Fomepizole: An Overview

D. Nagavalli*[1],
M.Pharm, Ph.D., Professor & H.O.D,
Department of Pharmaceutical Chemistry,
Adhiparasakthi College of Pharmacy,
Melmaruvathur, Tamil Nadu, India.

P. Nanthagopal [2]
Department of Pharmaceutical Chemistry,
Adhiparasakthi College of Pharmacy,
Melmaruvathur, Kancheepuram Distric,
The Tamil Nadu Dr. M.G.R Medical University
Chennai-28, Melmaruvathur - 603319, Tamil Nadu, India

Abstract:- **A competitive ADH inhibitor is 4-methylpyrazole, also known as foamepizole. It has been demonstrated in vitro that foamepizole [blocks alcohol dehydrogenase enzyme activity in the liver of canines, primates, and humans].Fomepizole is prescribed as an antidote for methanol or ethylene glycol poisoning or for use in cases of suspected methanol or ethylene glycol consumption, either alone or in conjunction with hemodialysis. When a patient has metabolic acidosis and a high Osmolar gap, it should be administered if toxic ethylene glycol or methanol intake is known or suspected to have taken place. Headache (14%), nausea (11%), dizziness, increased sleepiness, and unpleasant taste/metallic taste were the side effects that were described as being drug-related or having no known association. The concurrent use of fomepizole and medications that either increase or inhibit cytochrome P450 may result in reciprocal interactions. Antizol is recommended as an antidote for methanol or ethylene glycol poisoning, or for use in cases of suspected methanol or ethylene glycol consumption, either alone or in conjunction with hemodialysis.**

Key Words:- *Antidotes, Fomepizole, ADH Inhibitor.*

I. INTRODUCTION

Pyrazoles are aromatic heterocycles that contain two nitrogen atoms.

A medicine called fomepizole (4MP), a derivative of the drug pyrazole, has been suggested as an antidote for methanol and ethylene glycol poisoning.

4-Methylpyrazole is a particular antidote for the treatment of ethylene glycol poisoning and is sold under the brand name Antizol® (fomepizole) by Orphan Medical, Inc. It functions by preventing the enzyme alcohol dehydrogenase from converting the generally non-toxic ethylene glycol into the toxic metabolites that lead to kidney damage and metabolic acidosis.

- Alcohol dehydrogenase, the first enzyme in the metabolism of ethanol and other alcohols, is very competitively inhibited by the compound 4-methylpyrazole, or foamepizole. After consuming methanol or ethylene glycol, fomepizole can stop the development of hazardous metabolites. Furthermore, the need for dialysis may be avoided by administering

fomepizole for ethylene glycol or methanol poisoning before a substantial acidosis manifests. Since the release of fomepizole, ethanol likely won't be used to treat the majority of patients with ethylene glycol or methanol poisoning. This is especially true for instances involving young children, people using disulfiram, people who have taken many drugs or have altered their awareness, people who have pancreatitis or active liver disease, and hospitals without the lab resources to do quick ethanol tests (for treatment monitoring). Despite the high cost of fomepizole's acquisition, economic models have revealed that it could be more economical than ethanol.

- The primary mode of elimination of foamepizole is zero-order kinetics, however within two to three days, auto stimulation of cytochrome P-450 metabolism can occur. The medication can be dialyzed. Although it has been effectively used with PO administration and is well absorbed, this method is not authorized in the United States.

- A trustworthy history of consuming a dangerous amount but no measurements of blood levels are available (when used experimentally, this enables a 12-hour "window" after one dose to assess the patient);Metabolic acidosis and an unexplained elevated osmol gap; or Serum methanol or ethylene glycol concentration of 20 mg/dL or higher.

- Propylene glycol, diethylene glycol, triethylene glycol, glycol ethers (such as ethylene glycol ethyl ether, ethylene glycol butyl ether), and 1,4-butanediol are among the other compounds that alcohol dehydrogenase may break down into hazardous metabolites.

- All of these chemicals don't meet the requirements for fomepizole treatment or provide sufficient proof for better results. To eliminate the potentially dangerous parent chemical and concurrently stop the development of toxic metabolites, fomepizole treatment is said to be beneficial in case reports of poisonings from some of these other glycols (such as propylene glycol and diethylene glycol).

> *Objectives:*

- List the Fomepizole uses that the FDA has authorized.
- What is the Fomepizole's mode of action?.
- Review the side effects and warnings for taking foamizole.
- Summarize the interprofessional team's tactics for enhancing communication and care coordination in order to progress the use of the drug Fomepizole and enhance results.
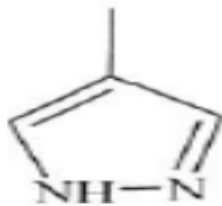- Docking –Study of Fomepizole.

Fig 1Fomepizole

> *Fomepizole – Physico -Chemical Properties*

Molecular Framework   Hetrocyclic Compound

Stereochemistry   ACHIRAL

Synonym   4-methylpyrazol, 4-carboxypyrazole, 4-hydroxymethylpyrazole

State	**Liquid**
Water Solubility	**559.0 mg/mL**

- *Solubility:* Fomepizole is soluble in water and very soluble in ethanol, diethyl ether, and chloroform.

pKa (Strongest Acidic)	15.82
pKa (Strongest Basic)	2.63
Hydrogen Acceptor Count	1
Hydrogen Donor Count	1
Polar Surface Area	28.68 Å^2
Refractivity	24.79 m3·mol-1
Polarizability	8.58 Å^3
Number of Rings	1
Molar Volume:	**77.2 ± 3.0 cm^3**
Parachor:	**198.6 ± 4.0 cm^3**
Index of Refraction:	**1.523 ± 0.02**
Surface Tension:	**43.7 ± 3.0 dyne/cm**

Density:	**0.99 g/cm^3**
Melting point (°C)	**25 °C (77° F)**
Boiling Point	**204 - 207°C**
Store	**20° to 25° C (68° to 77° F)**
Formulations:	**Injection**

- *Stability:*

Fomepizole For at least 24 hours, diluted in 0.9% sodium chloride injection or 5% dextrose injection stays stable and sterile.

When kept at room temperature or in a refrigerator. Preservatives are not present in Antizol®.

Maintain sterile conditions thus, and use within 24 hours of dilution. Use should be avoided if a solution exhibits haziness, particle debris, precipitate, discoloration, or leaking.

II.   CLINICAL PHARMACOLOGY

> *Mechanism of Action:*

- Alcohol dehydrogenase is competitively inhibited by Antizol® (fomepizole). Acetaldehyde is produced when ethanol is oxidized by the enzyme alcohol dehydrogenase.
- Alcohol Dehydrogenase also catalyzes the first stages of methyl alcohol and ethylene glycol's metabolism into their hazardous by products.
- The primary ingredient in the majority of antifreezes and coolants, ethylene glycol, is broken down into glycoaldehyde, which then through a series of consecutive oxidations to produce glycolate, glyoxylate, and oxalate.
- The primary metabolic by products responsible for the metabolic acidosis and renal damage seen in ethylene glycol toxicosis are glycolate and oxalate. Ethylene glycol has a fatal dosage of around 1.4 mL/kg in humans.
- Alcohol Dehydrogenase slowly converts methanol, the major ingredient in windshield wiper fluid, to formaldehyde, which is then oxidized by formaldehyde Dehydrogenase to produce formic acid.
- The metabolic acidosis and visual abnormalities (such as reduced visual acuity and probable blindness) linked to methanol poisoning are predominantly brought on by formic acid.
- Methanol is roughly 1-2 mL/kg deadly in humans. It has been demonstrated in-vitro that the livers of canines, primates, and humans all have the alcohol dehydrogenase enzyme. In vitro, alcohol dehydrogenase is 50% inhibited by fomepizole at a concentration of around 0.1 mol/L.
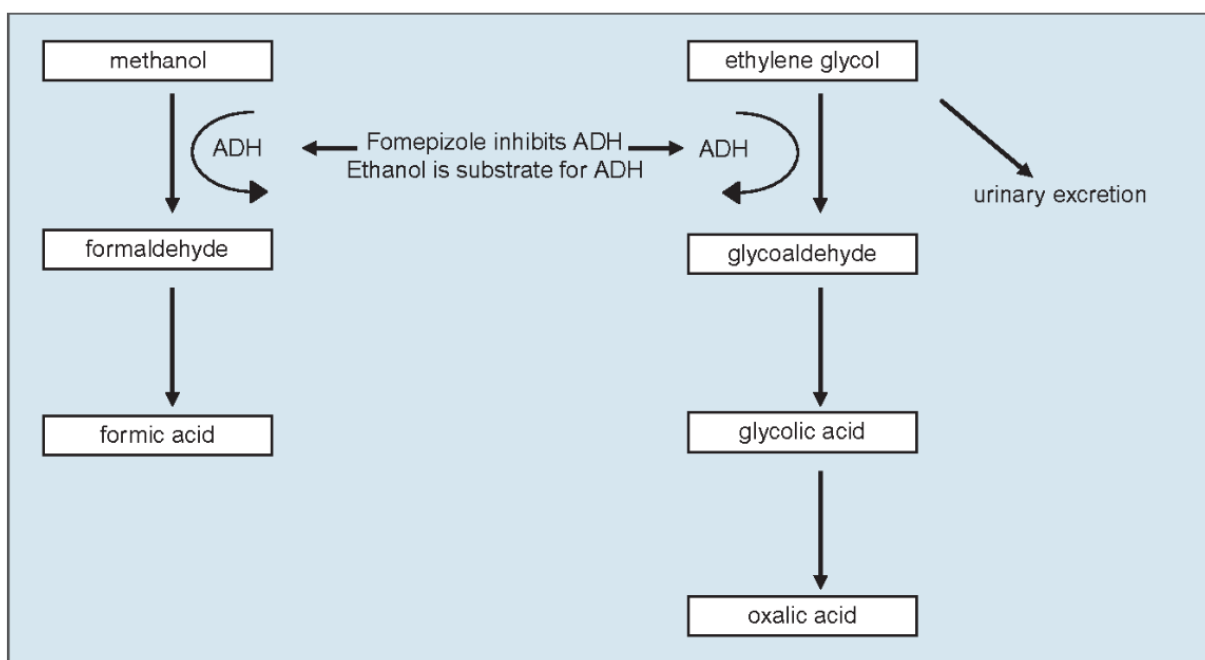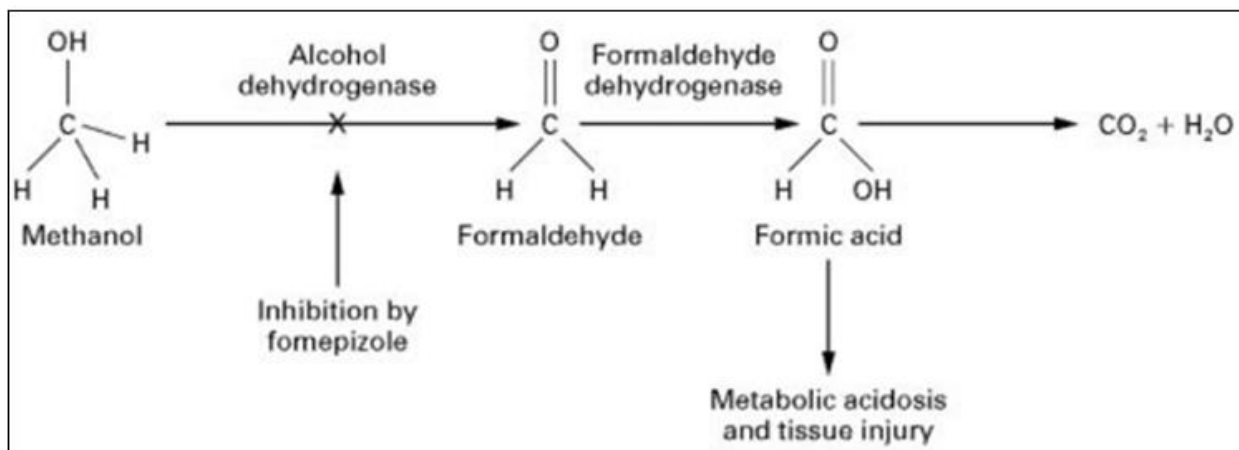
Fig 2 Mechanism of Action

- In a trial with dogs given a deadly dosage of ethylene glycol, three animals were given either the treatment (control group), ethanol, or foamizole. The three animals left untreated progressively become obtunded and moribund before passing away. All three dogs experienced extensive renal tubular injury at necropsy.

- Three hours after consuming ethylene glycol, fomepizole or ethanol reduced the metabolic acidosis and avoided renal tubular damage that is related to ethylene glycol intoxication.

- The conversion of methanol to formate, which is likewise mediated by alcohol dehydrogenase, has been shown to be inhibited by Antizol® at plasma concentrations of around 10 mol/L (0.82 mg/L) in monkeys.

- Based on these findings, Antizol® concentrations in humans have been targeted between 8 and 24 mg/L (100 to 300 mol/L) to ensure appropriate plasma concentrations for the efficient inhibition of alcohol dehydrogenase.

- The rate of elimination of moderate amounts of ethanol, which is likewise processed by the enzyme alcohol dehydrogenase, was greatly slowed down in healthy volunteers after oral administration of Antizol® (10–20 mg/kg).

III. OVERDOSAGE

Healthy volunteers who received 50 and 100 mg/kg dosages of Antizol® (with plasma concentrations of 290-520 mol/L, 23.8-42.6 mg/L) reported experiencing nausea, dizziness, and vertigo.

These doses are 3-6 times the recommended dose.

Most participants saw a brief dose-dependent CNS response, although one person experienced one that lasted up to 30 hours. Hemodialysis may be helpful in treating cases of overdosing with Antizol® since it is dialyzable.

IV. DOSAGE AND ADMINISTRATION

Table 1Fomepizole Dose (mg/kg Weight)

Fomepizole dose (mg/kg body weight)					
Loading dose	2nd dose (12 hours)	3rd dose (24 hours)	4th dose (36 hours)	5th dose (48 hours)	6th dose (60 hours)
15	10	10	10	7.5 to 15	5 to 15

➢ When dilution or administration of Antizol, avoid using polycarbonate syringes or needles that contain polycarbonate (including polycarbonate filter needles). The integrity of the polycarbonate-containing syringe and/or needle component may be compromised due to the interaction of foamepizole with polycarbonate.

➢ *Treatment Guidelines:*

- If ethylene glycol or methanol poisoning is left untreated, the normal course of the poisoning causes a buildup of hazardous metabolites, including formic acid (in the case of methanol overdose) and glycolic and oxalic acids (in the case of ethylene glycol poisoning).
- **These metabolites have the potential to cause mortality, acute tubular necrosis, calcium oxaluria, metabolic acidosis, nausea, vomiting, convulsions, stupor, and coma.**
- Because ethylene glycol and methanol concentrations in the blood decrease as they are converted to their respective metabolites, diagnosing these poisonings may be challenging. Therefore, serum electrolyte (anion gap) and/or arterial blood gas measurement results for both ethylene glycol and methanol concentrations, as well as acid base balance, should be regularly monitored and utilized to direct treatment.
- Using alcohol dehydrogenase inhibitors like Antizol®, the generation of harmful metabolites is prevented, and metabolic imbalances are corrected. Patients with substantial metabolic acidosis, renal failure, or high ethylene glycol or methanol concentrations (> 50 mg/dL).
- To get rid of methanol or ethylene glycol and their respective harmful byproducts, hemodialysing should be explored.

- *Treatment with Antizol®:*
On the basis of the patient's medical history, anion gap metabolic acidosis, increased osmolar gap, visual disturbances, oxalate crystals in the urine, or a documented serum ethylene glycol or methanol concentration greater than 20 mg/dL, start Antizol® treatment right away if you suspect methanol or ethylene glycol ingestion.

- *Hemodialysis:*
In the event of renal failure, considerable or increasing metabolic acidosis, or a determined ethylene glycol or methanol concentration of higher than or equal to 50 mg/dL, hemodialysis should be taken into consideration in addition to Antizol®.

Dialysis is necessary for patients to treat metabolic problems and bring ethylene glycol levels down to 50 mg/dL. Antizol® Treatment Termination: When ethylene glycol or methanol levels are undetectable or have dropped below 20 mg/dL, treatment with Antizol® may be stopped if the patient is asymptomatic and has a normal pH.

- *Dosing of Antizol®:*
After a loading dosage of 15 mg/kg, the patient should get doses of 10 mg/kg every 12 hours for 4 doses, then 15 mg/kg every 12 hours after that, continuing until the patient is asymptomatic and the ethylene glycol or methanol concentrations are undetectable or have been lowered to 20 mg/dL.

Each dosage has to be given slowly over the course of 30 minutes through intravenous infusion (see Administration). With renal dialysis, what dosage? When undergoing hemodialysis, the dosage of Antizol® (fomepizole) Injection should be raised to every four hours.

V. HOW SUPPLIED

For intravenous usage, Antizol® is provided as a sterile, preservative-free solution as follows: provided in bundles containing either one or four vials. Fomepizole is included in 1.5 mL (1 g/mL) of each vial.

Table 2 Antizol® Dosing in Patients Requiring Hemodialysis

DOSE AT THE BEGINNING OF HEMODIALYSIS	
If <6 hours since last Antizol® dose	**If ≥6 hours since last Antizol® dose**
Do not administer dose	Administer next scheduled dose

DOSING DURING HEMODIALYSIS
Dose every 4 hours

DOSING AT THE TIME HEMODIALYSIS IS COMPLETED	
Time between last dose and the end of hemodialysis	
<1 hour	Do not administer dose at the end of hemodialysis
1–3 hours	Administer 1/2 of next scheduled dose
>3 hours	Administer next scheduled dose

MAINTENANCE DOSING OFF HEMODIALYSIS
Give next scheduled dose 12 hours from last dose administered

➢ *Drug Interactions:*

- When administered to healthy volunteers in moderate quantities, oral doses of Antizol® (10–20 mg/kg), which inhibit alcohol dehydrogenase, markedly decreased the rate of elimination of ethanol (by around 40%).
- The same process also caused ethanol to reduce Antizol®'s rate of elimination (by around 50%). Concurrent use of Antizol® with medicines that stimulate or inhibit the cytochrome P450 system (such as phenytoin, carbamazepine, cimetidine, and ketoconazole), though this has not been researched, may result in reciprocal interactions. Carcinogenesis, Mutagenesis, and Fertility Impairment There have been no extensive animal studies to assess the possibility for cancer.
- In the absence of metabolic activity, the Escherichia coli tester strain WP2uvrA and the Salmonella typhimurium tester strain TA102 both produced good Ames test results. The in vivo mouse micronucleus test showed no sign of a clastogenic impact. When fomepizole (110 mg/kg) was given orally to rats for 40 to 42 days, the testicular mass reduced (by around 8%).
- Based on surface area (mg/m2), this dosage is roughly 0.6 times the daily exposure limit for humans. Rats treated with ethanol or fomepizole alone had similar reductions.
- In comparison to rats treated exclusively with either fomepizole or ethanol, the loss of testicular mass was much larger when fomepizole and ethanol were administered (around a 30% reduction).

- *Pregnancy:*
  Animal reproductive studies with the drug fomepizole have not been done, according to pregnancy category C.

- Additionally, it is unknown if Antizol®, when given to pregnant women, might damage the fetus or impact a woman's ability to reproduce. Pregnant women should only be administered Antizol® when absolutely necessary.

VI. ADVERSE REACTIONS

- In the 78 patients and 63 healthy volunteers who received Antizol® (fomepizole) Injection, headache was the adverse event that was reported the most frequently (14%).
- Dizziness (6%), increased sleepiness (6%), and nausea (11%), as well as a metallic or off taste (6%).

The following additional negative effects were recorded in this population's 3% or less of people using Antizol®:

➢ *Body as a Whole:*

- Pain during Antizol® injection, inflammation at injection site, lumbago/backache, and hangover are some of the symptoms. Cardiovascular: Phlebitis, shock, hypotension, sinus bradycardia, bradycardia, phlebosclerosis, and tachycardia.

- *Gastrointestinal:* diarrhea, transitory transaminitis, dyspepsia, heartburn, and reduced appetite.

➢ *Hemic /Lymphatic:*

Anemia, lymphangitis, disseminated intravascular coagulation, and eosinophilia/ hypereosinophilia Lightheadedness, seizure, agitation, feeling inebriated, face flushing, vertigo, nystagmus, anxiety, and "felt strange" are all signs of being nervous.

- Environmentally conscious respiratory: **pharyngitis and hiccups.**
- Skin/Appendages: rash and reactivity at the application site Additional Senses: Unusual odor, speech and vision abnormalities, momentary vision blur, and roar in the ear Urogenital: Anuria.

➢ *Pharmacokinetics:*

Even in individuals with normal renal function, the plasma half-life of Antizol® varies with dosage and has not been estimated.

➢ *Distribution:*

Antizol® quickly spreads throughout the body after intravenous administration.

The distribution's volume ranges from 0.6 L/kg to 1.02 L/kg.

➢ *Metabolism:*

Only 1-3.5% of the Antizol® (7–20 mg/kg oral and IV) given dosage was excreted unaltered in the urine in healthy volunteers, showing that metabolism is the primary mode of elimination. Antizol® in humans is mostly metabolized to 4-carboxypyrazole, which is eliminated in the urine in amounts between 80 and 85 percent of the dosage that was given.

The N-glucuronide conjugates of 4-carboxypyrazole and 4-hydroxymethylpyrazole, as well as 4-hydroxymethylpyrazole, are additional Antizol® metabolites that have been found in urine tests.

➢ *Excretion:*

Michaelis-Menten kinetics following acute dosages are the best way to describe the clearance of Antizol®, with saturable elimination happening at therapeutic blood concentrations [100-300 mol/L, 8.2-24.6 mg/L]. After roughly 30 to 40 hours, Antizol® significantly increases its clearance rate by quickly inducing its own metabolism through the cytochrome P450 mixedfunction oxidase system.

After enzyme induction, **elimination follows first-order kinetics**.

VII. PATIENT INSTRUCTION

➢ *Special Populations:*

- *Geriatric:*

There hasn't been enough research done on Antizol® (fomepizole) Injection to know if the pharmacokinetics are different for an elderly population.

- *Pediatric:*

There hasn't been enough research done on Antizol® to say whether or whether pediatric patients' pharmacokinetics are different.

- *Gender:*

Antizol® has not been thoroughly investigated to establish whether gender influences pharmacokinetics.

- *Renal Insufficiency:*

Antizol® metabolites are eliminated by the kidneys. There haven't been any conclusive pharmacokinetic studies to evaluate pharmacokinetics in people with renal impairment.
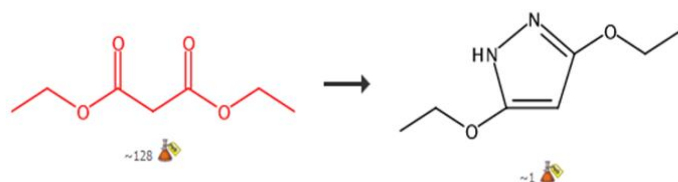
Referral number: 4721676 Antizol® is processed by the liver, although no conclusive pharmacokinetic studies have been carried out in individuals with hepatic illness.

VIII. SYNTHESIS OF FOMEPIZOLE
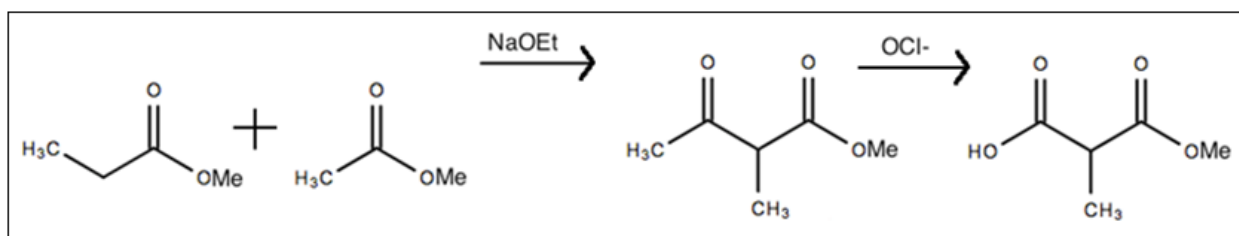
To begin, one would first create methylmalonic acid by creating the beta-ketoester, methyl acetopropionate, using a Claisen Condensation with methyl acetate and methyl propionate.

Then, one should be able to conduct a haloform reaction using hypochlorite to produce methyl malonic acid.

Stages	Notes	Yield
1.1 R: H₂N—NH₂ C:H₂SO₄, S:EtOH, 6 h, rt	solid-supported catalyst, green chemistry, sulfuric acid supported on zirconium n-propoxide nano catalyst used, reusable catalyst, Reactants: 1, Reagents: 1, Catalysts: 1, Solvents: 1, Steps: 1, Stages: 1 **Transformation:** 1. Formation of Nitrogen Heterocycles	85%

Similar to the reaction of methyl malonic acid with sulfuric acid, condensation of hydrazine acidified with sulfuric acid should lead to a pyrazole derivative.
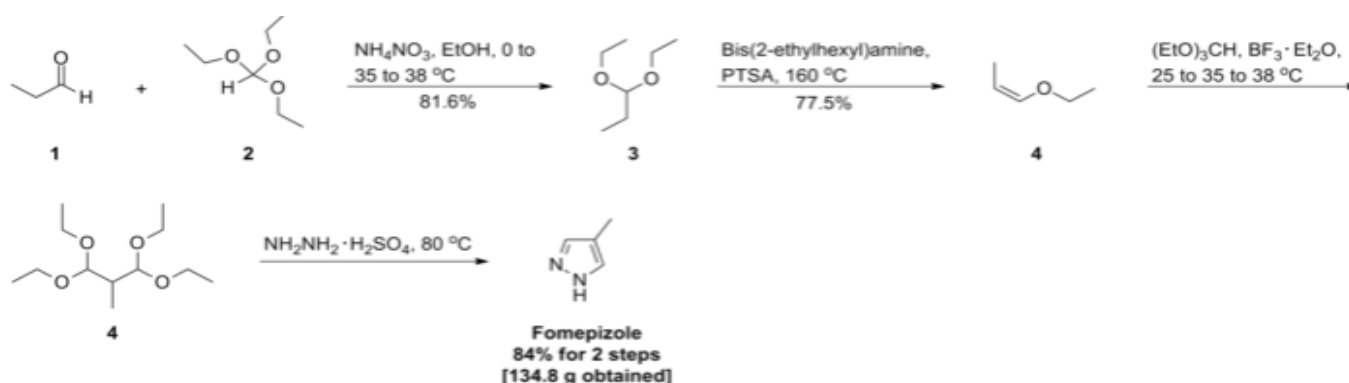
> *First step:*

Propionaldehyde and tri ethyl ortho- formate are interacted during the creation of 4-M P (FOMEPIZOLE), and the product is 1,1-diethoxypropane.

> *Second step:*

A catalyst made of an acid and an amine reacts neatly (without the use of a solvent) with the 1,1-diethoxypropane created in the first stage to create 1-ethoxy-l-propene (ethyl-1-propenyl ether).

> *Third step:*

Without distillation, this material is cleaned by washing and drying.

> *Fourth step:*

To create l,l,3,3-tetraethoxy-2-methyl propane ("TEMP"), the 1-ethoxy-l-propene from the third stage is combined with triethyl ortho-formate in the presence of boron trifluoride-diethyl etherate.

> *Fifth step:*

At high temperatures, the [TEMP from the third step reacts with hydrazine, a hydrazonium salt, or hydrazine hydrate to generate 4-methylpyrazole.]

The amount of acid needed in the second stage is very little; generally, 0.00015 to 0.008 mol, including 0.0002 to 0.006 mol, is used per mol of 1,1-diethoxypropane.

> *Hydrazine:*

To prevent yield losses due to incomplete reactions, hydrazine hydrate or a hydrazonium salt should ideally stay soluble in the reaction mixture. Because of this, a hydrazonium salt is frequently used.

The hydrazonium halides (fluoride, chloride, or iodide) and hydrazine hydrosulfate are acceptable hydrazonium salts. Typically, the temperatures used range from 70 to 85 °C, including 80 to 85 °C and 800 °C, for example.

> *Catalyst Using For FOMEPIZOLE Synthesis:*

The chosen acid normally has a pKa of 2.5, for example 2.2 or 2.0. The partly esterified derivatives of phosphoric acid, sulfuric acid, sulfuric acid hemiesters, and aliphatic or aromatic sulfonic acids are all acceptable acids.

Toluene and benzene sulfonic acids are particularly appropriate, while p-toluene sulfonic acid has shown to be extremely suited among the aromatic sulfonic acids.

Under the reaction circumstances, the amine and acid catalyst component shouldn't be flammable.

In light of this, the amine and acid should have a boiling point that is at least 10 degrees Celsius, generally at least 20 degrees Celsius, for instance 30 degrees Celsius, above the boiling points of the reaction products generated.

It is possible to employ primary, secondary, and/or tertiary aliphatic, cycloaliphatic, and aromatic amines, as well as heterocyclic compounds that include nitrogen, such as pyridines, piperidines, or quinolines.

Straight-chain and/or branched aliphatic amines are appropriate candidates.   `

Examples of amines include: **n-octyl, n-nonyl-, n-decyl-, n-dodecyl-, 2-ethylhexyl-, i- nonyl-, 3,5,5-trimethylhexyl-, di-n-butyl-, di-i-butyl-, di-amyl-, di-n-hexyl-, di-n-octyl-, di-2-ethylhexyl-, di-i-nonyl-, tri-n-propyl-, tri-n-butyl-, tri-n-pentyl-, tri-n-hexyl-, tri-n-octyl-, tri-2-ethylhexyl-, tri-n-nonyl-, tri-i-nonyl- and tri-n-decylamine.**

Isononyl amine, diamylamine, tri-n-butyl-amine, bis(2-ethylhexyl)amine, and di- Isononyl amine have proven particularly useful as the amine.

In the **fourth step, boron trifluoride-diethyl etherate (Et$_2$O-BF$_3$) acts as a catalyst.**

Table 3 Advantages & Disadvantages of Ethanol & Fomepizole

	ETHANOL	FOMEPIZOLE
Advantages	Available in clinical setting Extensive experience in the Netherlands Antidote in different alcohol poisonings Administration orally and intravenously	Minimal adverse effects Registered for ethylene glycol poisoning
Disadvantages	Dose calculations based on blood–alcohol levels Hospitalization in intensive care unit necessary during treatment Not officially registered as antidote	High costs Not available in all clinical settings Limited shelf life Not registered for methanol in the Netherlands Lack of experience in the Netherlands Little experience in other alcohol poisonings

Table 4 Doses of Ethanol & Fomepizole

	ETHANOL	FOMEPIZOLE
Loading dose:	$D_l = V_d \times B_w [C_t - C_m]$	$D_l = 15\ mg/kg \times B_w$
	D_l = loading dose [mg] V_d = volume of distribution [male 0.7 L/kg, female 0.6 L/kg] B_w = body weight [kg] C_t = target concentration ethanol [mg/L] C_m = measured concentration ethanol [mg/L]	D_l = loading dose [mg] B_w = body weight [kg]
Maintenance dose:	Dose per hour: $D_m = C_t \times V_{max} \times B_w/[K_m + C_t]$	Dose per 12 hours: $D_m = 10\ mg/kg \times B_w$ $D_{m'} = 15\ mg/kg \times B_w$
	D_m = maintenance dose [mg/h] V_{max} = maximum enzyme capacity [mg/kg.h] [adult, non-drinker: 75 mg/kg.h, chronic alcohol drinker 175 mg/kg.h] K_m = Michaelis-Menten-constant [138 mg/L]	D_m = maintenance dose [mg/12h] $D_{m'}$ = maintenance dose, after 60h [mg/12h]
Maintenance dose during haemodialysis:	Dose per hour: $D_{hd} = D_m + [Cl_d \times B_w]$	Dose per 4 hours: $D_{hd} = D_m$ $D_{hd'} = D_{m'}$ Dose per hour: $D_{hd\,ci} = 1\ mg/kg \times B_w$
	D_{hd} = maintenance dose during haemodialysis [mg/h] Cl_d = variable, dependent on artificial kidney and blood flow [mg/kg.h]	D_{hd} = maintenance dose during haemodialysis [mg/4h] $D_{hd'}$ = maintenance dose during haemodialysis, after 60h [mg/4h] $D_{hd\,ci}$ = maintenance dose during haemodialysis [mg/h]

IX. MONITORING OF PATIENTS

Throughout the experiment, every patient had a daily checkup and had heart monitoring.

- At baseline and afterwards at predetermined intervals, arterial blood gases, serum electrolytes, urea nitrogen, and creatinine were assessed.
- Urine was subjected to extensive toxicologic testing at the time of enrolment. Microscopical exams, complete blood counts, liver function tests, electrocardiograms, and urine analyses were carried out at the time of enrolment and every day throughout the research.
- At baseline and at specified intervals, spanning from 1 to 12 hours, until 24 hours after the plasma methanol content had dropped to below 20 mg per deciliter, plasma methanol, formic acid, ethanol, and fomepizole were tested.
- At specified intervals of two to four hours, the plasma concentrations of methanol, formic acid, and fomepizole were measured concurrently from the arterial and venous limbs of the dialyzer for patients who underwent hemodialysis.

X. TREATMENT PROTOCOL

The prescribed course of therapy included giving fomepizole along with clinically necessary intravenous infusions of glucose, electrolytes, and fluids.

All **patients received supplemental folate.**

If feasible, oxygenation was kept at a saturation level of more than 90%.

A loading dosage of 15 mg of fomepizole (Antizol, donated by Orphan Medical, Minnetonka, Minnesota) was given intravenously, and then bolus doses of 10 mg of fomepizole per kilogram were given every 12 hours after that.

To offset the onset of fomepizole metabolism, the bolus dosages were raised after 48 hours to 15 mg per kilogram, given every 12 hours.
.

Following the delivery of the loading dosage of fomepizole, patients received hemodialysis for any of the following reasons: an arterial pH that could not be maintained at 7.3 or higher; a serum methanol concentration of more than 50 mg per deciliter (15.6 mmol per liter); any of a predetermined set of visual symptoms and signs; a serum methanol concentration that declined at a rate of less than 0.05 unit per minute; an arterial pH that initially was less than 7.1; a decrease in the arterial pH of more than 0.05 unit; or a serum bicarbonate concentration of more than 5 mmol.

> *Fomepizole- Helps Overcome Antibiotic-Resistant Pneumonia in Mice*

Streptococcus pneumoniae has become the fourth-leading cause of mortality related to antibiotic resistance due to increases in multidrug resistance.

Researchers present a novel strategy to combat pneumonia brought on by infections with an opportunistic lung pathogen in a paper published in PLOS Biology: interference with the bacteria's fermentation metabolism. This might provide a potential therapeutic choice in the pressing requirement to identify fresh tactics for battling drug-resistant S. pneumoniae.

Using mice infected with a virulent, multidrug-resistant strain of S. pneumoniae as a proof-of-concept, University of Alabama at Birmingham researchers demonstrated that administering an existing medication—one that has already been approved by the US Food and Drug Administration to treat methanol poisoning—in combination with the antibiotic erythromycin significantly reduced disease. The combo treatment decreased bacterial load in the heart and spleen by 100 and 700 times, respectively, and by 95% in the lungs. Erythromycin by itself, or the FDA-approved medication alone, had no impact.

The FDA-approved medication, foamepizole, prevents bacteria from producing the enzyme alcohol dehydrogenase. The mice were given intratracheal infections with the highly erythromycin-resistant multidrug-resistant clinical isolate S. pneumoniae serotype 35B strain 162-5678. Notably, clinical reports have identified the S. pneumoniae 35B serotype as a developing multidrug-resistant serotype. The mice received a single injection of erythromycin with or without fomepizole 18 hours after infection.

The effectiveness of erythromycin and other antibiotics in vivo may be greatly increased by fumepizole or other medications that block bacterial metabolism, respectively.

This proof-of-concept experiment was built upon a vast base of basic research.

S. pneumoniae generates energy through fermentation and glycolysis. Pyruvate is transformed into lactate, acetate, and ethanol during fermentation, while NADH is oxidized to produce NAD+, which is necessary for glycolysis. Accordingly, it is essential for continuous energy generation, bacterial growth, and survival to maintain an accessible NAD+ pool, which is required for redox equilibrium.

Five enzymes involved in fermentation and the synthesis of NAD+ were altered in S. pneumoniae mutants, and it was discovered that the mutants' metabolisms were generally affected. The intracellular pool of ATP, the energy molecule of living cells, was drastically reduced in two of the mutants, one for lactate dehydrogenase and one for alcohol dehydrogenase. The

declines in the other three mutants were notable but less extreme.

The mutants' NAD+/NADH redox imbalances often prevented S. pneumoniae from producing its virulence components and from colonizing the mouse nasopharynx. As tested with three antibiotics, including erythromycin, that interfere with protein synthesis, two antibiotics that disrupt cell wall formation, and one antibiotic that targets DNA transcription, several of the alterations affected resistance to antibiotics.

A wildtype S. pneumoniae without mutations in alcohol dehydrogenase or the other enzymes was treated with fomepizole alone, and the researchers discovered that this led to redox imbalances. Fomepizole treatment of S. pneumoniae increased the sensitivity to antibiotics, according to in vitro experiments, which included a fourfold reduction in the minimum inhibitory concentrations of the medicines erythromycin and gentamicin.

"We also investigated whether fomepizole treatment affected the susceptibility of other anaerobic gram-positive bacteria to erythromycin or gentamicin, including other streptococcal pathogens, such as Streptococcus pyogenes, Streptococcus agalactiae, and Enterococcus faecium. "In most cases, including E. faecium, we observed a twofold to eightfold decreased minimal inhibitory concentration with fomepizole."

"Our findings suggest that drug-resistant gram-positive anaerobic bacteria might become more susceptible to antibiotics by limiting NAD+ regeneration pathways during infection, according to Orihuela. This offers therapeutic promise for the treatment of widespread infection and the elimination of microbes."

Pneumococcal illness causes more than 3 million hospital admissions yearly, and thousands of people die as a result.

➢ *Docking –Study of Fomepizole*

Studies on the drug fomepizole (4-Methyl-1H-pyrazole) in experimental, theoretical, hirschfeld surface, electronic excitation, and molecular docking.

- Density Functional Theory (DFT) computations were performed using the basis set 6-311++G (d,p). Hirshfeld surface analysis performed 3D and 2D surface analyses.
- 6-311++G(d,p) basis set and B3LYP approach were utilized to improve the vibrational modes and molecular structure.
- Tasks for the distribution of potential energy were effectively completed using VEDA (Vibrational Energy Distribution analysis).
- Atom in molecule theory (AIM)-derived binding energies, isosurface projection, and bioactivity of the aforementioned compound were examined.
- The chemical activity of the molecule was identified, and the HOMO-LUMO mapping are given. Additionally, Fukui Function and Molecular Electrostatic Potential (MEP) were used to determine the molecule's chemically active regions.
- A single pair of electrons undergoes electron excitation analysis from occupied to unoccupied orbitals. With the use of solvents, excited state hole and electron density distribution maps (EDD and HDD) were created.
- (NBO) Natural Bond Order. NBO analysis was used to study the links between donors and recipients.
- Hirshfeld surface analysis of intermolecular interactions revealed that 4-MP was primarily stabilized by the establishment of C—H/H—C contacts.
- By taking into account its further medical applications, drug-likeness and molecular docking were performed to ascertain the nature and interaction between ligand and protein, respectively.

➢ *Optimized Molecular Geometry*

- Figure 3 depicts the molecule with the title's optimized geometrical structure and labeled atoms.
- The named molecule's selected geometric parameters, including as bond angles and bond lengths, as estimated using the B3LYP technique and the 6-311++G(d,p) basis set.
- The estimated values for the investigated chemical were compared to the molecule's crystallographic information file (CIF).
- The chemical under study has a C1 point group. The RMSD values for the C-N bonds are given.
- of order to better mimic binding order, bond energy, vibrational wavenumber, and geometrical features of named molecules, this work used Density Functional Theory (DFT).
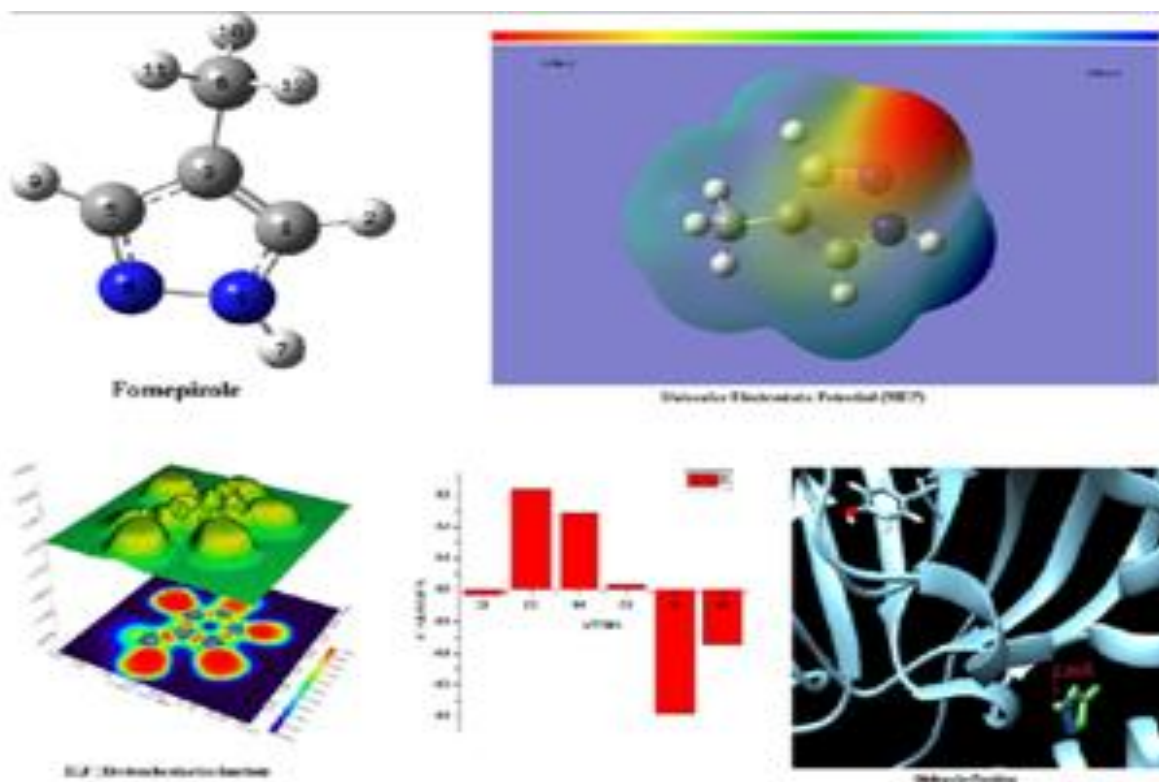
Fig 3 DOCKING – (Hirsch- feld) Surface, Electronic Excitation & Molecular Docking Studies. (Fomepizole)
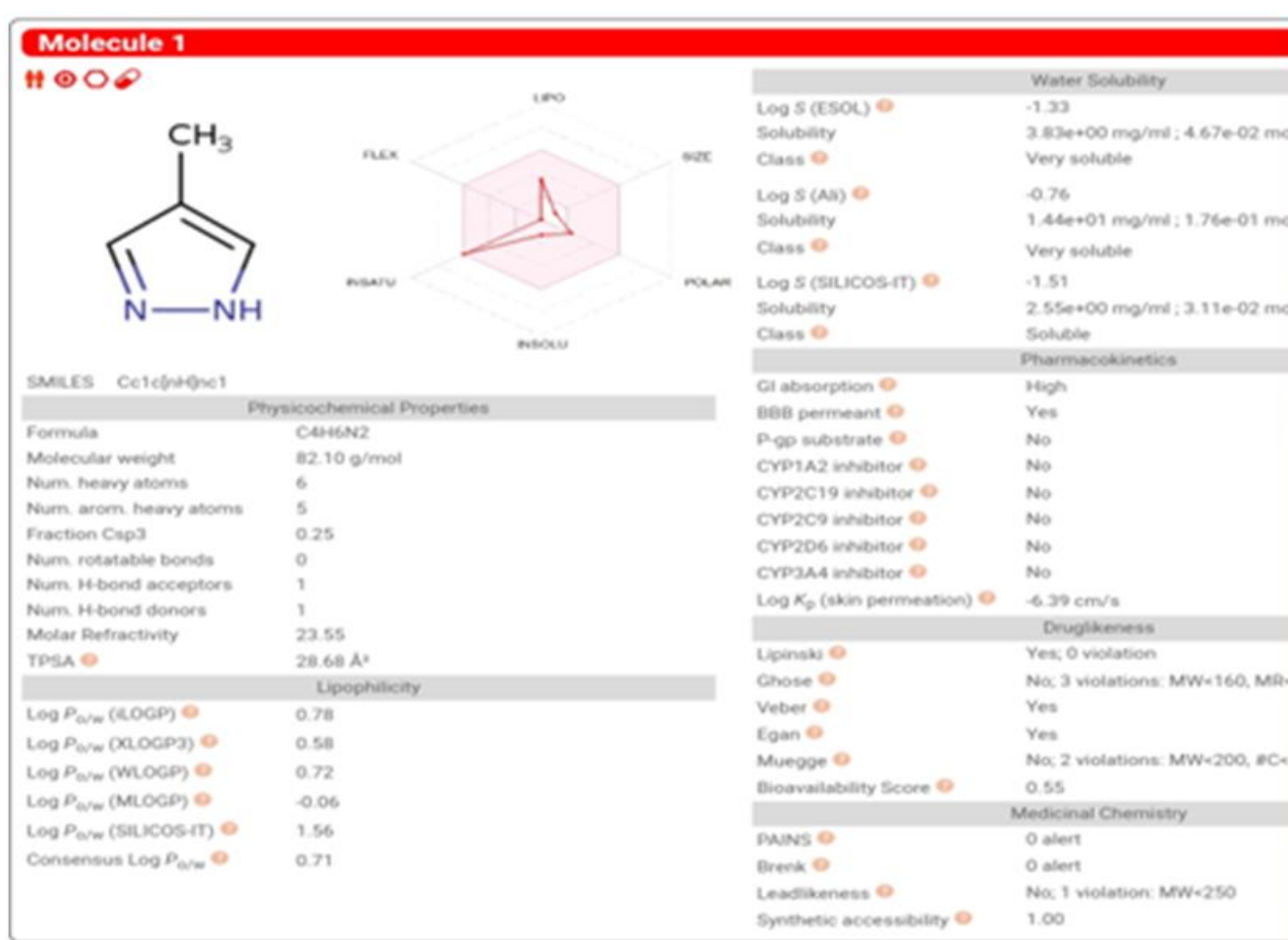
➢ *Swiss Adme - of Fomepizole*

Fig 4 Swiss Adme - of Fomepizole
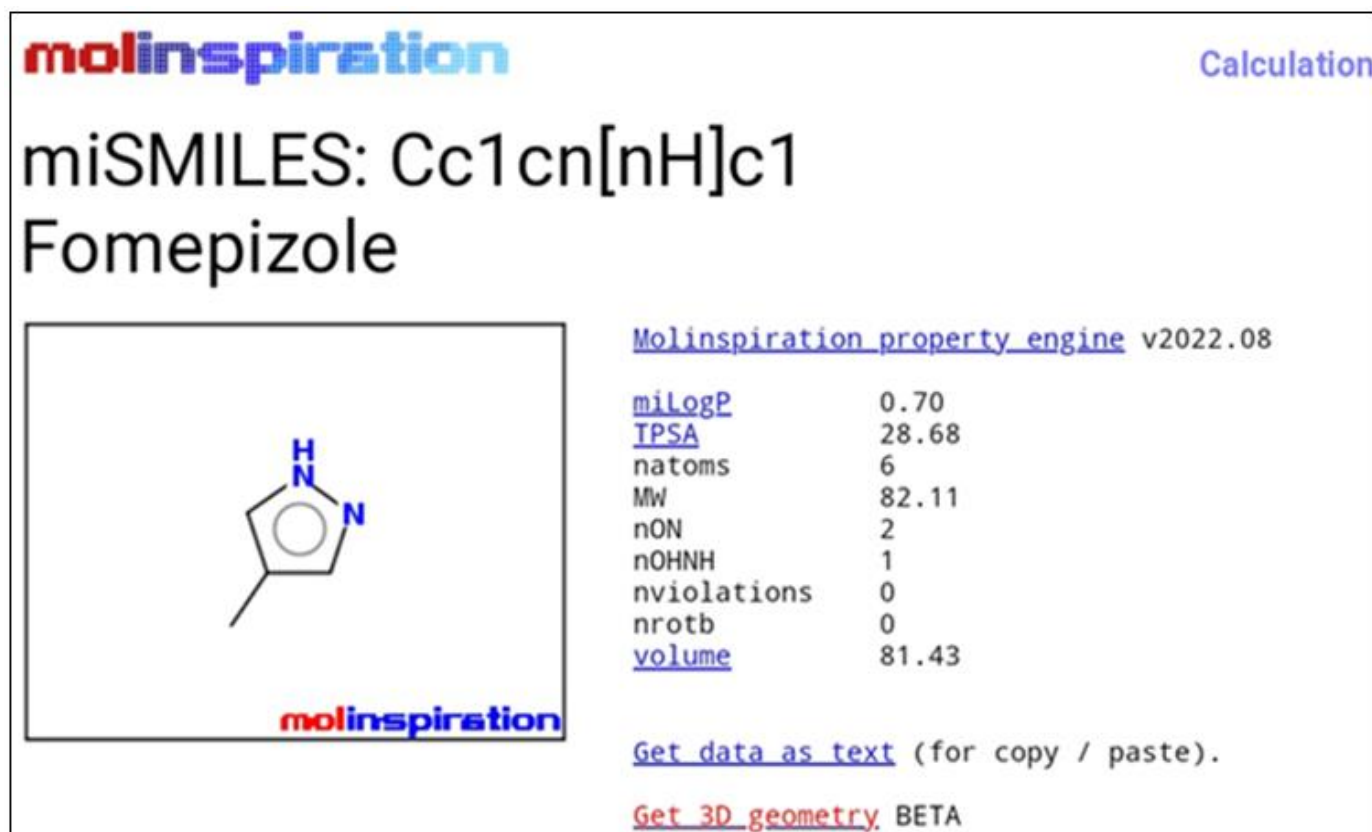
➢ *Mol Inspiration of Fomepizole*
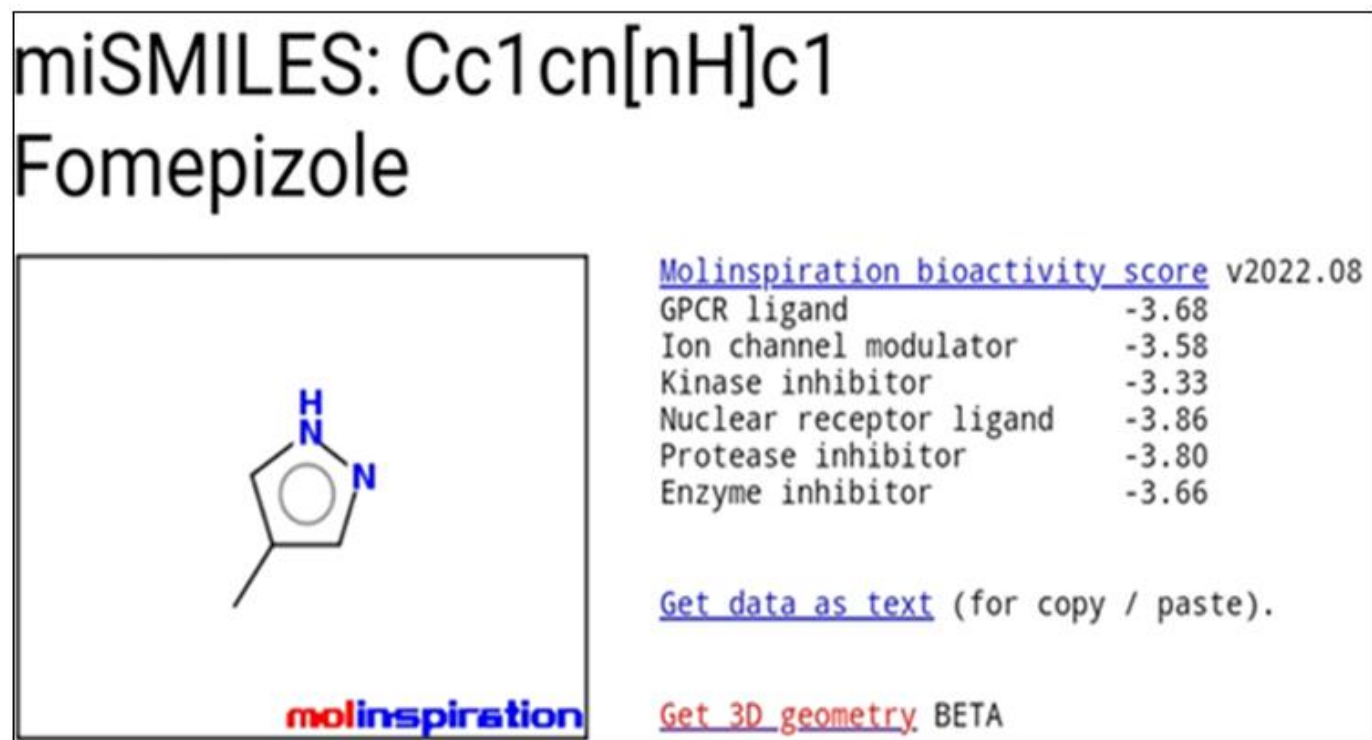

Fig 5 Mol Inspiration of Fomepizole

Fig 6 Mol Inspiration of Fomepizole

➢ *Fomepizole- RP- HPLC- (Analysis Method)*

Table 5 Fomepizole- RP- HPLC- (Analysis Method)

SAMPLE
Matrix: blood
Sample preparation: Condition a 100 mg Bond Elut SCX SPE cartridge with two 1 mL portions of MeOH and two 1 mL portions of 5 mM HCl. Mix 200 μL plasma with 800 μL 6.25 μM IS in 5 mM HCl, add to the SPE cartridge, wash with 1 mL MeOH:5 mM HCl 5:95, elute with 1 mL MeOH:250 mM pH 7.4 potassium phosphate buffer, inject a 100 μL aliquot.

HPLC VARIABLES
Guard column: 30 × 4 Nucleosil 120-5C18
Column: 100 × 4 Nucleosil 120-5C18
Mobile phase: MeOH:5 mM pH 6.0 potassium phosphate buffer 20:80
Flow rate: 0.8
Injection volume: 100
Detector: UV 220

CHROMATOGRAM
Retention time: 7
Internal standard: 3-methylpyrazole (6)
Limit of quantitation: 2.5 μM

KEY WORDS
plasma; SPE

REFERENCE
Diczfalusy, U.; Eklöf, R. Determination of 4-methylpyrazole in plasma using solid phase extraction and HPLC, *Biomed.Chromatogr.*, **1987**, *2*, 226–227.

SAMPLE
Matrix: blood, dialysate
Sample preparation: Mix 200 μL plasma with 10 μL 300 μg/mL IS in water, add 100 μL 15% trichloroacetic acid, mix, centrifuge at 10 000 g for 4 min. Mix a 150 μL aliquot of the supernatant with 100 μL 500 mM disodium hydrogen phosphate solution (pH ca. 7), inject a 50 μL aliquot. Inject a 200 μL aliquot of dialysate directly.

HPLC VARIABLES
Guard column: 4 × 4 5 μm LiChrospher 60 RP-select B
Column: 125 × 4 5 μm LiChrospher 100 RP-18
Column temperature: 40
Mobile phase: MeCN:5 mM pH 6 potassium phosphate buffer 7.5:92.5
Flow rate: 1.5
Injection volume: 50–200
Detector: UV 220

CHROMATOGRAM
Retention time: 4.9
Internal standard: 3-methylpyrazole (4.1)

Limit of quantitation: 300 ng/mL (plasma), 50 ng/mL (dialysate)

KEY WORDS
plasma

REFERENCE
Jobard, E.; Turcant, A.; Harry, P.; Le Bouil, A.; Allain, P. High-performance liquid chromatographic determination of 4-methylpyrazole in plasma and in dialysate, *J.Chromatogr.B*, **1997**, *695*, 444–447.

ANNOTATED BIBLIOGRAPHY
McMartin, K.E.; Collins, T.D.; Hewlett, T.P. High pressure liquid chromatographic assay of 4-methyl-pyrazole. Measurements of plasma and urine levels, *J.Toxicol.Clin.Toxicol.*, **1984**, *22*, 133–148.

➢ *GC- MS : Fomepizole*

m/z- 81----(Top Peak)
m/z- 82 ---(2nd Highest)
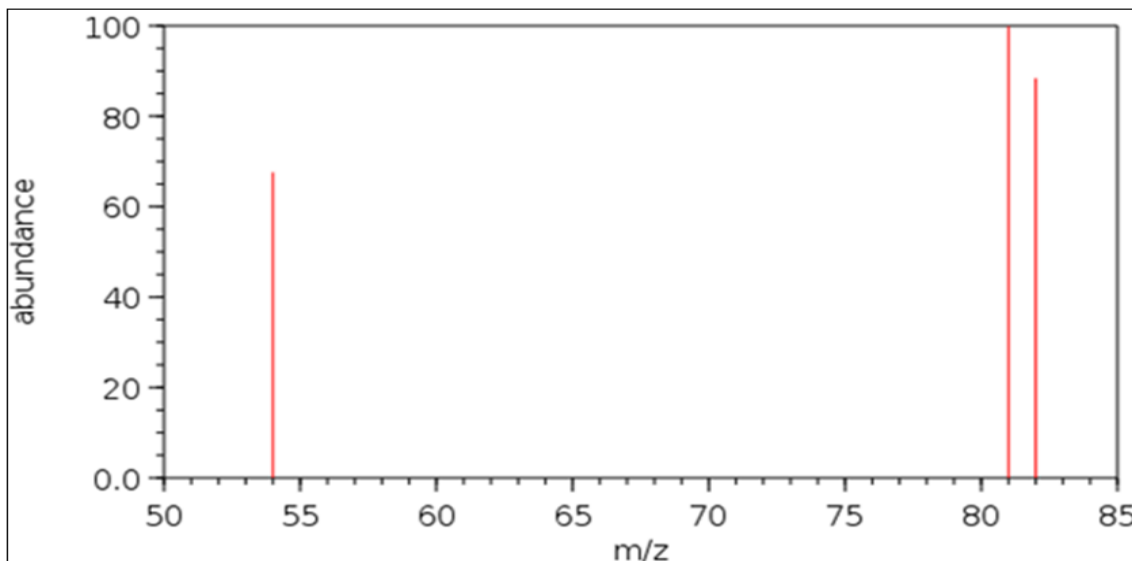**m/z- 54 ---(3rd Highest)**

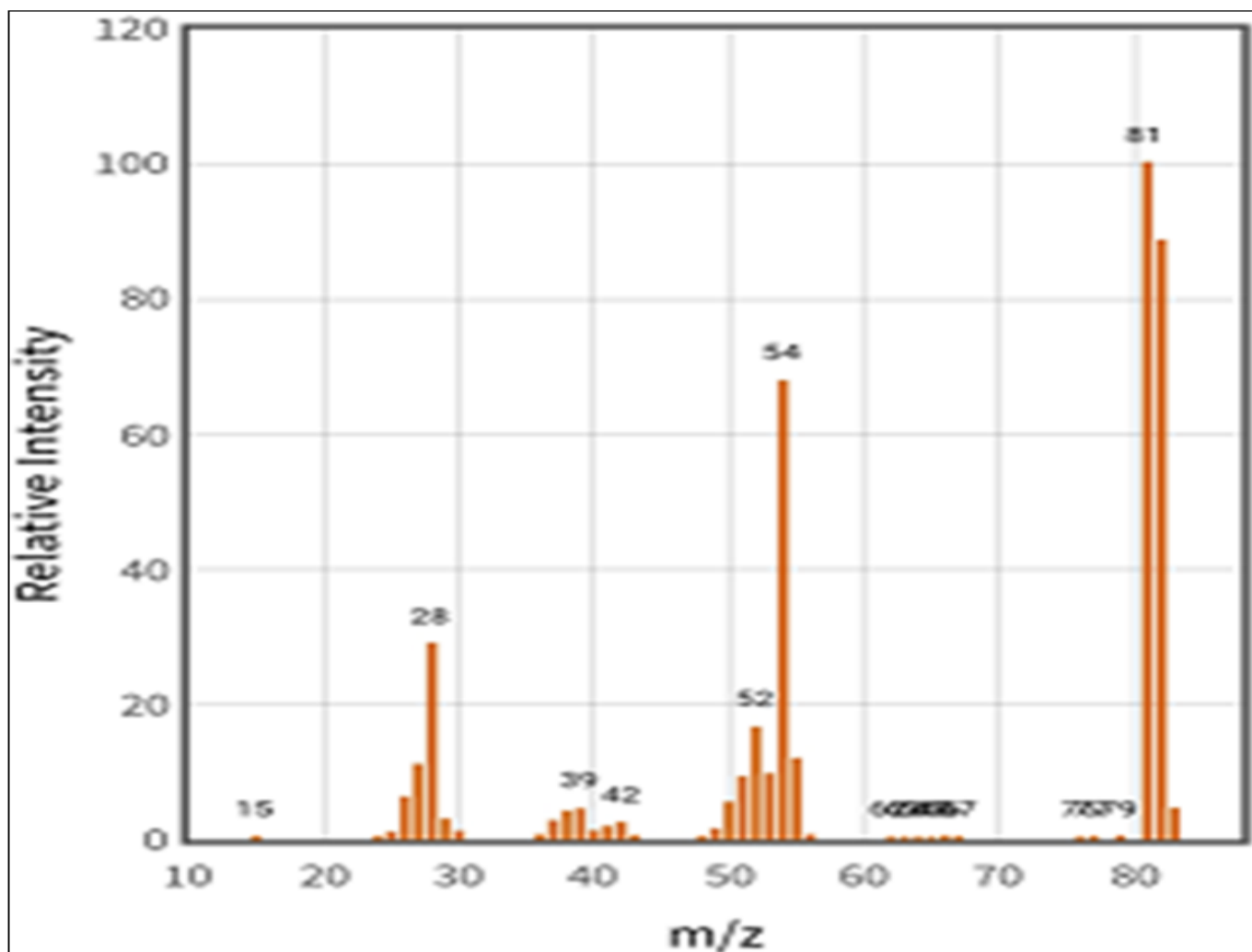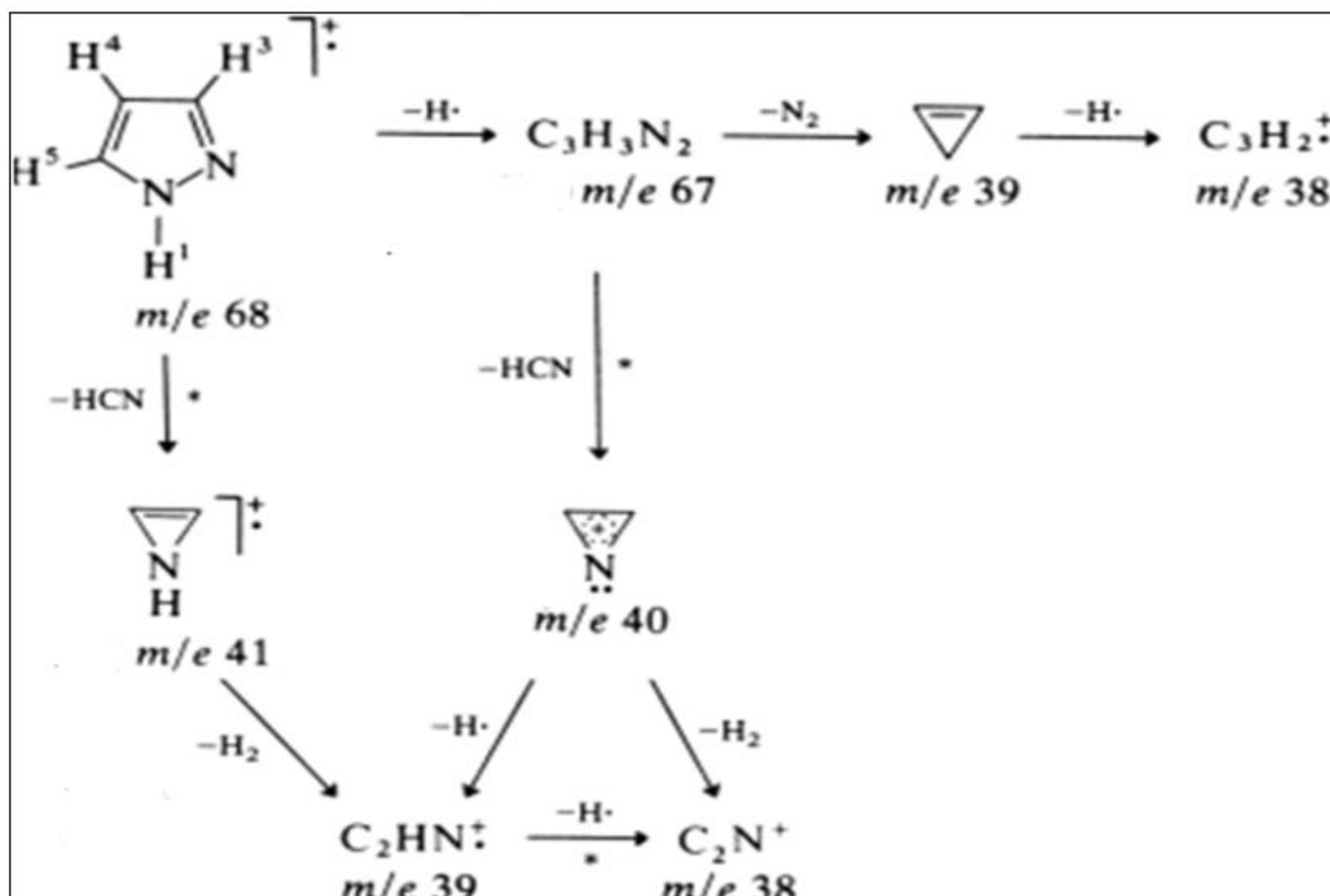Fig 7 Fomepizole El Mass Spectrum, Top peaks Displayed

Fig 8 Fomepizole Mass Spectrum

➢ *Fomepizole – Mass-Fragmentation Rule:*

XI. CONCLUSION

In conclusion, although there have been no instances of methanol poisoning in Asian children, fomepizole has been proposed as a safe and effective antidote for adults. In our example, we gave fomepizole to a 1-year-old infant who was 5-months old with the same dosing regimen as adults, and the metabolic acidosis promptly corrected without any side effects or long-term consequences. Consequently, we present this positive pediatrician experience as a useful instance in toxicological emergencies.

Ingesting poisonous alcohols like methanol and ethylene glycol is quite frequent and can be lethal. The liver's alcohol dehydrogenase (ADH) enzyme breaks down both alcohols into poisonous by products that cause an anion-gap metabolic acidosis and other negative consequences. Solvents, deicers, glass cleaners, as well as home-brewed alcoholic beverages (moonshine), all include methanol. It is converted to formic acid, which can harm the nervous system and impair eyesight by damaging the retina and optic nerve. The pleasant taste of ethylene glycol, which is included in antifreeze, braking fluids, and coolants, makes it appealing to both animals and young children. Glycolate and oxalic acid, two toxic metabolites of EG, can result in renal failure and neurological damage. Sadly, any drink can be lethal.

REFERENCE

[1]. Barceloux DG, et al. American Academy of Clinical Toxicology Practice Guidelines on the Treatment of Ethylene Glycol Poisoning. Ad Hoc Committee. J Tox Clin Tox 1999; 37(5):537-60.

[2]. Baud, FJ, Bismuth C, Garnier R, et al. 4-Methylpyrazole may be an alternative to ethanol therapy for ethylene glycol intoxication in man. Clin Toxicol 1986-87; 24(6):463-483.

[3]. Blair AH, Vallee BL. Some catalytic properties of human liver alcohol dehydrogenase. Biochemistry 1966; 5(6):2026-2034.

[4]. Blomstrand R, Ostling-Wintzell H, Lof A, McMartin K, Tolf BR, Hedstrom KG. Pyrazoles as inhibitors of alcohol oxidation and as important tools in alcohol research: an approach to therapy against methanol poisoning. Proc Natl Acad Sci 1979; 76(7):3499-3503.

[5]. Blomstrand R, Ingemansson SO, Jensen M, Hedstrom CG. Normal electroretinogram and no toxicity signs after chronic and acute administration of the alcohol dehydrogenase inhibitor 4-methylpyrazole to the cynomolgus monkey (Macaca Fascicularis)-a possible new treatment of methanol poisoning. Drug and Alcohol Dependence 1984; 13:9-20.

[6]. Brent J, et al. Fomepizole for the treatment of ethylene glycol poisoning. NEJM 1999; 340:832-838.

[7]. Brent J, McMartin K, Phillips S, Aaron C, Kulig K. Fomepizole For the Treatment of Methanol Poisoning. New England Journal Med 2001;344(6):424-429.

[8]. 8. Chou JY, Richardson KE. The effect of pyrazole on ethylene glycol toxicity and metabolism in the rat. Toxicology and Applied Pharmacology 1978; 43:33-44.

[9]. Clay KL, Murphy RC. On the metabolic acidosis of ethylene glycol intoxication. Toxicology and Applied Pharmacology 1977; 39:39-49.

[10]. Dang Vu B, Crouzier C, Hubert I, Galliot M, Baud FJ, Bourdon R. Analytical and pharmacokinetic study of 4-methylpyrazole, a new antidote for the treatment of ethylene glycol intoxication. Ann Fais Exp Chim 1992; 85(906):99-110.

[11]. Dial SM, Thrall MAH, Hamar DW. Efficacy of 4-methylpyrazole for treatment of ethylene glycol intoxication in dogs. Am J Vet Res 1994a; 55(12):1762-70.

[12]. Dial SM, Thrall MAH, Hamar DW. Comparison of ethanol and 4-methylpyrazole as treatments for ethylene glycol intoxication in cats. Am J Vet Res 1994b; 55(12):1771-82.

[13]. Dial SM, Thrall MA, Hamar DW. 4-methylpyrazole as treatment for naturally acquired ethylene glycol intoxication in dogs. JAVMA 1989; 195(1):73-6.

[14]. Donvan JW, et al. A comparison of fomepizole with hemodialysis vs. fomepizole alone in therapy of severe ethylene glycol toxicity. J Tox Clin Tox 1998; 36(5):451-452.

[15]. Feierman DE, Cederbaum AI. Increased content of cytochrome P-450 and 4- methylpyrazole binding spectrum after 4-methylpyrazole treatment. Biochem Biophy Res Comm 1985; 126(3):1076-1081.

[16]. Gavaler JS, Gay V, Egler K, Van Theil DH. Evaluation of the differential in vivo toxic effects of ethanol and acetaldehyde on the hypothalamic-pituitary-gonadal axis using 4- methylpyrazole. Alcoholism Clin Exper Res 1983; 7(3):332-336.

[17]. Grauer GF, Thrall MAH, Henre BA, Hjelle JJ. Comparison of the effects of ethanol and 4-methylpyrazole on the pharmacokinetics and toxicity of ethylene glycol in the dog. Toxicology Letters 1987; 35:307-14.

[18]. Hantson P, Wallemacq P, Brau M, Vanbinst R, Haufroid V, Mahieu P. Two cases of acute methanol poisoning partially treated by oral 4-methylpyrazole. Intensive Care Med 1999; 25(5):528-531.

[19]. Harry P, Turcant A, Bouachour G, Houze P, Alquier P, Allain P. Efficacy of 4- methylpyrazole in ethylene glycol poisoning: clinical and toxicokinetic aspects. Human & Exper Toxicol 1994; 13:61-64.

[20]. Jacobsen D. New treatment for ethylene glycol poisoning editorial (comment). N Engl J Med 1999; 340(11):879-81.

[21]. Jacobsen D, Barron SK, Sebastian S, Blomstrand R, McMartin KE. Non-linear kinetics of 4-methylpyrazole in healthy human subjects. Eur J Clin Pharmacol 1989; 37:599-604.

[22]. Jacobsen D, Sebastian CS, Barron SK, Carriere EW, McMartin KE. Effects of 4- methylpyrazole, methanol/ethylene glycol antidote, in healthy humans. J Emergency Med 1990; 8:455-461.

[23]. Jobard E, Harry P, Turcant A, Roy PM, Allain P. 4-Methylpyrazole and hemodialysis in ethylene glycol poisoning. Clin Toxicol 1996; 34(4):373-377.

[24]. Mc Martin KE, Makar AB, Martin A, Palese M, Tephly TR. Methanol poisoning I. The role of formic acid in the development of metabolic acidosis in the monkey and the reversal by 4-methylpyrazole. Biochemical Medicine 1975; 13:319-33.

[25]. Mc Martin KE, Martin-Amat G, Makar AB, Tephly TR. Methanol poisoning: Role of formate metabolism in the monkey. In: Thurman RG, WIlliamson JR, Drott H, Chance B eds. Alcohol & Aldehyde Metabolizing Systems. New York, NY: Academic Press; 1977b; 429-440.

[26]. Mc Martin KE, Hedstrom KG, Tolf B-R, Ostling-Wintzell H, Blomstrand R. Studies on the metabolic interactions between 4-methylpyrazole and methanol using the monkey as an animal model. Archives of Biochemistry and Biophysics 1980; 199(2):606-614.

[27]. Mc Martin KE, Brent J, and Meta Study Group. Pharmacokinetics of fomepizole (4MP) in patients. J Tox Clin Tox 1998; 36(5):450-451.

[28]. Magnusson G, Nyberg JA, Bodin NO, Hansson E. Toxicity of pyrazole and 4- methylpyrazole in mice and rats. Experientia 1972; 28(10):1198-200.

[29]. Moreau CL, et al. Glycolate kinetics and hemodialysis clearance in ethylene glycol poisoning. META Study Group. J Tox Clin Tox 1998; 36(7):659-66.

[30]. Pietruszko R. Human liver alcohol dehydrogenase – inhibition of methanol activity by pyrazole, 4-methylpyrazole, 4-hydroxymethylpyrazole and 4-carboxypyrazole. Biochemical Pharmacology 1975; 24:1603-1607.

[31]. Sivilotti M, et al. Pharmacokinetics of ethylene glycol and methanol during fomepizole therapy: Results of the meta trial. J Tox Clin Tox 1998; 36(5):451.

[32]. Sivilotti M, Burns M, McMartin K, Brent J. Reversible blindness in methanol poisoning treated with fomepizole. Journal of Toxicology - Clinical Toxicology 1998; 36(5):514.

[33]. Wax P, et al. Effect of fomepizole (4MP) on ethanol elimination in ethylene glycol (EG) and methanol poisoned patients. J Tox Clin Tox 1998; 36(5):451-452. 34. Antizol® Product Monograph. Paladin Labs Inc., dated November 20, 2006.