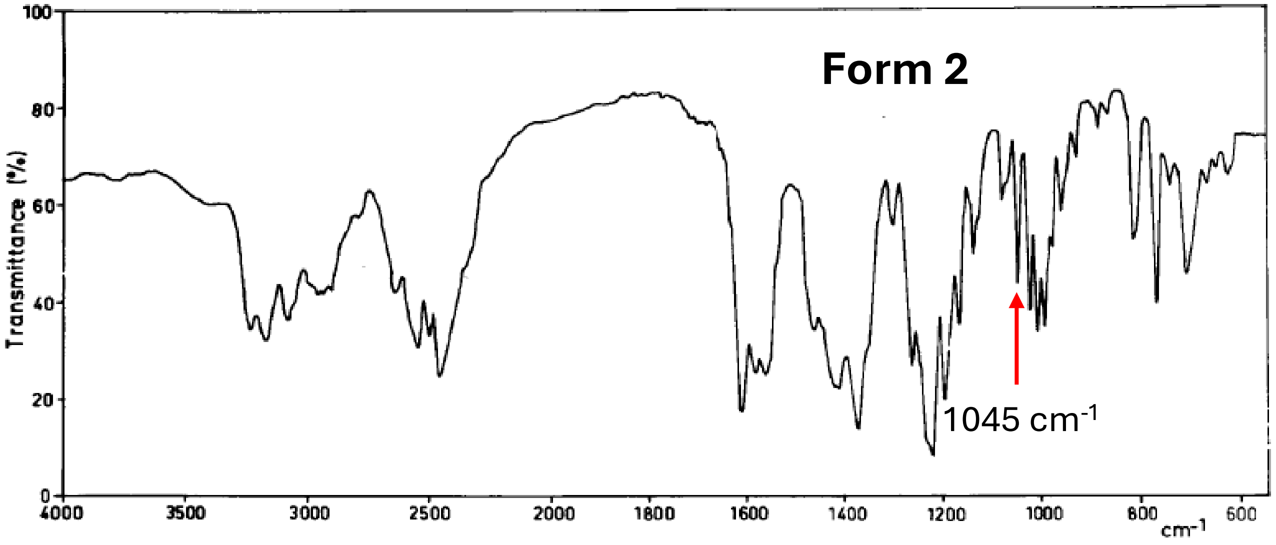


Concerns of *N*-Nitrosodimethylamine (NDMA) Formation From Ranitidine



A New Polymorphic Form





- Subsequent batches showed increasing amounts of **Form 2** and the same procedure failed to yield the original **Form 1**.

- **Form 2** provided better filtering and drying characteristics, with nearly the same solubility
  - Note that once fully solubilized, the forms were identical and showed the same bioactivity

- Glaxo applied for a new patent for the process of making **Form 2** in 1981 and was approved in 1985.

EXAMPLE 1 PREPARATION OF FORM 2 RANITIDINE HYDROCHLORIDE

One equivalent (about 5.3 ml) of concentrated hydrochloride acid was added to a solution of ranitidine (20 g) in a mixture of propan-2-ol (130 ml) and water (4 ml) at 45°. The mixture was heated at 50° whilst a further quantity of propan-2-ol (68 ml) was added and the resulting solution was then stirred at 50° to allow the product to crystallise. The slurry was cooled to 10° to 12° and the product was filtered off, washed with propan-2-ol (2×27 ml) and dried at 50° under reduced pressure to give Form 2 ranitidine hydrochloride (21 g) m.p. 139°–141°.

Litigation Surrounding Polymorphic Forms

Rantidine HCl (Zantac) was released in 1984 and by 1991 was the world's best-selling drug at $3.44 billion per year

*Glaxo's 1978 patent on **Form 1** was planned to expire in 1995, and by 1990 several generic companies were planning to release a generic version of **Form 1***

Novopharm (TeVa) Enters the Scene:

- **1990** – Novopharm begins their formulation of **Form 1**, protected by the Hatch-Waxman Act of 1984
    - Common occurrence for generic companies to use branded product to test their reformulation; thus, Novopharm purportedly began with Zantac (**Form 2**)

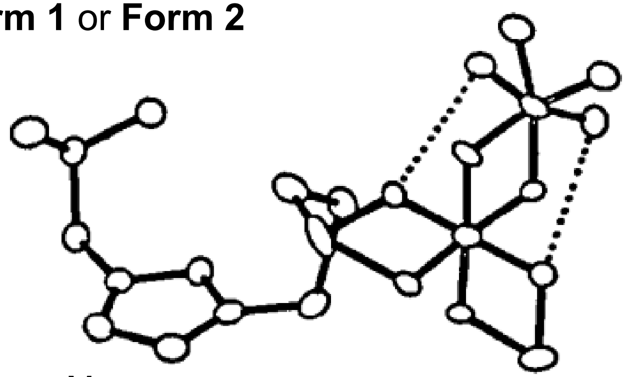
- **1991** – Failure to obtain **Form 1** by Novopharm led them to believe **Form 1** never existed and would invalidate the **Form 2** patent in 1985, so they filed an ANDA to market **Form 2** generically in 1995

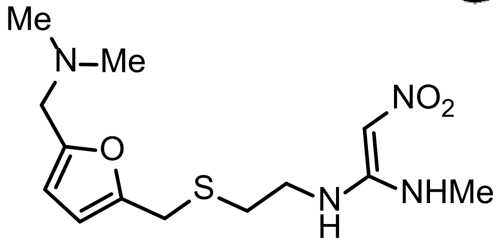
- **1993** – Glaxo vs Novopharm trial occurred where Glaxo claimed Novopharm's facilities were contaminated with seed crystals of **Form 2**
    - The court found this testimony noncredible, so Glaxo had to provide proof that **Form 1** was created
    - The court examined Dr. David Collins notebook as evidence of creating **Form 1**, as well as an independent synthesis by Sir Jack Baldwin in 1993 at Oxford University, where no **Form 2** had ever been present and obtained **Form 1**
    - Glaxo's **Form 2** patent (1985) was found to be valid, and a generic version of **Form 2** was restricted until 2002.

Bucar, D. J.; *et. al. Angew. Chem. Int. Ed.* **2015**, *54*, 6972. Bradshaw J. In '*Chronicles of Drug Discovery'* Lednicer D. Bernstein, J. In '*Polymorphism in the Pharmaceutical Industry*'

What’s the Composition of **Forms 1** and **2**?

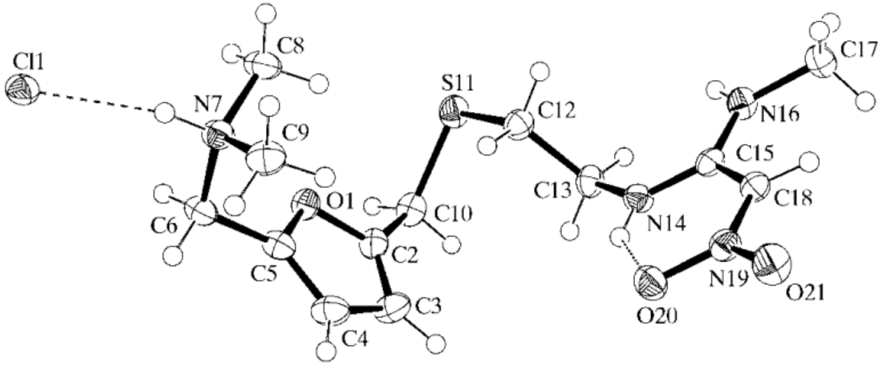
- **No single crystal structure of Ranitidine HCl published until 1990 by Ishida**
  - Two concerns: 1) Crystallization was performed using acetonitrile, which is not the patented procedure for **Form 1** or **2;** 2) There is no other characterization data (i.e., FTIR) to indicate that the polymorph is **Form 1** or **Form 2**



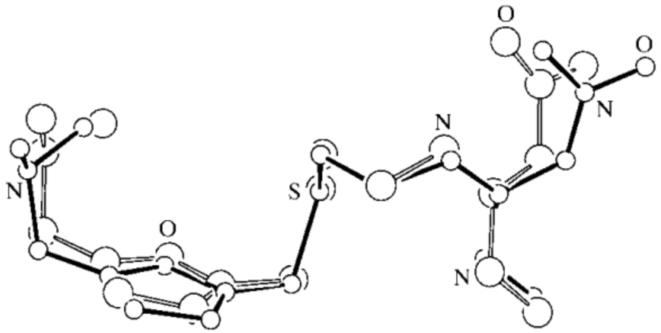


- **High degree of disorder in 1,1-diamine-2-nitroethene moiety**
  - Proposed to arise from equimolar distribution of *E*- and *Z*- enamine isomers

- **Second crystal structure of Ranitidine HCl reported by Hempel in 2000:**
  - Uses conditions in patent for **Form 1** crystallization, still no FTIR analysis



- **Highly ordered with sole formation of *Z*-enamine isomer**



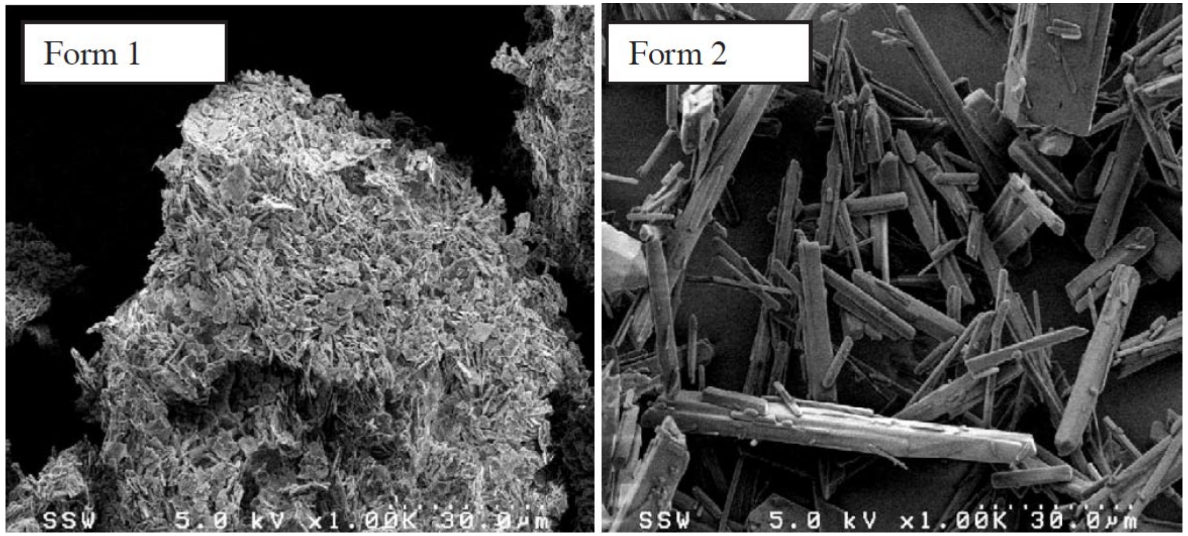
  - Clear alignment with *Z*-isomer from Ishida’s data (Hempel = small circles and Ishida = big circles)

Ishida, T. *et. al.; Acta Crystallogr. Sect. C* **1990**, *46*,1893. Hempel, A. *et al.; Acta Crystallogr. Sect. C* **2000**, *56*, 1048.

Further Investigation of Polymorphic Forms

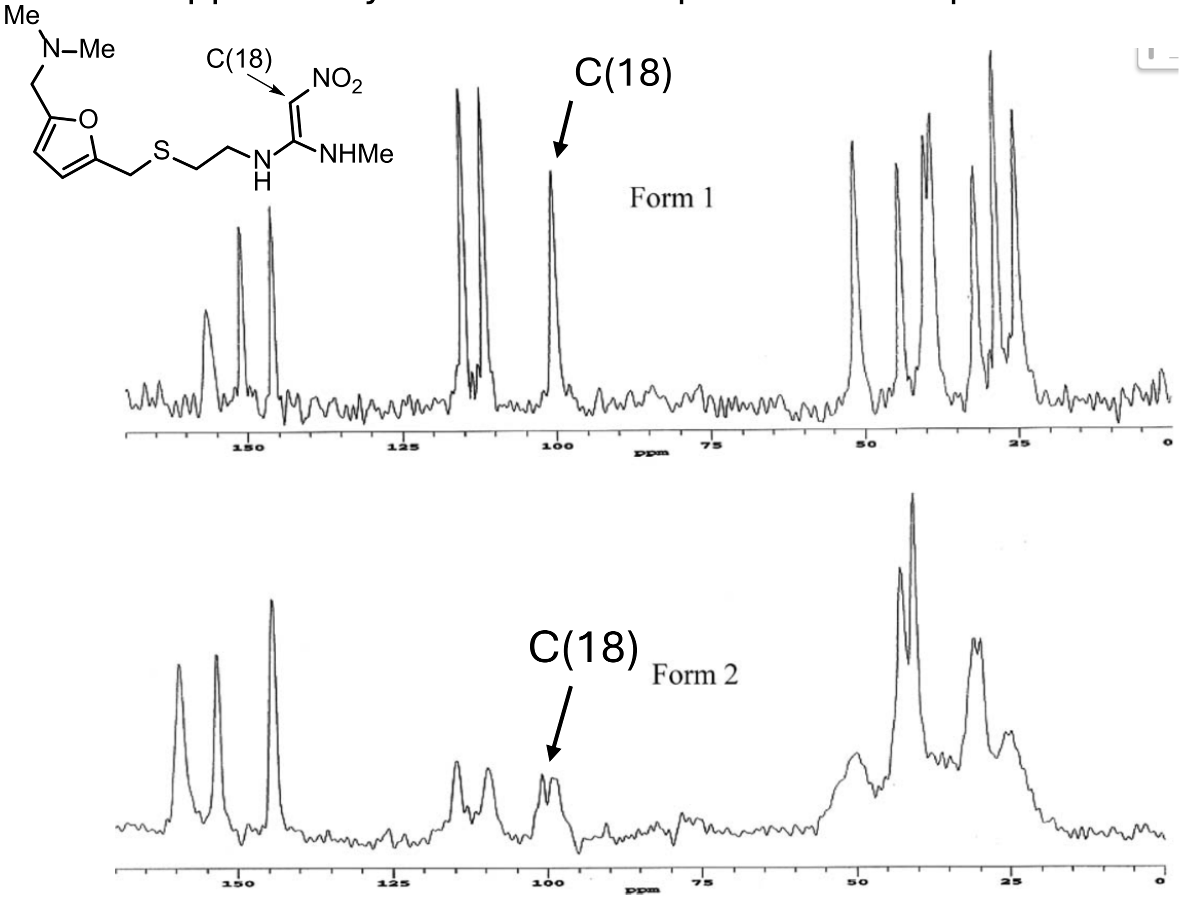
- First detailed study of both polymorphs reported by Mirmehrabi in 2004:
  - Performed recrystallization in anhydrous IPA (**Form 1**, CA patent claims this route works) and IPA with 2.5 w% water (**Form 2**, US patent process)

- Single crystals were not obtained for **Form 1** as they were too small, but **Form 2** did obtain crystals
  - Characterized by FTIR, SEM, Solid-state ^{13}C NMR, and X-ray Diffraction



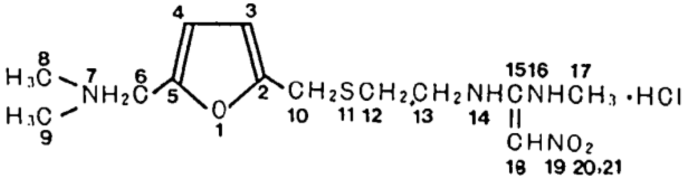
SEM image of Ranitidine HCl ***Forms 1*** *&* ***2***

- Solid-state ^{13}C NMR displays clear differences between the two forms
  - Singlet of C(18) in Form 1, indicative of order, while C(18) in Form 2 is a doublet, indicating disorder and is supported by decreased sharpness of other peaks



A Different Interpretation of the Crystal Data

- The single crystal data of **Form 2** by Mirmehrabi is in agreement with that of Ishida, but Mirmehrabi proposes a different structure due to bond length disagreements



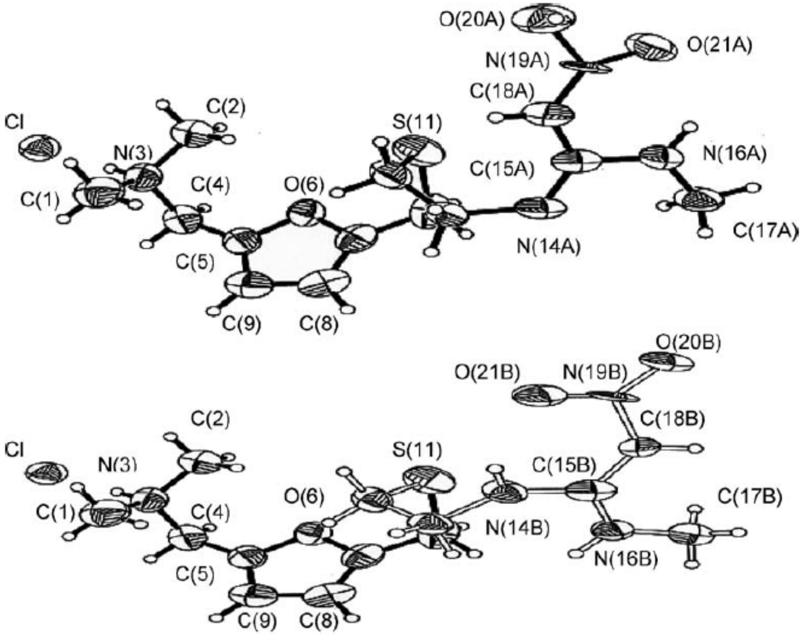
Ishida:

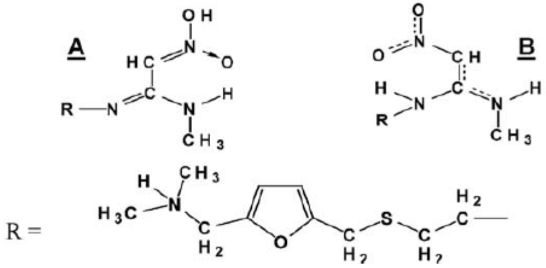
N(14)—C(15)	1·371 (5)
N(14′)—C(15)	1·434 (5)
C(15)—N(16)	1·431 (6)
C(15)—N(16′)	1·449 (5)
C(15)—C(18)	1·357 (6)
C(15)—C(18′)	1·347 (5)
N(16)—C(17)	1·460 (6)
N(16′)—C(17)	1·373 (6)
C(18)—N(19)	1·416 (6)
C(18′)—N(19)	1·419 (5)
N(19)—O(20)	1·145 (5)
N(19)—O(20′)	1·305 (5)
N(19)—O(21)	1·343 (5)
N(19)—O(21′)	1·172 (4)

Mirmehrabi:

N(14A)–C(15A)	1.262(3)
C(15A)–C(18A)	1.391(4)
C(15A)–N(16A)	1.439(3)
N(16A)–C(17A)	1.430(12)
C(18A)–N(19A)	1.22(2)
N(19A)–O(21A)	1.27(2)
N(19A)–O(20A)	1.40(3)
C(12B)–C(13B)	1.480(14)
C(13B)–N(14B)	1.458(8)
N(14B)–C(15B)	1.424(2)
C(15B)–C(18B)	1.368(3)
C(15B)–N(16B)	1.313(2)
N(16B)–C(17B)	1.405(13)
C(18B)–N(19B)	1.48(3)
N(19B)–O(20B)	1.20(2)
N(19B)–O(21B)	1.23(4)

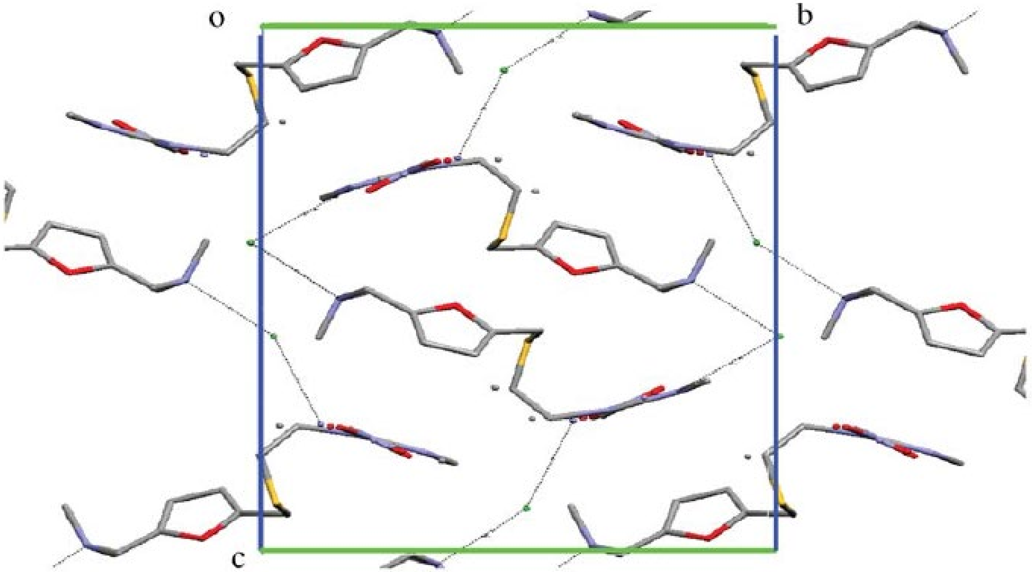
- Shorter distance of N(14A)-C(15A) and C(18A)-N(19A) leads Mirmehrabi to propose a 1:1 mixture of the enamine and nitronic acid tautomers as the composition of **Form 2**

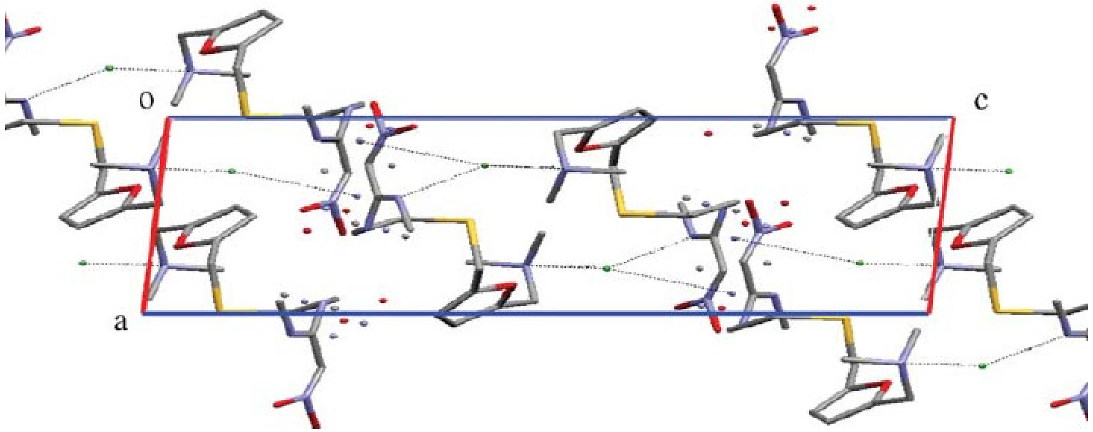




Mirmehrabi, M. *et. al.; J. Cryst. Growth* **2004**, *260*, 517

Mirmerhabi's Hypothesis for **Form 1** vs **Form 2** Production





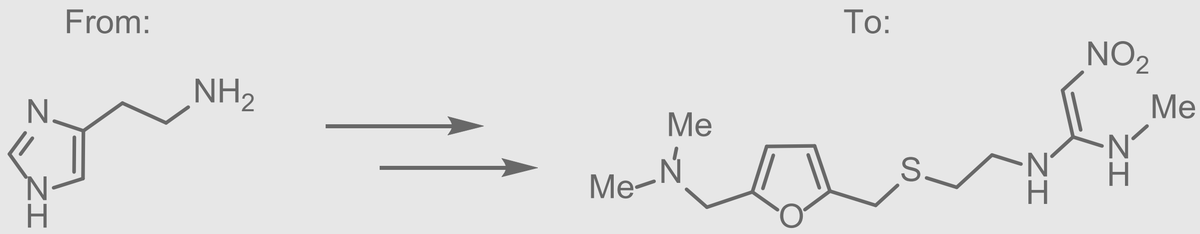
- Aqueous/strong H-bond donor solvents disrupt intramolecular hydrogen bonds
  - The nitro group can easily rotate around C(15)-C(18) and form hydrogen bonds with other solute molecules, leading to an enhanced cluster formation and crystal growth rate.
  - Furthermore, the amine nitrogen atoms can establish spatial hydrogen bonding with chlorine of the other molecules.
- Anhydrous, less polar solvents, intramolecular hydrogen bonds are strong
  - Decreased conformational freedom about the C(15)-C(18) bond.
  - Forms highly ordered crystals but results in poor crystal growth due to restricted hydrogen bonding between other molecules.

Mirmehrabi, M. *et. al.; J. Cryst. Growth* **2004**, *260*, 517

Rohani, S. *et. al. OPRD* **2005**, *9*, 858.

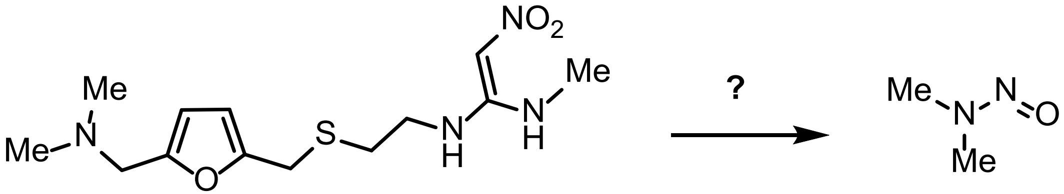
Presentation Overview

Discovery of H_2-Receptors and Their First Marketed Antagonists, Cimetidine and Ranitidine



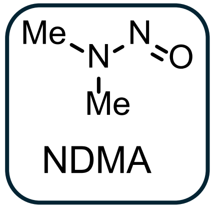
Sudden Development of a New Polymorphic Form of Ranitidine

Concerns of *N*-Nitrosodimethylamine (NDMA) Formation From Ranitidine

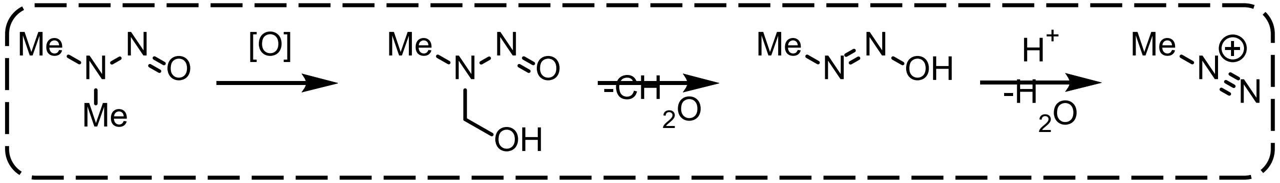


Intro to Nitrosamines and Their Health Impact

Nitrosamines, specifically *N*-nitrosodimethylamine (NDMA), are recognized as probable human carcinogens:

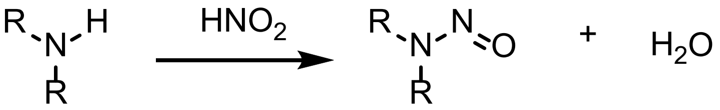


Proposed metabolism of NDMA to generate methyldiazonium cation:

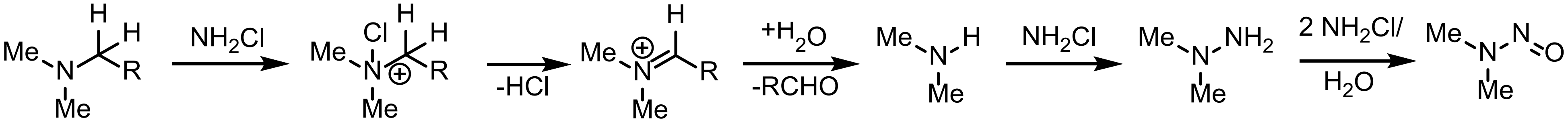


Two primary ways of formation:

Treatment of a 2^{o} amine with a nitrosating reagent:



Reaction of a 2^{o} or 3^{o} amine with chloramine:



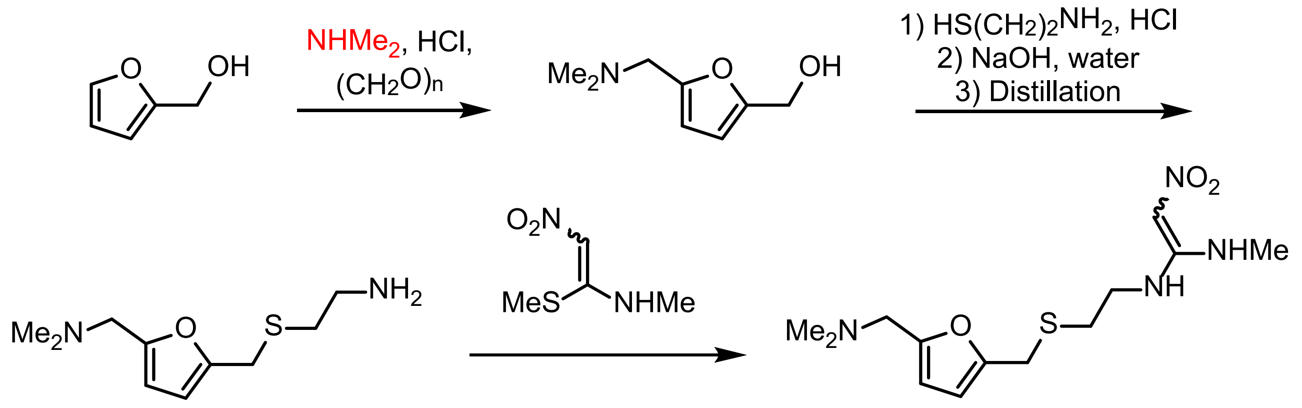
Proposed source of nitrosamine formation during wastewater chlorination

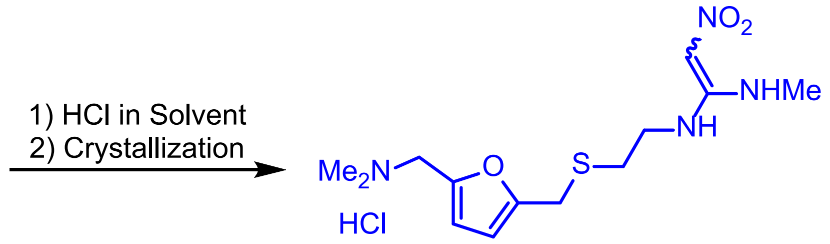
The Recall of Zantac

- **June 2019** – FDA is alerted by Valisure that Zantac contained high levels of NDMA
- **April 2020** – FDA requests removal of all ranitidine products from market due to NDMA impurity
- **December 2020** – GSK releases OPRD paper detailing their investigations into NDMA formation

Primary question: NDMA formation requires a 2º or 3º amine and a nitrosating source, so where does the nitrosating source come from in ranitidine given the nitro group is a higher oxidation state?

Evaluating the Process Route:





No clear nitrosating source used in route, only dimethylamine

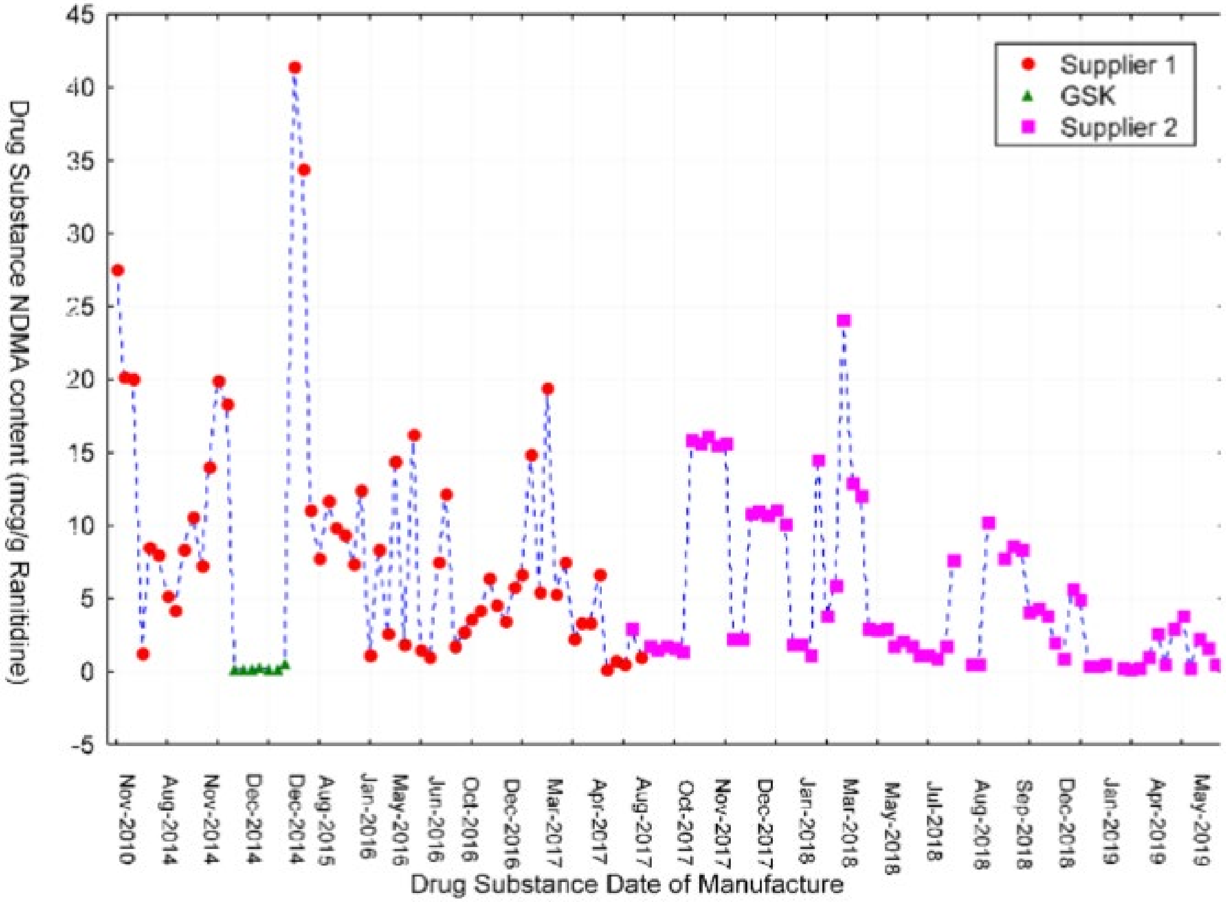
Sodium nitrite used to produce intermediate, but is 3 steps from contacting dimethylamine intermediate and is distilled prior to use

No NDMA present in freebase intermediate

https://www.ema.europa.eu/en/documents/press-release/ema-review-ranitidine-medicines-following-detection-ndma_en.pdf
https://www.fda.gov/news-events/press-announcements/fda-requests-removal-all-ranitidine-products-zantac-market
King, F. J. *et. al.*; *Org. Process Res. Dev.* **2020**, *24*, 2915.

NDMA Content Across Suppliers/Manufacturing Processes

No clear indicator that NDMA would be formed during manufacturing of ranitidine, so trends were evaluated for NDMA concentration among batches from suppliers:



Different formulations of ranitidine were also examined for NDMA content:

material	no. of batches tested	NDMA content range observed (mcg/g)[a]
drug substance	134	0.11−>9.9[b]
film-coated tablets	119	0.24−7.6
effervescent tablets	32	0.52−2.1
IV solution	55	0.24−1.1
syrup	24	<0.68−2.7

Overall trends:

1. NDMA content increases with age of batch
2. Range of NDMA content in all drug formulations was lower than that of drug substance
3. Concentration of NDMA in drug substance increases relative to drug formulation using the same batch (i.e., NDMA formation ceases when product is formulated

King, F. J. *et. al.; Org. Process Res. Dev.* **2020**, *24*, 2915.

Short-Term Stability Study

4 batches of ranitidine were stored under accelerated conditions (i.e., 60 °C, uncontrolled humidity):

Process 1 vs 2 varies solely in crystallization conditions

day	batch detail: supplier 2, process 1 DOM Aug 2019 NDMA (mcg/g)	supplier 2, process 1 DOM Nov 2019 NDMA (mcg/g)	supplier 2, process 2 DOM Dec 2019 NDMA (mcg/g)	GSK DOM Dec 2014 NDMA (mcg/g)
0	0.33	ND	ND	0.2
3	6.3	3.6	<LOQ (0.17)	0.36
7	7.7	7.4	0.28	0.39
46	not tested	38	2	not tested
115	not tested	66	3.3	not tested
rate of formation over 7 days (mcg/g per day)	1.05	1.06	0.04	0.03

parameter	GSK	supplier 2, process 1	supplier 2, process 2
solvent composition[a]	IPA	IPA/MeOH (approx. 70:30)	IPA/MeOH (approx. 40:60)
total solvent volume[a,b]	8.7	3.5	2.5
water concentration[a,c]	3.6%	not added to the process	3.4%
crystallization temperature	50 °C	10–25 °C	10–25 °C
observed rate of NDMA formation[d]	slow	fast	slow

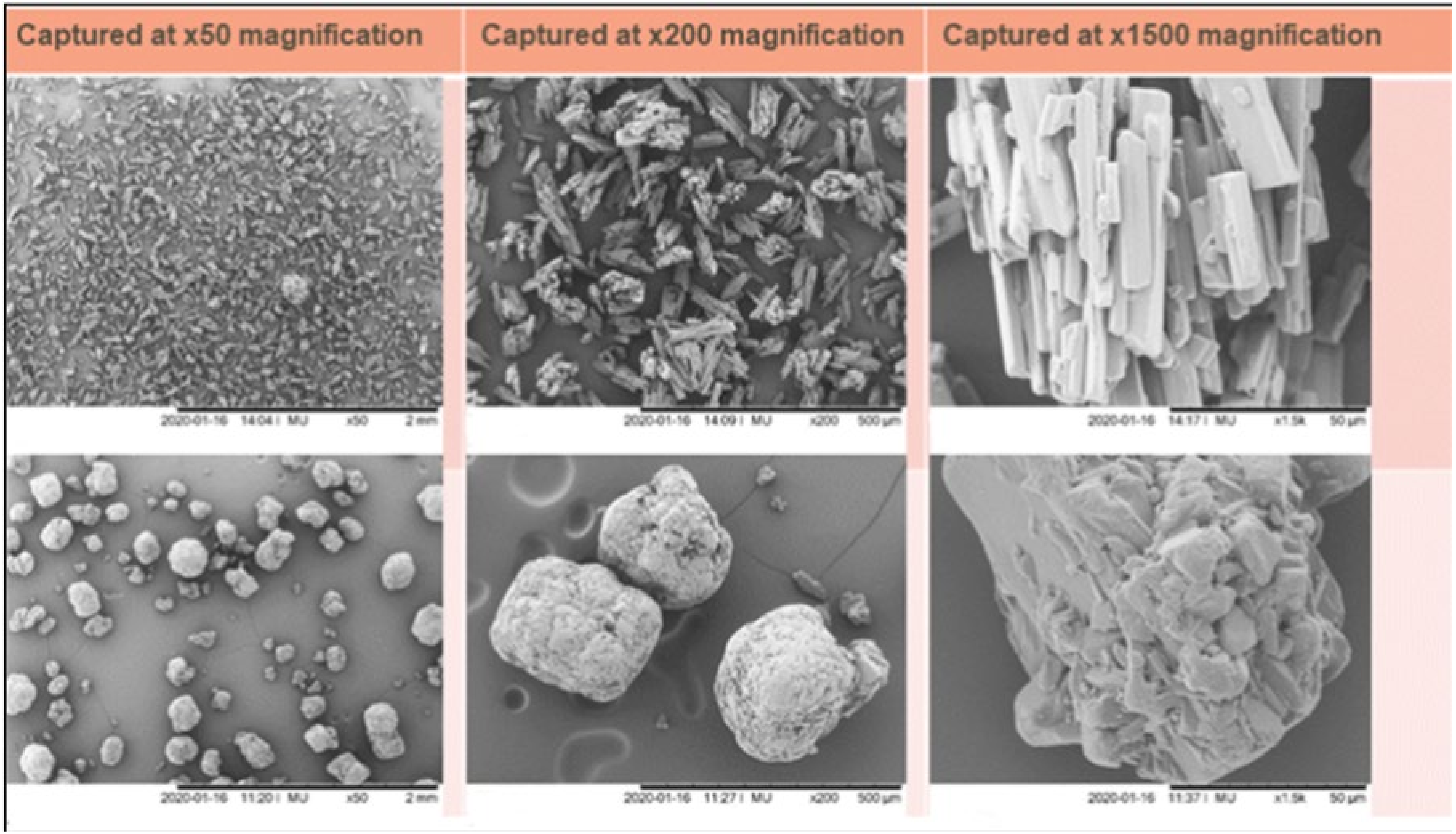
[b]Volume of the solvent as a ratio to the input weight of the ranitidine free base. [c]% v/v water in the overall crystallization mixture.

Rate of NDMA formation significantly greater for Process 1, which uses crystallization conditions reminiscent of obtaining **Form 1** vs **Form 2**… but XRPD analysis showed both batches from both processes were **Form 2**

Physical Property Discrepancies

Process 2

Process 1



Greater adsorption of water and lower onset of decomposition (<150 ^{o}C)

Physical Property Discrepancies

Second accelerated condition study but varying relative humidity:

[b]Samples were above highest calibration standard

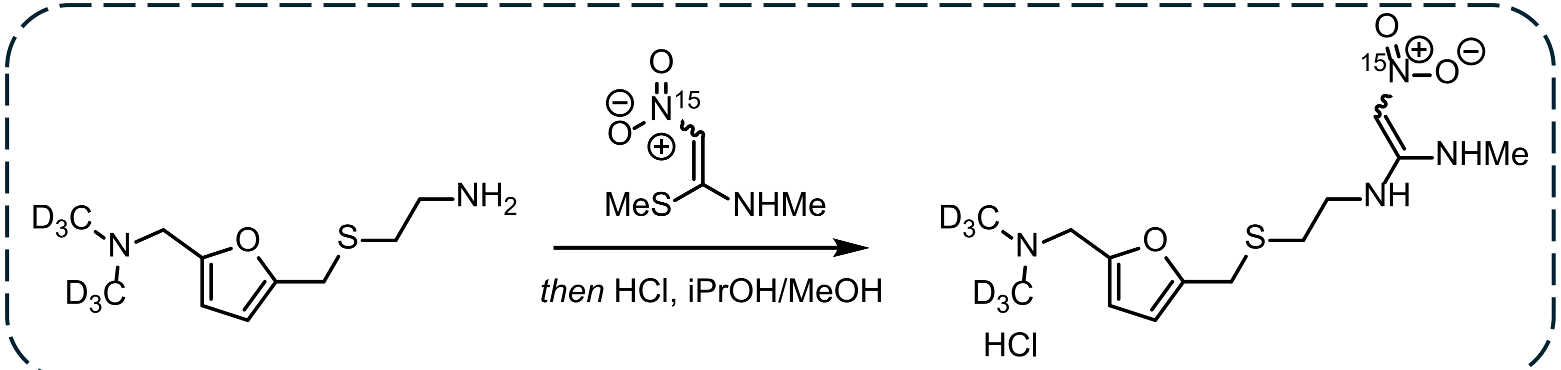
temperature (°C)	RH (%)	batch ID	test	initial	day 3	day 10	day 21
50	10	process 2	NDMA content (mcg/g)	ND		0.06[c]	0.13
			total impurities by HPLC (% area)	0.17		NT	0.23
			description	NT		white solid	white solid
50	75	process 2	NDMA content (mcg/g)	ND		8.6[1]	22.0[b]
			total impurities by HPLC (% area)	0.17		NT	24.0
			description	NT		orange oil	brown oil
60	30	process 1	NDMA content (mcg/g)	0.33		29.0[b]	47.1[b]
		process 2	NDMA content (mcg/g)	ND		0.19	0.80
			total impurities by HPLC (% area)	0.17		NT	0.46
			description	NT		white solid	pale-yellow solid
60	65	process 1	NDMA content (mcg/g)	0.33		68.4[b]	12.5[b]
		process 2	NDMA content (mcg/g)	ND		50.9[b]	31.8[b]
			total Impurities by HPLC (% area)	0.17		NT	47.6
			description	NT		dark-brown oil	dark-brown oil

Water drastically accelerates the rate of NDMA formation, where process 2 generates a product with columnar crystals that do not adsorb moisture as easily as process 1

King, F. J. *et. al.; Org. Process Res. Dev.* **2020**, *24*, 2915.

Isotopically Labeled Study

M + 7 ranitidine hydrochloride was prepared:



Portion of batch was combined in 1:1 mixture with non-isotope labeled ranitidine HCl

Evaluation for intra- vs. intermolecular process for NDMA formation:

days stored at 60 °C	+7 NDMA content	+6 NDMA content	+1 NDMA content	NDMA content
labeled ranitidine hydrochloride unblended				
0	ND	ND	ND	ND
7	strong signal	ND	ND	ND
25	strong signal	ND	ND	ND
labeled ranitidine hydrochloride blended with unlabeled ranitidine hydrochloride				
0	ND	ND	ND	ND
7	weak signal	ND	weak signal	ND
25	present	present	present	present

Conclusive evidence of intermolecular process, but exact mechanism of NDMA formation is still unknown

King, F. J. *et. al.; Org. Process Res. Dev.* **2020**, *24*, 2915.

Zantac's Legacy

While GSK sold the rights of Zantac to Sanofi in 1998, it still cost them $2.2 billion over 26 years later:

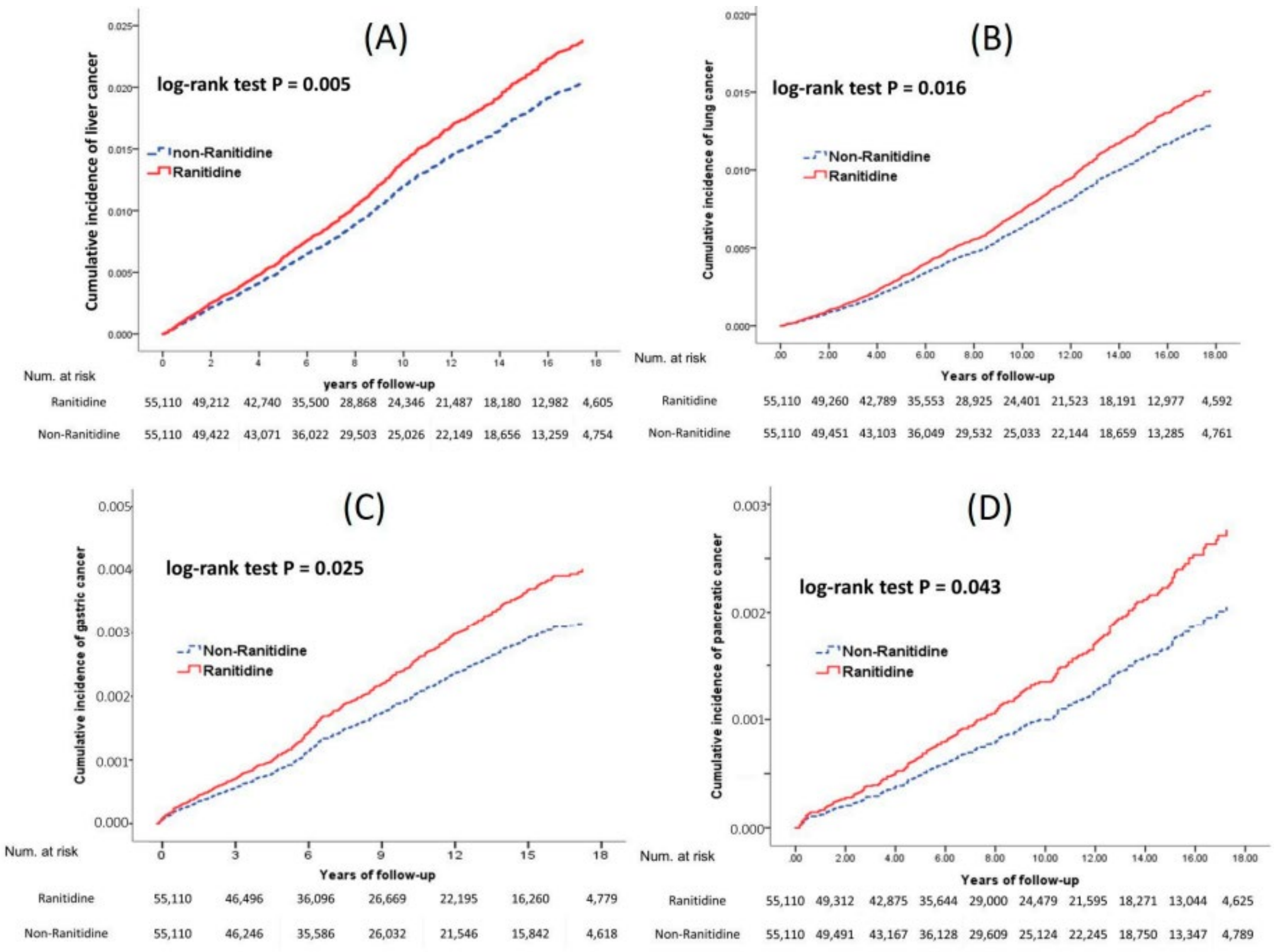
Stock-exchange announcement
For media and investors only

Issued: 9 October 2024, London UK

Statement: Zantac (ranitidine) litigation – settlement agreements reached

- GSK to resolve 93% (approximately 80,000 cases) of U.S. state court Zantac product liability cases for up to $2.2 billion
- Separate settlement of *qui tam* complaint for $70 million
- Settlements agreed with no admission of liability
- No change to GSK's growth agenda or investment plans

More publications appearing that correlate cancer incidence with prolonged ranitidine consumption:

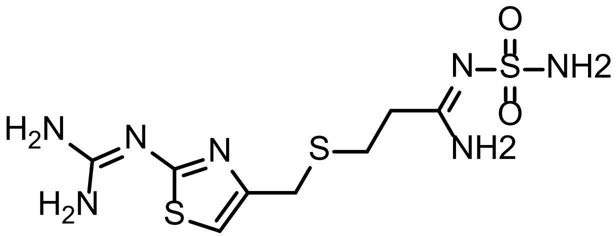


Wang, C.H. *et al.; Int. J. Environ. Res. Public Health* **2022**, *19*(19), 12469

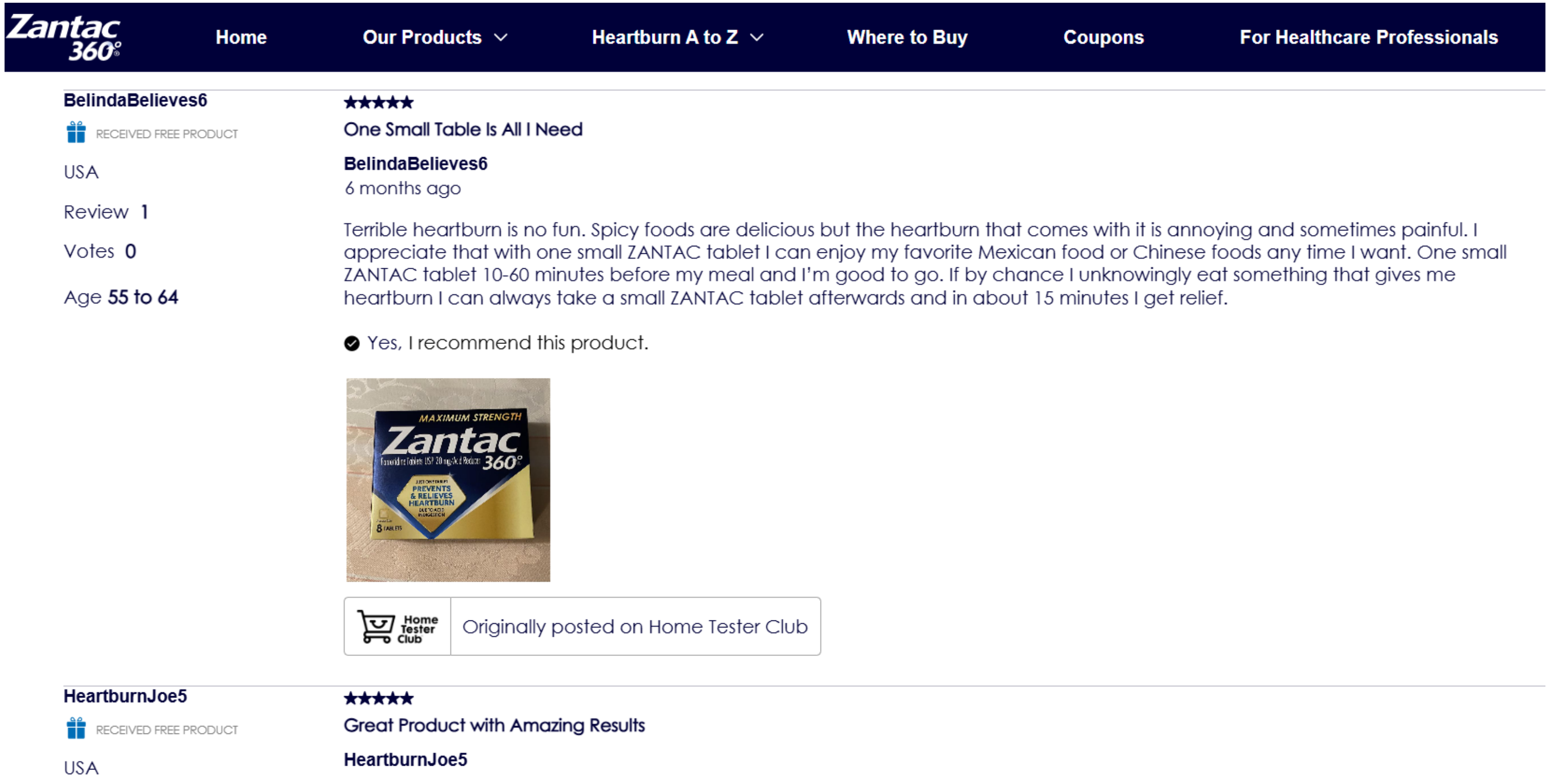
Future of Zantac

Currently, all ranitidine formulations are no longer available over-the-counter, effectively ending Zantac…

Except for the rebranded Zantac 360 released in September 2021 by Sanofi

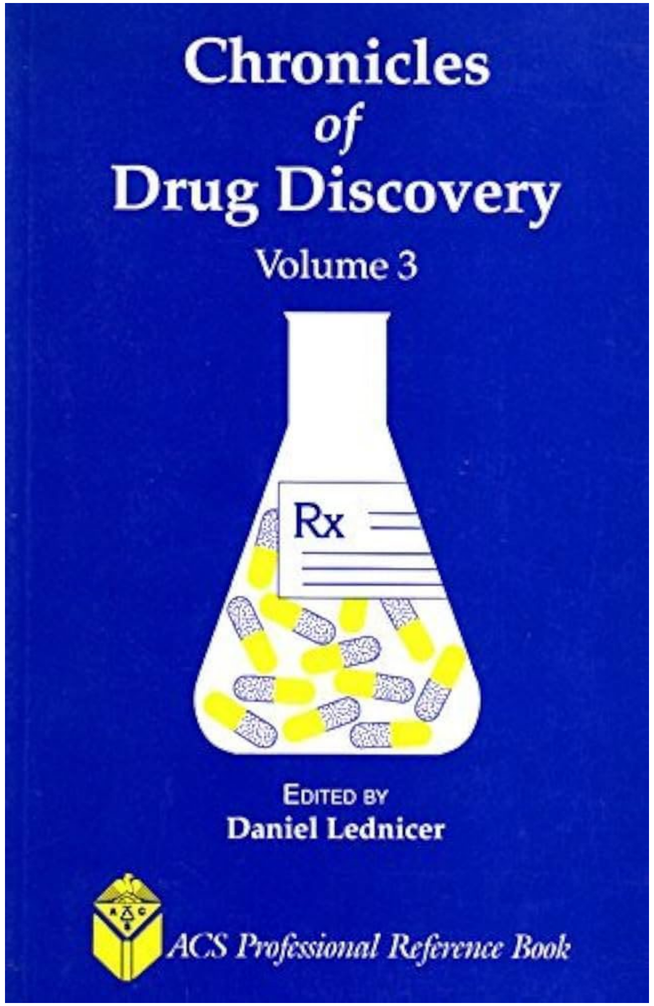


Zantac 360 website seems to have great reviews at the moment:

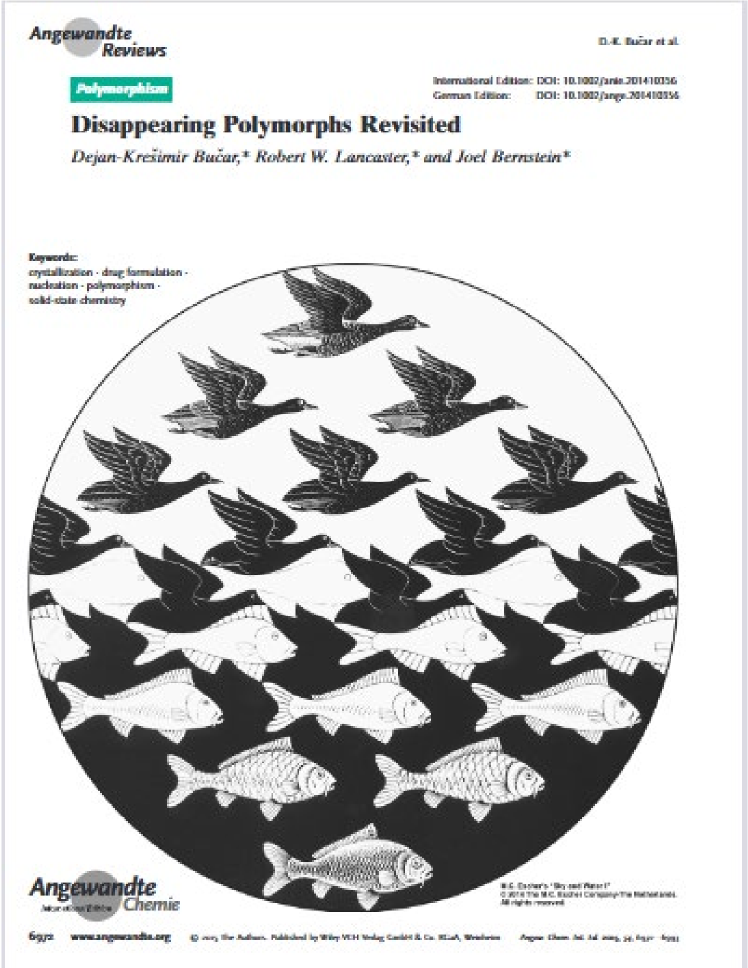


Further Reading

Detailed history of Ranitidine from worker John Bradshaw



Minireview covering several examples of lost polymorphic forms


Angewandte Reviews

D.-K. Bučar et al.

Polymorphism

International Edition: DOI: 10.1002/anie.201410356
German Edition: DOI: 10.1002/ange.201410356

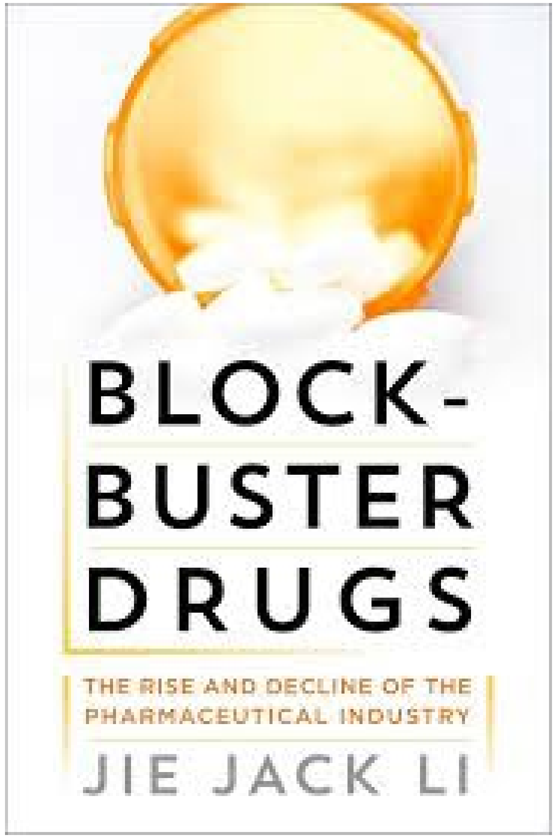
Disappearing Polymorphs Revisited

Dejan-Krešimir Bučar,* Robert W. Lancaster,* and Joel Bernstein*

Keywords:
crystallization · drug formulation · nucleation · polymorphism · solid-state chemistry

Angewandte Chemie

Fun read about cimetidine, ranitidine, and other influential pharmaceuticals



Bucar, D. J.; *et. al. Angew. Chem. Int. Ed.* **2015**, *54*, 6972.

Questions?