



MASARYK UNIVERSITY

Nové organické sloučeniny s cílenou biologickou aktivitou

Kamil Paruch

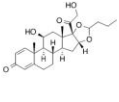
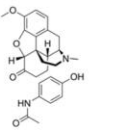
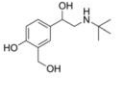
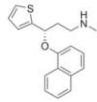
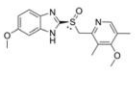
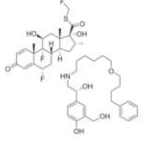
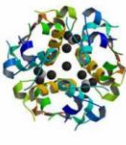
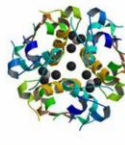
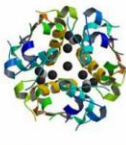
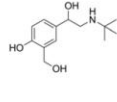
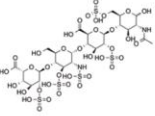
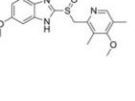
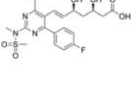
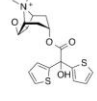
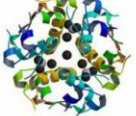
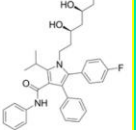
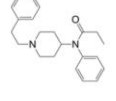
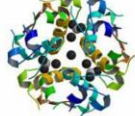
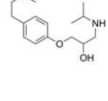
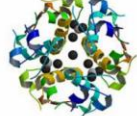
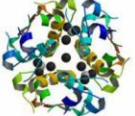
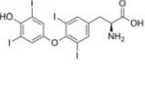
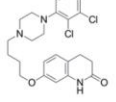
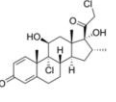
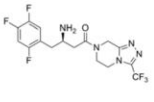
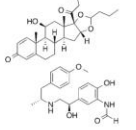
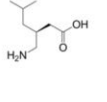
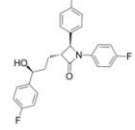
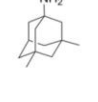
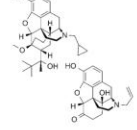
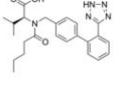
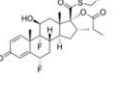
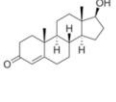
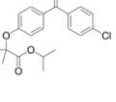


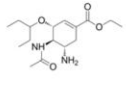
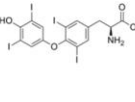
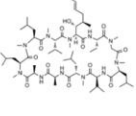
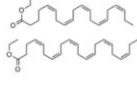
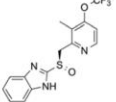
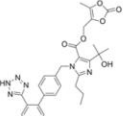
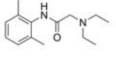
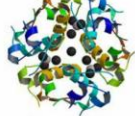

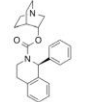
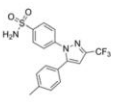
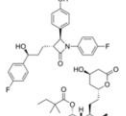

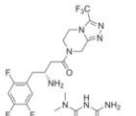
1990-1995: Mgr. organická chemie; PřF MU, Brno

1996-2000: PhD. organická chemie; Columbia University, New York, USA

2001-2008: drug discovery, Schering-Plough, New Jersey, USA

2009-nyní: Ústav chemie PřF MU & FNUSA-ICRC, Brno

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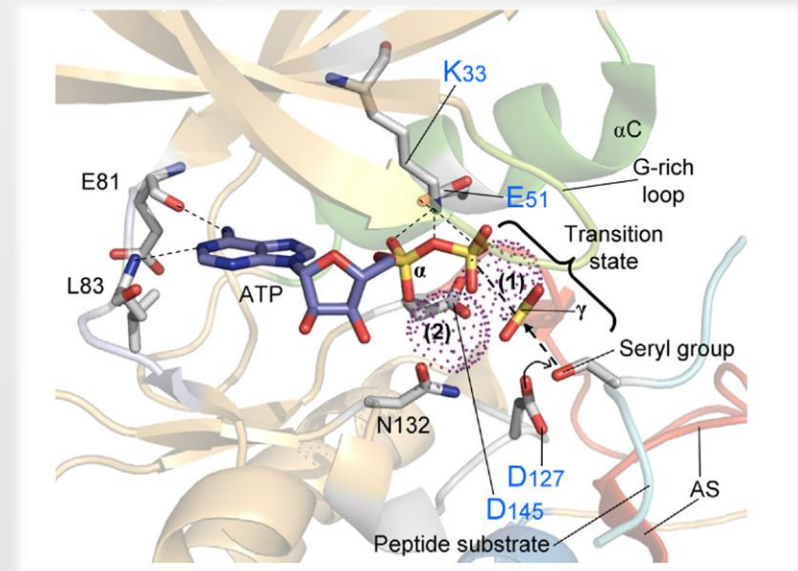
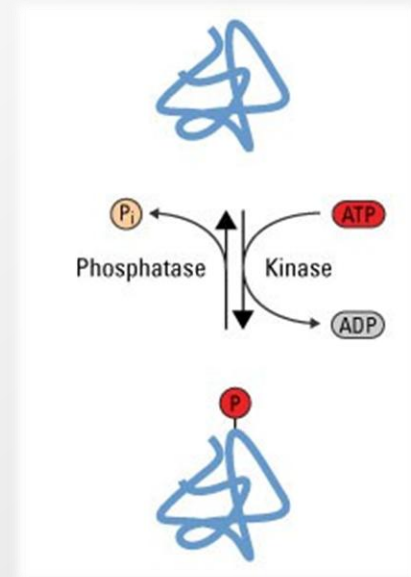
<p>1 Budesonide (Budesonide)</p>  <p>ALM DER RES Approved 1997</p>	<p>2 Hydrocodone/APAP (Hydrocodone & Acetaminophen)</p>  <p>Nervous System Approved 1982</p>	<p>3 Proair HFA (Salbutamol)</p>  <p>Respiratory System Approved 2004</p>	<p>4 Cymbalta (Duloxetine)</p>  <p>Nervous System Approved 2004</p>	<p>5 Nexium (Esomeprazole)</p>  <p>Alimentary Tract & Metabolism Approved 2001</p>	<p>6 Advair Diskus (Fluticasone Propionate & Salmeterol)</p>  <p>Respiratory System Approved 2000</p>	<p>7 Lantus (Insulin Glargine)</p>  <p>Endocrine System Approved 2000</p>	<p>8 Lantus SoloSTAR (Insulin Glargine)</p>  <p>Endocrine System Approved 2000</p>	<p>9 OneTouch (Insulin Glargine)</p>  <p>Endocrine System Approved 2006</p>	<p>10 Ventolin HFA (Salbutamol)</p>  <p>Respiratory System Approved 2001</p>
<p>11 Enoxaparin (Enoxaparin)</p>  <p>BBO MSK Approved 1993</p>	<p>12 Omeprazole (Omeprazole)</p>  <p>Alimentary Tract & Metabolism Approved 1989</p>	<p>13 Crestor (Rosuvastatin)</p>  <p>BBO CAR Approved 2003</p>	<p>14 Spiriva (Tiotropium)</p>  <p>Respiratory System Approved 2004</p>	<p>15 Levemir (Insulin Detemir)</p>  <p>Endocrine System Approved 2005</p>	<p>16 Atorvastatin (Atorvastatin)</p>  <p>BBO CAR Approved 1996</p>	<p>17 Fentanyl (Fentanyl)</p>  <p>NER ONC Approved 1968</p>	<p>18 NovoLog FlexPen (Insulin Aspart)</p>  <p>Endocrine System Approved 2000</p>	<p>19 Metoprolol (Metoprolol)</p>  <p>Cardiovascular System Approved 1978</p>	<p>20 NovoLog (Insulin Aspart)</p>  <p>Endocrine System Approved 2000</p>
<p>21 Humalog (Insulin Lispro)</p>  <p>Endocrine System Approved 1996</p>	<p>22 Synthroid (Levothyroxine)</p>  <p>Endocrine System Approved 2002</p>	<p>23 Abilify (Aripiprazole)</p>  <p>Nervous System Approved 2002</p>	<p>24 Nasonex (Mometasone)</p>  <p>Respiratory System Approved 1997</p>	<p>25 Januvia (Sitagliptin)</p>  <p>Endocrine System Approved 2006</p>	<p>26 Symbicort (Budesonide & Formoterol)</p>  <p>Respiratory System Approved 2006</p>	<p>27 Lyrica (Pregabalin)</p>  <p>MSK NER Approved 2004</p>	<p>28 Zelta (Ezetimibe)</p>  <p>BBO CAR Approved 2002</p>	<p>29 Namenda (Memantine)</p>  <p>Nervous System Approved 2003</p>	<p>30 Suboxone (Buprenorphine & Naloxone)</p>  <p>Nervous System Approved 2002</p>
<p>31 Diovan (Valsartan)</p>  <p>CAR END Approved 1996</p>	<p>32 Flovent HFA (Fluticasone Propionate)</p>  <p>Respiratory System Approved 1996</p>	<p>33 AndroGel (Testosterone)</p>  <p>Genito-Urinary & Sex Hormone Approved 2000</p>	<p>34 Fenofibrate (Fenofibrate)</p>  <p>BBO CAR END Approved 1993</p>	<p>35 Remicade (Infliximab)</p>  <p>END MSK Approved 1998</p>	<p>36 OneTouch Ultra</p>  <p>Endocrine System Marketed 2006*</p>	<p>37 Tamiflu (Oseltamivir)</p>  <p>Anti-Infective Approved 1999</p>	<p>38 Levothyroxine (Levothyroxine)</p>  <p>Endocrine System Approved 2000</p>	<p>39 Restasis (Cyclosporine)</p>  <p>Sensory Organ Approved 2002</p>	<p>40 Lovaza (Omega 3-Acid Ethyl Esters)</p>  <p>Cardiovascular System Approved 2004</p>
<p>41 Dextilant (Dexlansoprazole)</p>  <p>Alimentary Tract & Metabolism Approved 2007</p>	<p>42 Benicar (Olmesartan)</p>  <p>CAR END Approved 2002</p>	<p>43 Lidoderm (Lidocaine)</p>  <p>CAR DER NER RES SEN Approved 1948</p>	<p>44 Humalog KwikPen (Insulin Lispro)</p>  <p>Endocrine System Approved 1996</p>	<p>45 Oxycontin (Oxycodone)</p>  <p>END MSK Approved 2010</p>	<p>46 VESicare (Solifenacin)</p>  <p>Genito-Urinary & Sex Hormone Approved 2004</p>	<p>47 Celebrex (Celecoxib)</p>  <p>MSK ONC Approved 1998</p>	<p>48 Vytorin (Ezetimibe & Simvastatin)</p>  <p>BBO CAR Approved 2004</p>	<p>49 Enbrel (Etanercept)</p>  <p>Musculo-Skeletal System Approved 1998</p>	<p>50 Janumet (Metformin & Sitagliptin)</p>  <p>Alimentary Tract & Metabolism Approved 2007</p>

Proteinové kinázy

- >500 enzymů (ca. 1.7% lidského genomu)
- ATP fosfotransferázy
 - katalyzují reverzibilní fosforylaci
 - důležitý signální mechanismus
 - regulace mnoha procesů v buňce



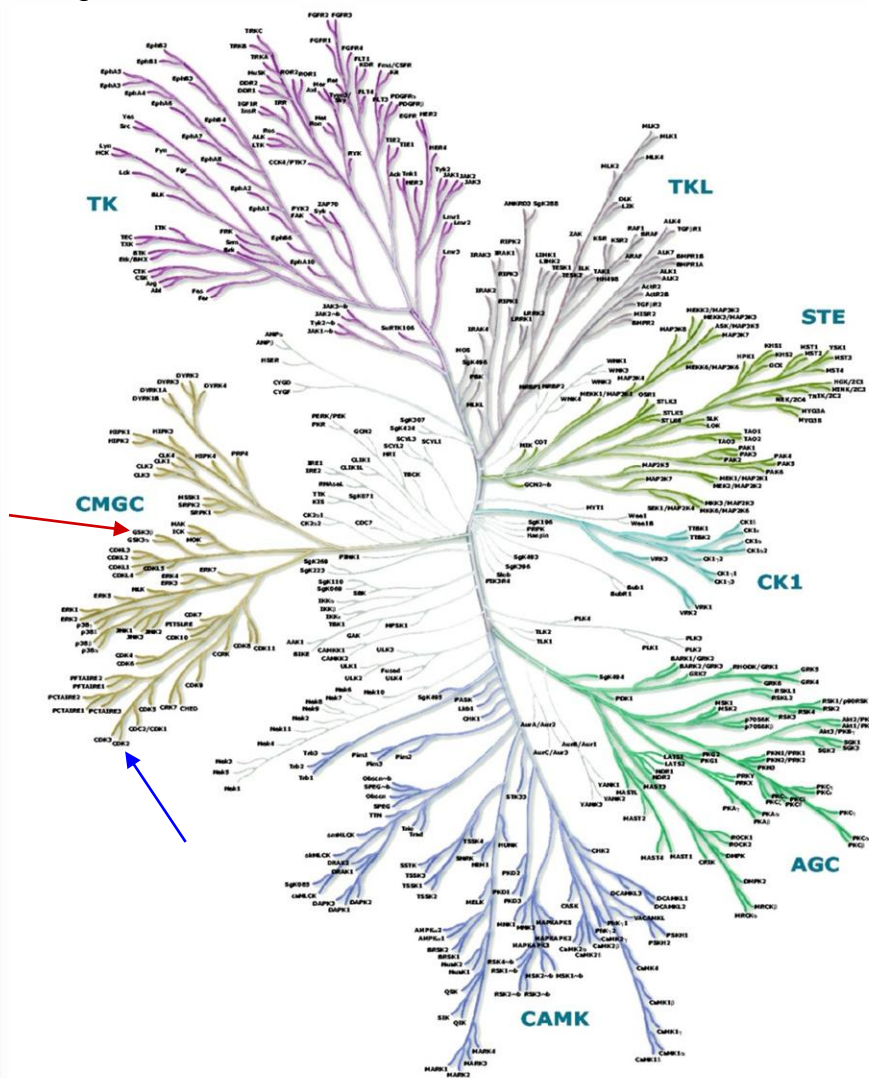
- inhibitory proteinových kináz - „hot topic“
v současném (farma) výzkumu
(>70 substancí schváleno pro klinické použití)



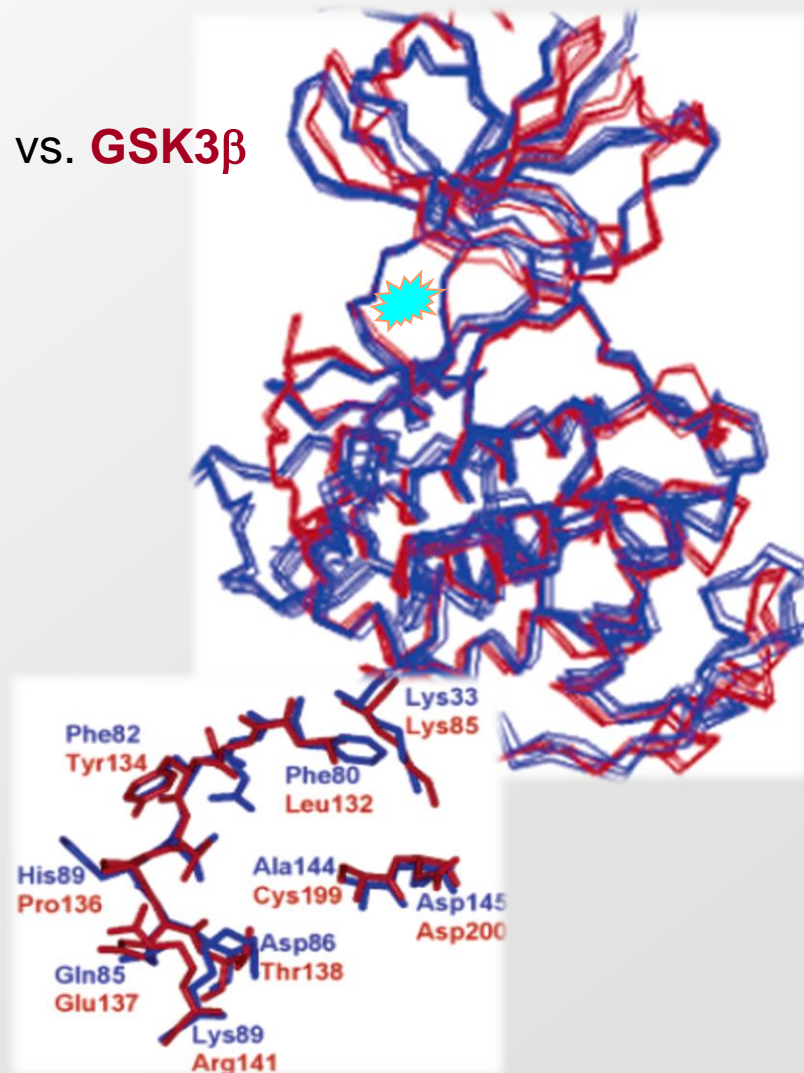
Podobnost proteinových kináz

human kinome: >500 kináz

Manning, G. et al. *Science* 2002, 298, 1912.



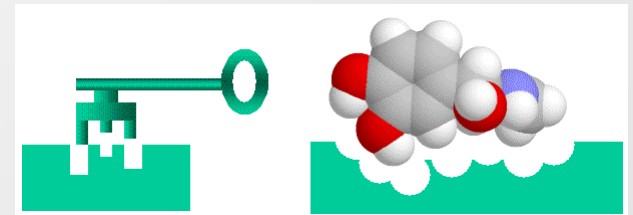
CDK2 vs. GSK3β



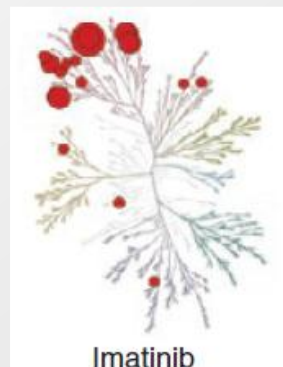
Selektivní vs. neselektivní inhibitory

(léčivo vs. selektivní „sonda“ pro molekulární biologii)

- hledání selektivního „klíče“ = inhibitoru pro pouze jeden z více než 500 velmi podobných „zámků“ - kináz



Staurosporine
*neselektivní
inhibitor*



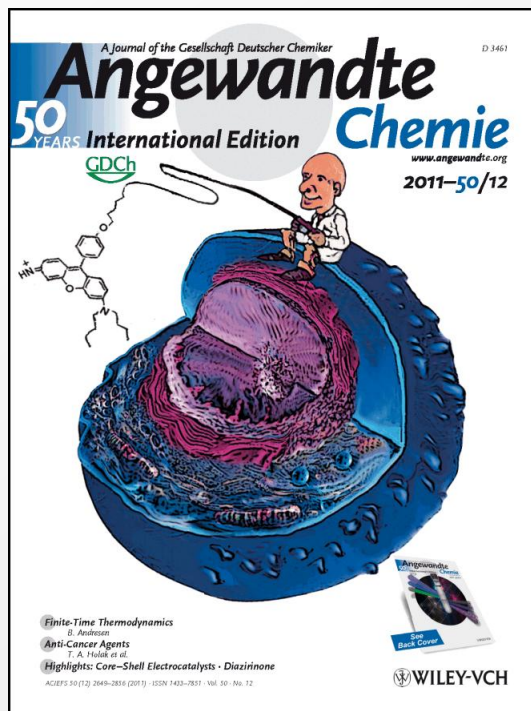
Imatinib
*selektivní
inhibitor*



Lapatinib
*vysoce
selektivní
inhibitor*



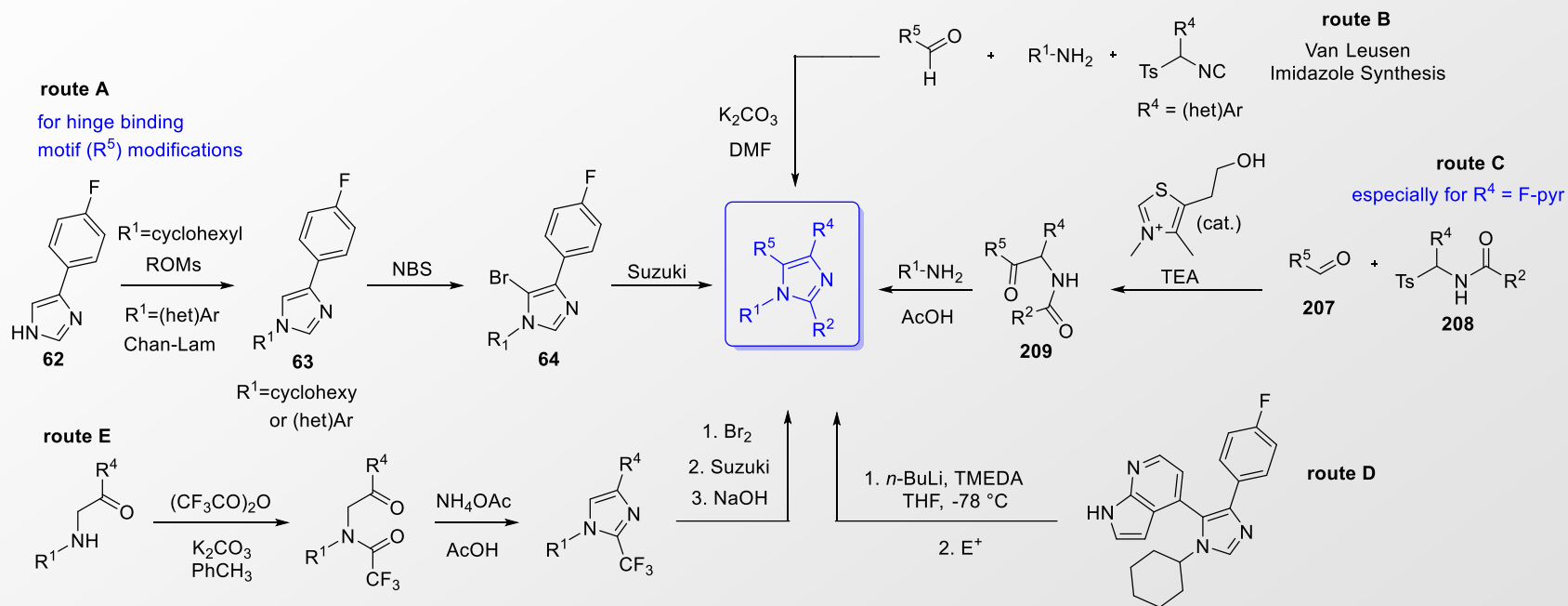
Identifikace biologicky aktivních sloučenin je (stále) značně empirický proces



organická chemie: účinné postupy k přípravě nových sloučenin
„molecular Lego“

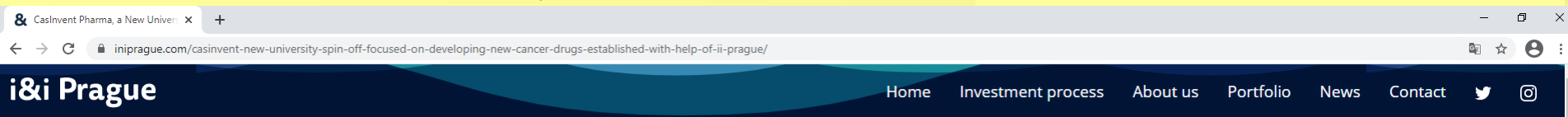


Různé cesty přípravy inhibitorů kinázy CK1



Inhibitory kinázy CK1

- inhibice CK1 α : nová možnost léčby leukemie AML



CasInvent Pharma, a New University Spin-Off Focused on Developing Cancer Drugs Established with Help of i&i Prague!

A new spin-off company, CasInvent Pharma, a.s., has been established by Masaryk University (MU) in cooperation with its investment partner, i&i Prague, s.r.o. (Ltd), in order to facilitate further development of new compounds that could be used to treat certain types of leukaemia, lymphoma and solid tumours. The company will test the compounds that inhibit the enzyme Casein Kinase 1 (CK1) which is responsible, among other things, for the migration of leukaemia cells into lymphoid organs.



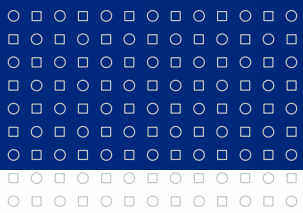
The research groups of Vítězslav Bryja and Kamil Paruch from the Faculty of Science MU have been studying and developing these compounds for a long time now. Thanks to the

Laboratory of Organic Synthesis and Medicinal Chemistry

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- personnel
 - Dr. Kamil Paruch (Ph.D. Columbia University)
 - Dr. Jakub Švenda (Ph.D. Harvard University)
 - 6 postdocs,
 - 5 doctoral students,
 - 10 BS/MS/high school students,
 - 3 technicians
- modern laboratories in new campus
- state-of-the-art instrumentation
(e.g. in-house 500 MHz NMR, autopurification LC/MS, semi-prep. chiral HPLC etc.)





The End

