

# Načrtovanje in sinteza učinkovin - VAJE

- Načrtovanje sinteze
  - 1. vaja
    - Načrtovanje alternativne sinteze
- Računalniško podprto načrtovanje učinkovin
  - 2. vaja
    - Filtriranje in priprava kemijskih knjižnic
    - Iskanje spojin v kemijskih knjižnicah na osnovi 2D in 3D podobnosti
  - 3. vaja
    - Virtualno reševanje in analiza vezave učinkovine v aktivno mesto
- Kolokvija ni, je pa lahko kakšno vprašanje na izpitu
- Opravljene vaje pogoj za pristop k izpitu

Univerza v Ljubljani  
Fakulteta za farmacijo



Katedra za farmacevtsko kemijo

## Načrtovanje alternativne sinteze

1. vaja pri predmetu Načrtovanje in sinteza učinkovin

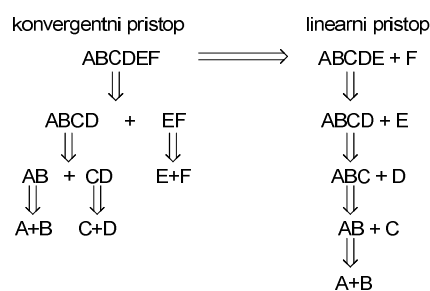
## Sinteza zdravilnih učinkovin

- delitev sinteznih pristopov

- totalna sinteza
- delna sinteza
- biosinteza

- potek sinteze

- linearni
- konvergentni

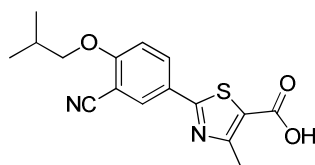


## Retrosintezna analiza

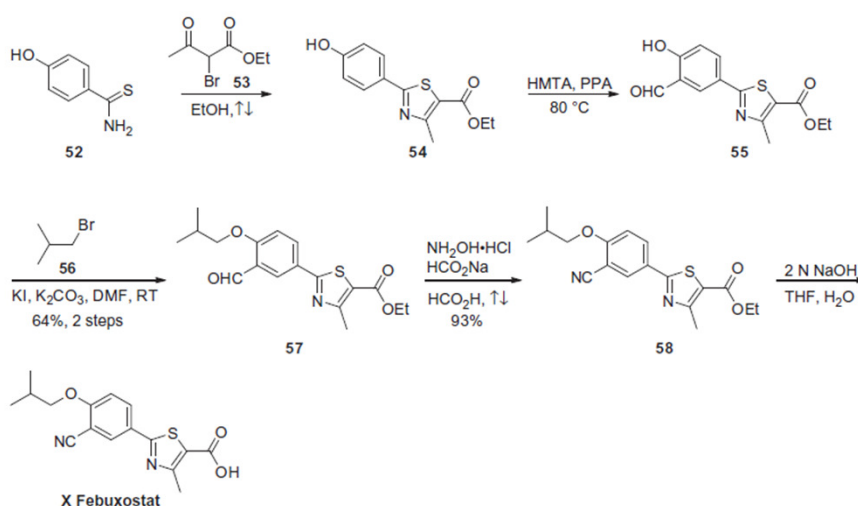
- ciljno molekulo sistematično razgradimo do enostavnih, znanih spojin s pomočjo znanih kemijskih reakcij
  - sintoni
  - sintezni ekvivalenti
- prekinitve kemijskih vezi – nastaneta dva sintona:
  - elektronakceptorski in elektrondonorski sinton
  - elektronevtralna radikalska sintona
  - elektronevtralna neradikalska sintona
- funkcionalne skupine
  - pretvorba funkcionalne skupine (*functional group interconversion – FGI*)
  - dodajanje funkcionalne skupine (*functional group addition – FGA*)
  - odstranitev funkcionalne skupine (*functional group removal – FGR*)

## Primer – sinteza febuksostata

- ZU za zdravljenje hiperurikemije – nenormalnega povečanja koncentracije sečne kisline v krvi
- Inhibitor ksantinske oksidaze



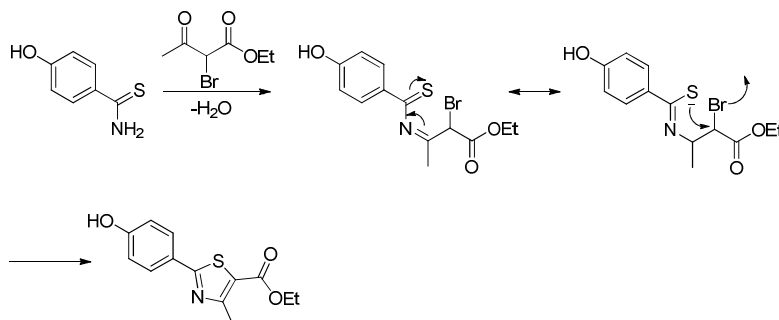
## Sinteza febuksostata



Scheme 10. Synthesis of febuxostat (X).

## Sinteza tiazola

- Mehanizem sinteze tiazolnega obroča

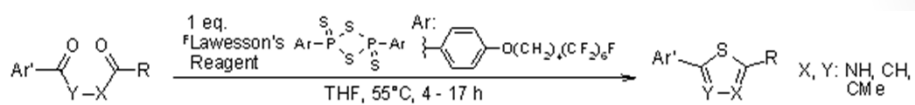


- Alternativa?

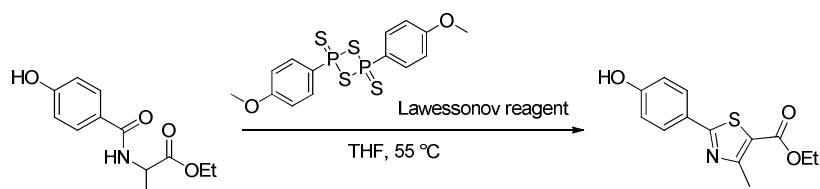
- <http://www.organic-chemistry.org/synthesis/heterocycles/thiazoles.shtml>
- SciFinder Scholar

## Sinteza tiazola

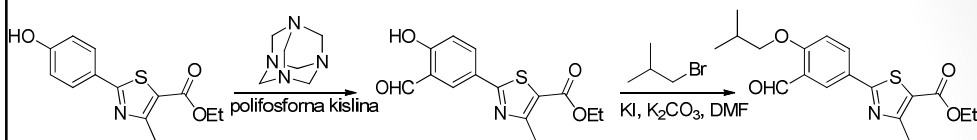
- Predlog alternativne sinteze



Z. Kaleta, B. T Makowski, T. Soos, R. Dembinski, *Org. Lett.*, **2006**, *8*, 1625-1628

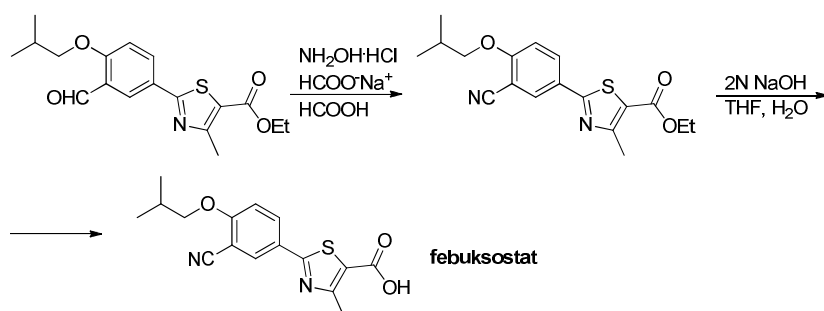


## 2. in 3. stopnja



- 2. stopnja: formiliranje – Duff-ova reakcija  
([http://en.wikipedia.org/wiki/Duff\\_reaction](http://en.wikipedia.org/wiki/Duff_reaction))
- alternativa:  $\text{CHCl}_3$ , 3 KOH – Reimer-Tiemannova reakcija – uvedba formilne skupine na orto mesto
- 3. stopnja: alkiliranje fenolne OH skupine
  - vloga  $\text{K}_2\text{CO}_3$  in KI

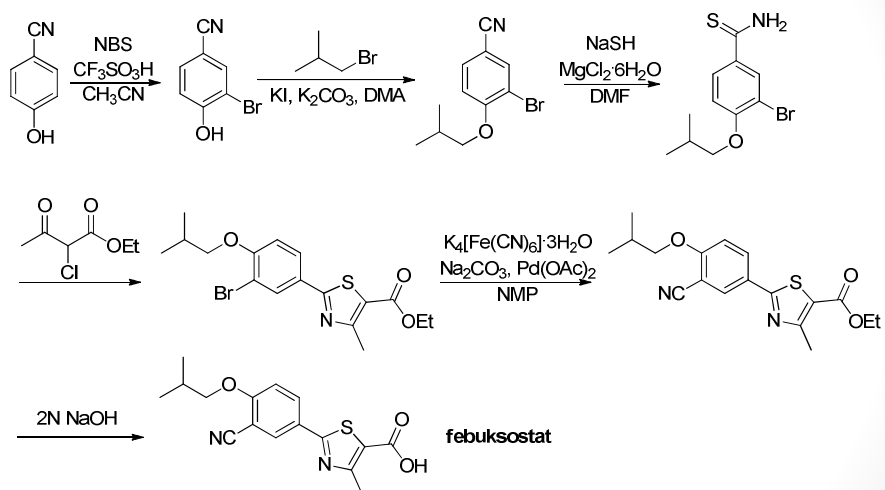
## 4. in 5. stopnja



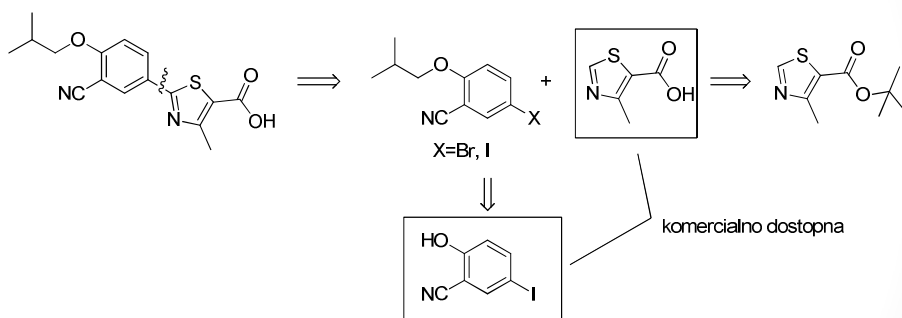
- 4. stopnja – sinteza aldoksima in sledeča dehidracija do nitrila
- 5. stopnja – alkalna hidroliza estra



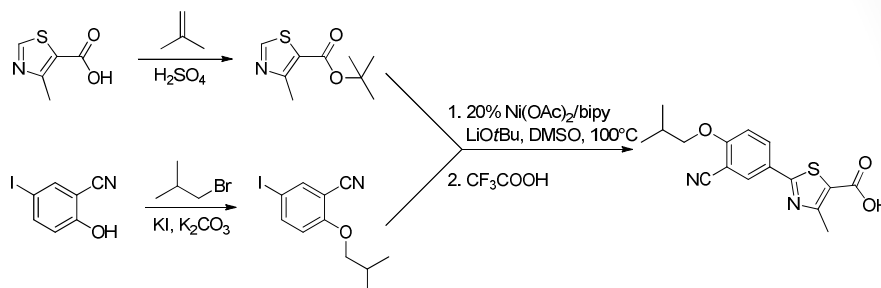
## Alternativna sinteza 1



## Retrosintezna analiza 2



## Alternativna sinteza 2



- 1. stopnja: sinteza *t*-butilnega estra – zaščita
- 2. stopnja: alkiliranje fenolne OH
- 3. stopnja: z nikljem katalizirano ariliranje tiazola (Yamamoto *etal*, Chem. Eur. J. **2011**, *17*, 10113-10122)
- 4. stopnja: acidoliza – odščita *t*-Bu estra

## SciFinder Scholar

- <http://www.ctk.uni-lj.si/zbirke/SciFinder.html>
- potrebna je registracija

**Centralna tehniška knjižnica Univerze v Ljubljani**  
Trg republike 3, 1000 Ljubljana, +386 (1) 200 34 00 fax +386 (1) 425 66 67, e-mail: [post@ctk.uni-lj.si](mailto:post@ctk.uni-lj.si)

### SciFinder Scholar

Zbirka SciFinder Scholar je od 30.12.2011 dostopna le na spletnem vmesniku. Za uporabo spletnega vmesnika se je potrebno registrirati. Registracija je možna le iz računalnikov, ki so v prostorih UL, uporaba od doma je možna le preko VPN fakultete. Pri registraciji morate navesti svoje ime, priimek in veljaven elektronski naslov ter določiti uporabniško ime in geslo. Za uporabniško ime predlagamo "imepriimek" (brez narekovajev) ali pa kar e-mail, geslo pa mora biti dolgo najmanj sedem znakov, pri čemer mora biti v geslu vsaj ena številka, ena velika črka in en od posebnih znakov (@, #, %) - več o geslih izveste [tukaj](#). Na koncu si morate izbrati tudi varnostno vprašanje in določiti odgovor nanj, ki boste potrebovali v primeru, da boste geslo pozabili.

[Registracija](#)

Po uspešno končanem prvem delu registracije dobite na svoj elektronski naslov sporočilo, v katerem morate klikniti na poslano povezavo. S tem je registracija končana in lahko pričnete uporabljati SciFinder Scholar. Trenutno so na novem vmesniku možni 3 sočasni uporabniki.

**Novi SciFinder Scholar: (<https://scifinder.cas.org>)**

Prosimo, da se po končanem delu obvezno odjavite s klikom na povezavo "Sign Out", ki je v levem zgornjem kotu pod napisom "SciFinder". Če okno samo zaprete, vaša seja traja še 20 minut in v tem času se namesto vas ne more prijaviti nov uporabnik.

[Pogoji uporabe](#) (dovoljeno Uni-Lj)      [Seznam zbirk](#)      [Navodila](#)      [help-desk@ctk.uni-lj.si](mailto:help-desk@ctk.uni-lj.si) (01) 2003 444

© CTK      Zadnja sprememba: 28.3.2012      [Webmaster](#)



# SciFinder Scholar



**SciFinder®** The choice for chemistry research.™

### Sign In

Username

Password

Remember my username

[Forgot Username or Password?](#)

Your SciFinder username and password are assigned to you alone and may not be shared with anyone else.

### Welcome to SciFinder!

**2012 Nobel Prize-Winning Chemistry Research Documented in CAS Databases**

CAS congratulates the 2012 Nobel Laureates in Chemistry, Dr. Robert J. Lefkowitz and Dr. Brian K. Kobilka, who were honored "for their studies of G-protein-coupled receptors."

For more information on their research as documented in the CAS Databases, visit [www.cas.org](http://www.cas.org).

**New SciFinder Features Help Increase Your Productivity**

The latest SciFinder update improves precision and evaluation of reaction answer sets and new SciPlanner import and export options allow you to more easily collaborate with other SciFinder users.

To learn more about these enhancements, visit [What's New in SciFinder](#).


**Daily Reaction Updates Now in SciFinder**

The most frequently updated reaction content available just got better. New single- and multi-step reactions and synthetic

[About SciFinder](#) | [SciFinder Support and Training](#) | [CAS Databases](#)

CAS is a division of the American Chemical Society

# SciFinder Scholar



Explore References
Explore Substances
Explore Reactions

Welcome Thomir Tomasic | Sign Out

## Explore References

Research Topic

Author Name

Company Name

Document Identifier

Journal

Patent

Tags

Examples:  
*The effect of antibiotic residues on dairy products*  
*Photocyanation of aromatic compounds*

**Publication Year(s)**

Examples: 1995, 1995-1999, 1995-, \*1995

**Document Type(s)**

<input type="checkbox"/> Biography	<input type="checkbox"/> Dissertation	<input type="checkbox"/> Patent
<input type="checkbox"/> Book	<input type="checkbox"/> Editorial	<input type="checkbox"/> Preprint
<input type="checkbox"/> Clinical Trial	<input type="checkbox"/> Historical	<input type="checkbox"/> Report
<input type="checkbox"/> Commentary	<input type="checkbox"/> Journal	<input type="checkbox"/> Review
<input type="checkbox"/> Conference	<input type="checkbox"/> Letter	

**Language(s)**

<input type="checkbox"/> Chinese	<input type="checkbox"/> German	<input type="checkbox"/> Polish
<input type="checkbox"/> English	<input type="checkbox"/> Italian	<input type="checkbox"/> Russian
<input type="checkbox"/> French	<input type="checkbox"/> Japanese	<input type="checkbox"/> Spanish

**Author Name**

Last \*  First  Middle

**Company Name**

Examples:  
*Minnesota Mining and Manufacturing*  
*DuPont*

# SciFinder Scholar

SciFinder®

Welcome Thomir Tomasic | Sign Out

Explore References   Explore Substances   Explore Reactions

## Explore Reactions

Reaction Structure   Reaction Structure

Click to Edit

Solvent(s)

Non-participating Functional Group(s)

Number of Steps   
Examples: 1, 1-3, 1-, -3

Classification(s)  Biotransformation    Catalyzed    Chemoselective    Combinatorial    Electrochemical    Gas-phase    Non-catalyzed    Photochemical    Radiochemical    Regioselective    Stereoselective

Source(s)  Any source    Patents only    Sources other than patents

Publication Year(s)   
Examples: 1995, 1995-1999, 1995-, -1995

# SciFinder Scholar

Reaction Editor

Draw or change atoms or bonds.   [Shortcut Keys](#)

Atom Shortcuts

Structure Editor:

- Structure
- Reaction
- Markush

Get reactions where the structure(s) are:

- Variable only at the specified positions
- Substructures of more complex structures

OK   Cancel

C6H7NO (query)   Scale 100   109,13

# SciFinder Scholar

Reaction Editor

Draw or change atoms or bonds. Shortcut Keys

Get Reactions - role definition

Get reactions where this structure is:

a product

OK Cancel

Drawing Editor:

Structure

Reaction

Markush

Get reactions where the structure(s) are:

Variable only at

the specified positions

Substructures of

more complex structures

OK

Cancel

N C H O S N P Cl Br F I Si Scale 100

C<sub>6</sub>H<sub>7</sub>N O (query) 109,13

# SciFinder Scholar

SciFinder®

Welcome Thomir Tomasic | Sign Out

Explore References Explore Substances Explore Reactions

Explore Reactions

Reaction Structure

Reaction Structure

product

Click image to change structure or view detail

Search type:  Allow variability only as specified  Substructure

Solvent(s)  Select Solvents

Non-participating Functional Group(s)  Select Groups

Number of Steps

Examples: 1, 1-3, 2, -3

Classification(s)

Biotransformation  Electrochemical  Radiochemical

Catalyzed  Gas-phase  Regioselective

Chemoselective  Non-catalyzed  Stereoselective

Combinatorial  Photochemical

Source(s)

Any source  Patents only  Sources other than patents

Publication Year(s)

Examples: 1995, 1995-1999, 1995, -1995

Search

# SciFinder Scholar

The screenshot displays the SciFinder Scholar web interface. At the top, the SciFinder logo is visible. Below it, a navigation bar includes 'Welcome Thomis Tomasic | Sign Out' and 'Reaction Structure variable only at spe... > reactions (103)'. The main content area is titled 'Reactions' and shows a list of 103 reactions. The first reaction is selected and viewed in detail. The reaction scheme shows the reduction of 2,4-dinitrophenol to 2,4-diaminophenol, with a 100% yield indicated. The reaction conditions are listed as: 1.1 R:NaBH<sub>4</sub>, C:Ag, C:1317-61-9, C:SiO<sub>2</sub>, S:H<sub>2</sub>O, rt. The 'Notes' section describes the catalyst as a solid-supported catalyst prepared and used on magnetite nanoparticles/SiO<sub>2</sub>. The 'References' section cites a paper by Shi, Juan-Soo et al. (Appl. Catal., A, 2012, 413-414, 170-175). A red arrow points to the 'Full Text' link in the references. On the right side, there is an 'Analysis' panel with a 'Catalyst' filter and a table of catalyst counts.

**Analysis Panel:**

Catalyst	Count
Pd	10
1034343-98-0	3
Ag	3
Carbon	3
Ni	3
Pd(OAc) <sub>2</sub>	3
Pt	3
69073-98-9	2
Al <sub>2</sub> O <sub>3</sub>	2
Hg(OAc) <sub>2</sub>	2

**Reaction Details:**

**Steps/Stages:**  
1.1 R:NaBH<sub>4</sub>, C:Ag, C:1317-61-9, C:SiO<sub>2</sub>, S:H<sub>2</sub>O, rt

**Notes:**  
solid-supported catalyst, catalyst prepared and used, catalyst on magnetite nanoparticles/SiO<sub>2</sub>, kinetics studied, Reactants: 1, Reagents: 1, Catalysts: 3, Solvents: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

**References:**  
Facile synthesis of silver-deposited silanized magnetite nanoparticles and their application for catalytic reduction of nitrophenols. [Full Text](#)  
By Shi, Juan-Soo et al. *Appl. Catal., A*, 2012, 413-414, 170-175