

Molecular bismuth compounds, a panacea for human disease?

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Main Group Elements and Medicine

Table 1
Biological activities of tellurium-based compounds.

Compounds	Biological activity	Reference
AS101	Anti-inflammatory activity	[10–13]
	Anti-viral activity	[14,15]
	Chemosensitization of cancer cells	[16]
	Prevention of chemotherapy induced toxicity	[17]
SAS	Anti-angiogenic activity	[18]
Organotelluroxetane RF-07	Anti-epileptic activity	[19]
3-Ethyl-3'-methyl-thiatelluracarboxyanine iodide	Anti-tumor activity	[20]
Unsymmetrical diorganyl-tellurium dichlorides	Bacteriocidal effect against Gram-negative bacteria	[21]
Chloro-telluroxetane	Anti-viral activity	[22]
Bis-vinyl organotellurane	Anti-oxidant activity	[23]
Diaryl tellurides	Anti-oxidant activity	[23]
NDBT	Anti-oxidant activity	[23]
Sulfonic acid-derived organotelluriums	Anti-parasitic activity	[24]

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Autoimmunity Reviews 13 (2014) 1230–1235

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

The effect of the novel tellurium compound AS101 on autoimmune diseases

Gilad Halper, Benjamin Sredni *

C.A.R. Institute, The Seldin AIDS and Immunology Research Center, The Mina & Everard Goodman Faculty of Life Sciences, Bar-Ilan University, Ramat-Gan 52900, Israel

Bismuth and Medicine

gastric and duodenal ulcers:



De-Nol®
(coll-Bi subcitrate)



Pepto-Bismol®
(Bi subsalicylate)



Pylorid®
(rantidine Bi citrate)

262 or 524 mg/ml

Main Group Elements and Medicine

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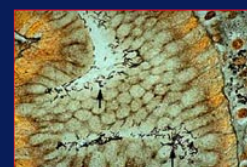
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Helicobacter pylori

Harms stomach lining

Stimulates immune response

Inflammation



http://www.pcsq.org.uk/html/dis_helicobacter.html

Copyright: Luke Marshall, www.hpylori.com.au

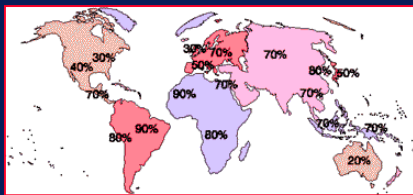
C & N News, October 10, 2005



Bismuth compounds and cancer

Bismuth compounds: **pro-drugs**

Helicobacter pylori



<http://www.helico.com/>

Bismuth compounds and cancer

Bismuth compounds: **pro-drugs**

H.p. causative agent for gastrointestinal cancers

WHO: class 1 carcinogen

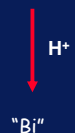
Mechanism of action (?):

Helicobacter pylori :



IPNET.LAB
The Interactive Pathology Laboratory

Bismuth subsalicylate



Inactivates F1-ATPase

Binding to transferrin and lactoferrin

Bismuth compounds and cancer

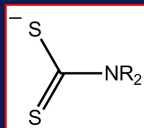
Bismuth compounds: **pro-drugs**

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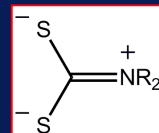
Combine bismuth with 'useful' thiols

Dithiocarbamates in biology



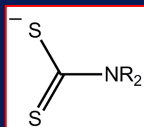
Dithiocarbamates in biology

Significant contribution of:



- a very effective chelator for metals

Dithiocarbamates in biology



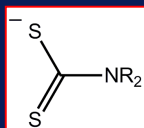
Radiation therapy: inhibition of SOD

Metal dithiocarbamates in medicine

Cu:	Wilson's disease
Ru:	anti-viral
Sn:	anti-microbial
Fe:	anti-HIV
Pt, Pd, Sn & Au:	anti-tumour potential

Hogath (2012)

Dithiocarbamates in biology



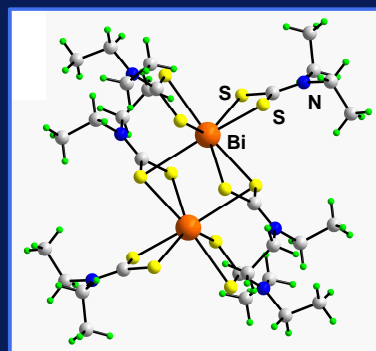
Radiation therapy: inhibition of SOD

Anti-cancer effects:

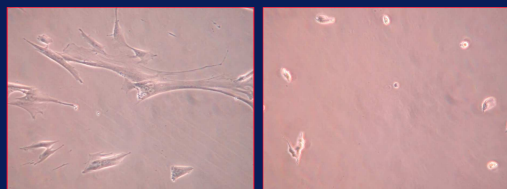
reduces alkylation of DNA

combination therapy with cisplatin

Dimeric structure of $\{\text{Bi}(\text{S}_2\text{CNEt}_2)_3\}_2$



MRC-5 Cells



normal

treated

Taxol (Paclitaxel®)

Natural product:
Pacific Yew



Six 100 year old trees / one patient
Ceased harvesting 1993

<http://www.research.fsu.edu/researchr/fall2002/taxol.html>

Cytotoxicity (ID₅₀: ng/ml):

	IGROV-1	MCF-7
cisplatin	169	699
DOX	60	10
MTX	7	18
ETO	580	2594
Bi(dedtc)₃	< 3.2	4
TAX	< 3.2	< 3.2

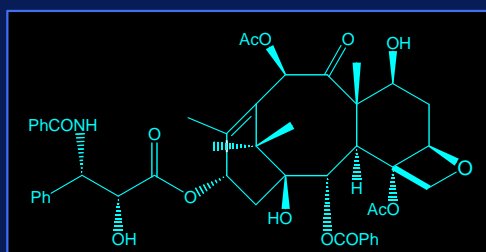
Synthesis of Taxol (Paclitaxel®)

Semi-synthetic route:
taxane from English
yew tree - 35% yield



ChemEngNews 2003 Sept. 15th

Taxol (Paclitaxel®)



Ovarian & breast cancers, Kaposi's sarcoma,
non-small-cell lung cancer

Synthesis of Taxol (Paclitaxel®)

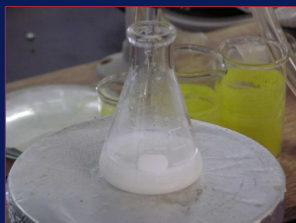
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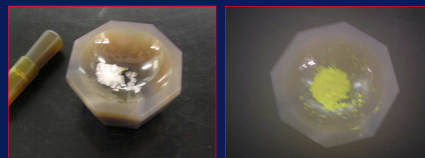
Multi-step organic synthesis
e.g. Holton synthesis: 40 steps - 2% yield

ChemEngNews 2003 Sept. 15th

Preparation of $\{\text{Bi}(\text{S}_2\text{CNEt}_2)_3\}_2$



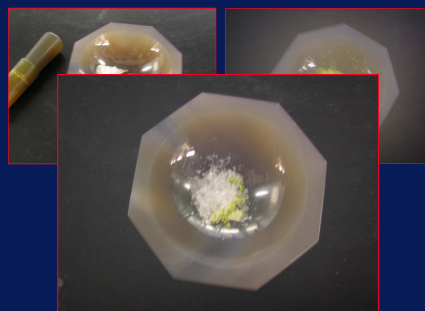
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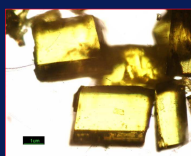
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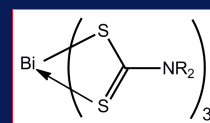


Preparation of $\{\text{Bi}(\text{S}_2\text{CNEt}_2)_3\}_2$



Structure/activity relationship

Alkyl chain	$\text{Me} < \text{Et} > \text{Pr} > \text{Bu}$
Branching	$\text{Pr} > \text{Pr} \& \text{Bu} > \text{Bu}$
Ring	$n = 4 > n = 7$
Aromatic	inactive



Maximum Tolerated Dose - Balb/C mice

Four to five weeks old

Male and Female

Controls -
20 day max.

via intraperitoneal
injection (i.p.)



Anti-tumour activity - Balb/C Nude mice



Maximum Tolerated Dose - Balb/C mice

$\text{Bi}(\text{S}_2\text{CNEt}_2)_3$: 7 mg Bi / kg

$\text{Bi}(\text{S}_2\text{CNBu}_2)_3$: > 50 mg Bi / kg

Oral administration

$\text{Bi}(\text{S}_2\text{CNEt}_2)_3$: ~ 50 mg Bi / kg

Anti-tumour activity - Balb/C Nude mice



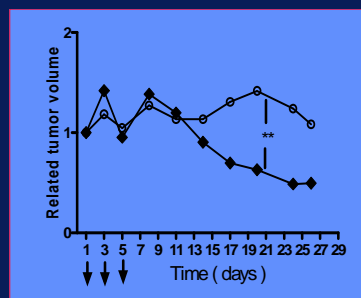
MTD - Balb/C mice
- Ovar: Ovarian cancer

MTD = 7 mg Bi / kg

ID_{50} = < 3.2 ng Bi / kg

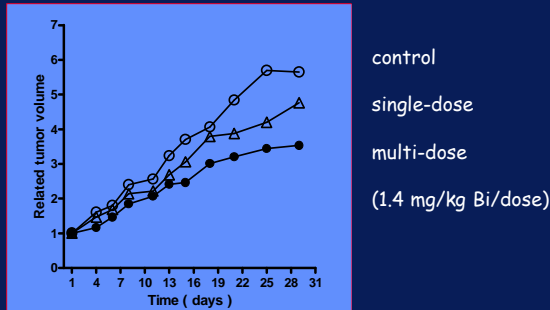
"Therapeutic index"
= > 2.2×10^6

Anti-tumour activity: OVCAR

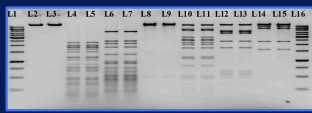
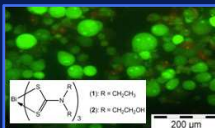


TWI: 54%
(day 26)

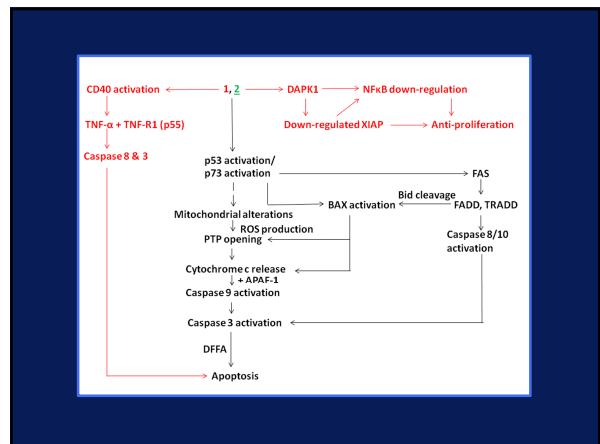
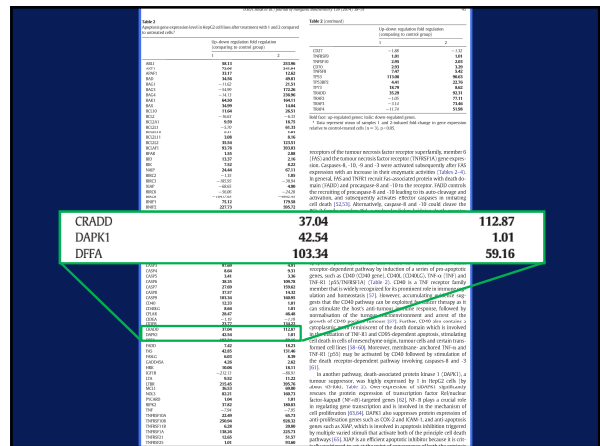
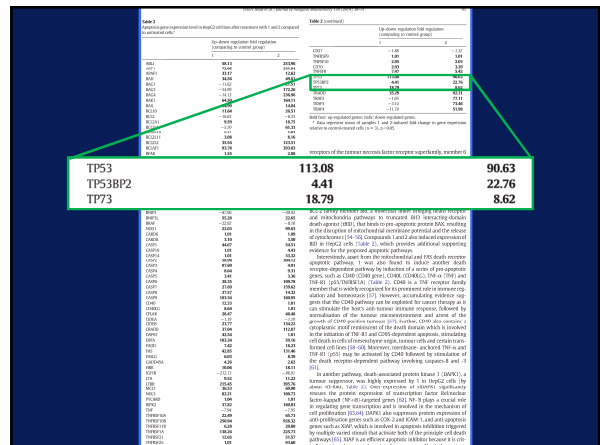
Anti-tumour activity: HT-29

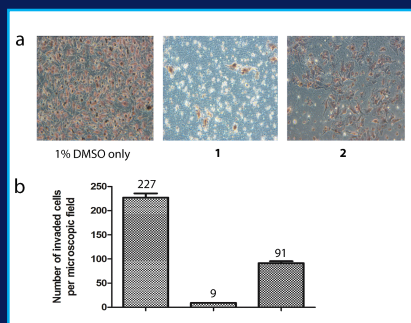


HepG2 cell death: apoptosis

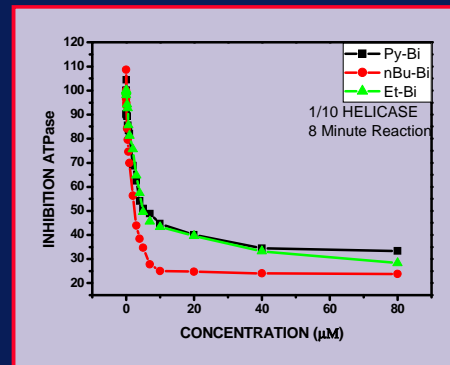


Membrane permeability, DNA fragmentation, caspase activities and PCR-array analysis indicate extrinsic and intrinsic pathways





Cell cycle analysis, ROS, cytochrome C, cell invasion...



Sun Hongzhe *et al.*

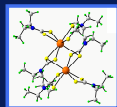
Killing *Helicobacter pylori*

MIC₉₀ (μg/ml)

Average of 16 strains



Et	N(CH ₂) ₄	n-Bu	BSS
4	8	256	16



with A/Prof Ho Bow & Sook Yin Lui

Anti-bacterial activity



Bactericidal against *Streptococcus pneumoniae*

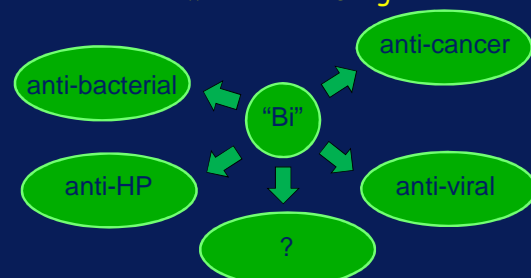
Avian Flu Severe Acute Respiratory Syndrome



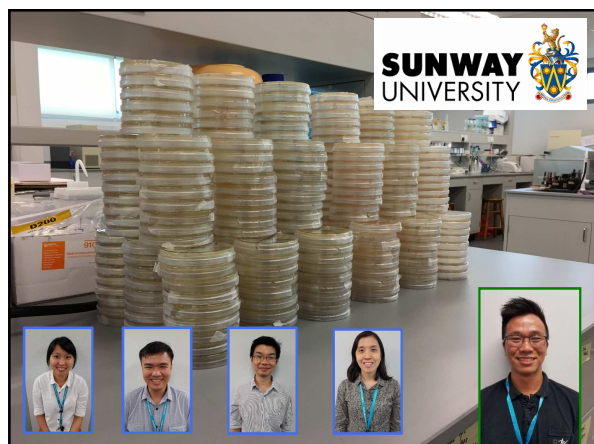
<http://www.smh.com.au>

<http://www.gerbusters.com.sg>

Bismuth-Based Drugs



Exciting potential for medicine with important advances waiting to be made!



Announcement



7th Asian Conference on Coordination Chemistry (ACCC7)
22-26 July 2019 / Kuala Lumpur, Malaysia
(Organised by Institut Kimia Malaysia)

You are welcome to visit the conference's website at www.accc7.org.my for updates on ACCC7 or you can email us at accc7@ikm.org.my for further details.