EFFICIENT SIMULTANEOUS MATCHING OF MULTIPLE SMARTS USING THE CHEMAXON TOOLKITS

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OVERVIEW

- Chemical Pattern Matching
- Efficient Single Pattern Matching
- Multiple Pattern Matching
- Toolkit Code Generation
- Performance Figures
- Conclusions

PREVIOUS WORK

- Efficient Protein and Nucleic Acid Perception from Simple Atomic Connectivity

  www.daylight.com/meetings/mug96/sayle/sayle.html

  Describes algorithms for perceiving protein sequence and PDB atom names from SMILES, MDL or XYZ file of a protein.

- 1st Class SMARTS patterns

  www.daylight.com/meetings/emug97/Sayle/

  Describes SMARTS syntax and SMARTS algebra, a set of semantics preserving transformations that can be used to optimize SMARTS patterns.

CHEMICAL PATTERN MATCHING

- The identification of a specific subgraph within a graph, also known as *subgraph isomorphism*
- Typically to identify a functional group or substructure in a molecule connection table.
- Query patterns are typically specified as SMARTS, MDL query files, CDX or Marvin files.
- Matching is performed using
  - Ullman's isomorphism algorithm [1970]
  - McGregor's backtracking search [1981]

CHEMICAL DATABASE SEARCHING

- Although a backtracking atom-by-atom match is very efficient for matching a single pattern against a single molecule, well known optimizations exist for scanning a large database of target molecules.
  - Fingerprint screening/inverted indices
  - Character frequency (histogram) screening
  - “Triage” substructure identification

  http://www.daylight.com/meetings/emug00/Sayle/substruct.html

TOOLKIT (SMARTS?) PERFORMANCE

- Time taken to find O=[C,N]aa[N,O;!H0] hits in 250,251 SMILES of the NCI August 2000 data.
- Most time is typically spent on molecule I/O.

ToolKit	Times (secs)
ChemAxon JChem v5.5	58.8
RDKit v2011_03_2	131.2
OpenBabel v2.3.0	272.5
PerlMol	2107.9
CDK v1.2.10	DNF

CHEMINFORMATICS APPLICATIONS

- Compound Filtering
- Fingerprint generation
  - Database clustering
- Atom Typing
  - Property prediction

FILTERING RADIOACTIVE COMPOUNDS

- A molecule is radioactive if any of its atoms are radioactive. An atom is radioactive if its is not "stable".
- If an isotope is specified it must be one of the 255 known stable nuclides, otherwise the corresponding element must have at least one stable isotope.
- Elements H to $_{82}$Pb, with exceptions of $_{43}$Tc and $_{61}$Pm.
- Hence stable is "[0#1,1#1,2#1,0#2,3#2,4#2…]".
- Hence, radioactive is "[!0,!#1;!1,!#1;!2,!#2;…]".

RADIOACTIVE SMARTS

[!0,!#1;!1,!#1;!2,!#1;!0,!#2;!3,!#2;!4,!#2;!0,!#3;!6,!#3;!7,!#3;!0,!#4;!9,!#4;!0,!#5;!10,!#5;!11,!#5;!0,!#6;!12,!#6;!13,!#6;!0,!#7;!14,!#7;!15,!#7;!0,!#8;!16,!#8;!17,!#8;!18,!#8;!0,!#9;!19,!#9;!0,!#10;!20,!#10;!21,!#10;!22,!#10;!0,!#11;!23,!#11;!0,!#12;!24,!#12;!25,!#12;!26,!#12;!0,!#13;!27,!#13;!0,!#14;!28,!#14;!29,!#14;!30,!#14;!0,!#15;!31,!#15;!0,!#16;!32,!#16;!33,!#16;!34,!#16;!36,!#16;!0,!#17;!35,!#17;!37,!#17;!0,!#18;!36,!#18;!38,!#18;!40,!#18;!0,!#19;!39,!#19;!41,!#19;!0,!#20;!40,!#20;!42,!#20;!43,!#20;!44,!#20;!46,!#20;!0,!#21;!47,!#21;!0,!#22;!46,!#22;!47,!#22;!48,!#22;!49,!#22;!50,!#22;!0,!#23;!51,!#23;!0,!#24;!50,!#24;!52,!#24;!53,!#24;!54,!#24;!0,!#25;!55,!#25;!0,!#26;!54,!#26;!56,!#26;!57,!#26;!58,!#26;!0,!#27;!59,!#27;!0,!#28;!58,!#28;!60,!#28;!61,!#28;!62,!#28;!64,!#28;!0,!#29;!63,!#29;!65,!#29;!0,!#30;!64,!#30;!66,!#30;!67,!#30;!68,!#30;!70,!#30;!0,!#31;!69,!#31;!71,!#31;!0,!#32;!70,!#32;!72,!#32;!73,!#32;!74,!#32;!0,!#33;!75,!#33;!0,!#34;!74,!#34;!76,!#34;!77,!#34;!78,!#34;!80,!#34;!0,!#35;!79,!#35;!81,!#35;!0,!#36;!79,!#36;!80,!#36;!82,!#36;!83,!#36;!84,!#36;!86,!#36;!0,!#37;!85,!#37;!0,!#38;!84,!#38;!86,!#38;!87,!#38;!88,!#38;!0,!#39;!89,!#39;!0,!#40;!90,!#40;!91,!#40;!92,!#40;!94,!#40;!96,!#40;!0,!#41;!93,!#41;!0,!#42;!92,!#42;!94,!#42;!95,!#42;!96,!#42;!97,!#42;!98,!#42;!0,!#44;!96,!#44;!98,!#44;!99,!#44;!100,!#44;!101,!#44;!102,!#44;!104,!#44;!0,!#45;!103,!#45;!0,!#46;!102,!#46;!104,!#46;!105,!#46;!106,!#46;!108,!#46;!110,!#46;!0,!#47;!107,!#47;!109,!#47;!0,!#48;!106,!#48;!108,!#48;!110,!#48;!111,!#48;!112,!#48;!114,!#48;!0,!#49;!113,!#49;!0,!#50;!112,!#50;!114,!#50;!115,!#50;!116,!#50;!117,!#50;!118,!#50;!119,!#50;!120,!#50;!122,!#50;!124,!#50;!0,!#51;!121,!#51;!123,!#51;!0,!#52;!120,!#52;!122,!#52;!123,!#52;!124,!#52;!125,!#52;!126,!#52;!0,!#53;!127,!#53;!0,!#54;!124,!#54;!126,!#54;!128,!#54;!129,!#54;!130,!#54;!131,!#54;!132,!#54;!134,!#54;!136,!#54;!0,!#55;!133,!#55;!0,!#56;!130,!#56;!132,!#56;!134,!#56;!135,!#56;!136,!#56;!137,!#56;!138,!#56;!0,!#57;!139,!#57;!0,!#58;!136,!#58;!138,!#58;!140,!#58;!142,!#58;!0,!#59;!141,!#59;!0,!#60;!142,!#60;!143,!#60;!145,!#60;!146,!#60;!148,!#60;!0,!#62;!144,!#62;!149,!#62;!150,!#62;!152,!#62;!154,!#62;!0,!#63;!153,!#63;!0,!#64;!154,!#64;!155,!#64;!156,!#64;!157,!#64;!158,!#64;!160,!#64;!0,!#65;!159,!#65;!0,!#66;!156,!#66;!158,!#66;!160,!#66;!161,!#66;!162,!#66;!163,!#66;!164,!#66;!0,!#67;!165,!#67;!0,!#68;!162,!#68;!164,!#68;!166,!#68;!167,!#68;!168,!#68;!170,!#68;!0,!#69;!169,!#69;!0,!#70;!168,!#70;!170,!#70;!171,!#70;!172,!#70;!173,!#70;!174,!#70;!176,!#70;!0,!#71;!175,!#71;!0,!#72;!176,!#72;!177,!#72;!178,!#72;!179,!#72;!180,!#72;!0,!#73;!180,!#73;!181,!#73;!0,!#74;!182,!#74;!183,!#74;!184,!#74;!186,!#74;!0,!#75;!185,!#75;!0,!#76;!184,!#76;!187,!#76;!188,!#76;!189,!#76;!190,!#76;!192,!#76;!0,!#77;!191,!#77;!193,!#77;!0,!#78;!192,!#78;!194,!#78;!195,!#78;!196,!#78;!198,!#78;!0,!#79;!197,!#79;!0,!#80;!196,!#80;!198,!#80;!199,!#80;!200,!#80;!201,!#80;!202,!#80;!204,!#80;!0,!#81;!203,!#81;!205,!#81;!0,!#82;!204,!#82;!206,!#82;!207,!#82;!208,!#82]

COMPARATIVE PERFORMANCE

	ChemAxon 5.5 (Java)	
	Total	Match
Time to read file	47.57s	
Time to match '[!0]'	53.74s	6.17s
`radioactive.sma`	65.05s	17.48s

INTERPRETERS VS COMPILERS

- Most SMARTS matchers are implemented as “interpreters”, that parse the SMARTS string at run-time, build an internal parse tree, and then repeatedly traverse this at match-time.
- This is analogous to scripting in Perl or Python.
- For static patterns, the SMARTS may be compiled (parsed and optimized) ahead of time for faster execution at match-time.
- This is analogous to compilation in C or Fortran.

GENERATED JCHEM SOURCE CODE

```
static boolean isRadioactive(chemaxon.struc.Molecule mol) {
  int count = mol.getAtomCount();
  for (int i=0; i<count; i++) {
    chemaxon.struc.MolAtom atom = mol.getAtom(i);
    switch (atom.getAtno()) {
    case 1:
      switch (atom.getMassno()) {
      case 0:
      case 1:
      case 2:
        break;
      default:
        return true;
      }
      break;
```

COMPILED MATCHING PERFORMANCE

	ChemAxon 5.5 (Java)	
	Total	Match
Time to read file	47.57s	
Time to match '[!0]'	53.74s	6.17s
`radioactive.sma`	65.05s	17.48s
isRadioactive code	47.60s	0.03s
Speed-up	~1.38x	~700x

PATSY "BACKEND" TARGETS

- ChemAxon (Java)
- OEChem (C++/Python/Java)
- OpenBabel (C++)
- RDKit (C++/Python)
- CDK (Java)
- Cinfony/Pybel (Python)
- Pipeline Pilot (PilotScript)
- Isentris (Cheshire)
- PerlMol (Perl)

GENERATED OECHEM SOURCE CODE

```
#include <oechem.h>

bool isRadioactive(const OEChem::OEMolBase &mol) {
  OESystem::OEIter<OEChem::OEAtomBase> atom;
  for (atom = mol.GetAtoms(); atom; ++atom) {
    const OEChem::OAtomBase *aptr = atom;
    switch (aptr->GetAtomicNum()) {
    case 1:
      switch (aptr->GetIsotope()) {
      case 0:
      case 1:
      case 2:
        break;
      default:
        return true;
```

ISOMORPHISM COUNTING

- Match counts are frequently used in filtering apps.
- A benchmark of match iteration performance is to count the isomorphisms of ferrocene (to itself).
- SMILES: C12C3[Fe]1456789(C2C4C53)C1C6C7C8C91
- The correct answer is 200.
- OpenEye's OEChem v1.7 takes 3.461s
- A (Patsy) compiled C++ matcher using the same version of OEChem takes only 0.008s (400x).

MATCH GENERATORS

- Almost all cheminformatics toolkits provide a mechanism for returning the set of matchings of a given query pattern against a target.
- Most such implementations are “eager”; determining all solutions in advance.
- A more efficient, but technically more challenging solution, is to provide a “lazy” iterator (called a generator in python) reducing both run-time and memory.

TRIPOS SYBYL ATOM TYPES

# Carbon atom types	
[#6+]	C.cat
[c]	C.ar
[$(C#*),$(C(=*)=*)]	C.sp
C=*	C.sp2
[#6]	C.sp3

#Oxygen atom types	
[$(OC=O),$(O=CO)]	O.co2
O=*	O.2
[#8]	O.3

# Nitrogen atom types	
[nX2]	N.ar
[#7X4]	N.4
NC=[O,S]	N.am
[NX2]=*	N.2
[$(N=*),$(N*=*),$(Na),n]	N.pl3
[#7]	N.3

# Hydrogen atom type	
[#1]	H

IUPAC SUFFIX ATOM TYPES

- OpenEye's Lexichem internally uses a system of ~1034 atom types for determining the principal suffix during IUPAC name generation.

[CX3](=[OX1])-[OX1-]	carboxylate
[CX3](=[OX1])-[OHX1]	carboxylic acid
[CX3](=[OX1])-[OX2]	carboxylic acid ester
[CX3](=[OX1])-[NX3]	amide
[CX3](=[OX1])-[NX3]-[NX3]	hydrazide
[CX3H]=[OX1]	aldehyde
[CX3H0]=[OX1]	ketone
[OHX1]-[#6]	alcohol

MORGAN MATCHING

- An efficient way of matching multiple suitable acyclic patterns is to use a method much like Morgan's algorithm for canonical graph labels.
- In a first pass each vertex is assigned an atom type based purely on its constitution.
- In subsequent passes, each atom's type is updated based on its type and the types of its neighbours.

MORGAN MATCHING IN LEXICHEM

- In a first pass, atoms are assigned: 1 for [CX3v4], 2 for [OD1H0], 3 for [OD1H1], 4 for [NX3] and so on.
- In a second pass, the types of neighbours are used to update types: such that 1s can become 5 if they have neighbours of types 2 and 3, 6 if they have 2 and 4, and 4s can become 7s if they have a nbor of type 4.
- In a third pass, amides (type 6) can become type 8 (hydrazides) if they have a nbor of type 7 (hydrazine).

- All 1034 atom types are fully assigned in four passes.

MDL MACCS 166-BIT KEYS

- MDL's public key set of 166 substructure fragments is widely used in 2D chemical similarity and clustering applications.
- OpenBabel, RDKit, CDK and others distribute the set of 164 SMARTS patterns corresponding to each bit of the binary fingerprint.
- For an excellent discussion on "MACCS SMARTS pattern definitions" see Andrew Dalke's post at

  http://www.mail-archive.com/rdkit-discuss@lists.sourceforge.net/msg01727.html

MDL 166-BIT MACCS KEYS

- 150 regular patterns, 8 atom pattern counts and 6 complex pattern counts.
- Relationships between patterns non-obvious
  - BIT 137 (HETEROCYCLE) [!C;!c;R]
  - BIT 120 (HETEROCYCLIC ATOM > 1) [!#6;R]
- Counting semantics is unusual
  - BIT 127 (A$A!O > 1) [#8]!@*@* → [#8]!@[R]
- Monoatomic vs. polyatomic SMARTS
  - BIT 112 (AA(A)(A)A) *~*(~*)(~*)~* → [!D0!D1!D2!D3]

    Not the same as [X4] or [D4]!

MACCS ELEMENT BITS

- 20 bits may trivially be set using a table or by "switch"ing on the atomic number of the atom
  - BITS 2 (ATOMIC NO > 103), 3 (GROUPS IVA, VA and VIA), 4 (ACTINIDES), 5 (GROUPS IIB and IVB), 6 (LANTHANIDES), 7 (GROUPS VB, VIB and VIIB), 9 (GROUP VIII), 10 (GROUP IIA), 12 (GROUP IB and IIB), 18 (GROUP IIIA), 20 (SI), 27 (I), 29 (P), 35 (GROUP IA), 42 (F), 46 (BR), 88 (S), 103 (CL), 161 (N) and 164 (O).
- But with a switch statement, BIT 134 (HALOGEN), defined as [F,Cl,Br,I] can also be handled, by setting multiple bits for some elements.

TO COUNT OR NOT TO COUNT #1

- Theoretically its is more efficient to count (single atom) patterns than repeat them multiple times in the SMARTS string.
- Consider BIT 140 (O>3): [#8].[#8].[#8].[#8]
- This should be more efficient as count([#8]) > 3.
- The first scans a molecule with 3 oxygens 16 times!

- Alas as mentioned earlier poor implementations of “count” may always allocate memory proportional to the number oxygens in the molecule (think protein!)

TO COUNT OR NOT TO COUNT #2

- For (polyatomic) SMARTS the book keeping associated with checking “unique” matches may significantly impact performance.
- However sometimes it is possible/beneficial to transform “unique” counts into “exhaustive” counts.
- BIT 130 (QQ > 1): [!#6!#1]~[!#6!#1]
- In this case, it is possible and faster to eliminate the duplicate checking for ucount([!#6!#1]~[!#6!#1]) > 1 and instead test for count([!#6!#1]~[!#6!#1]) > 2.

MACCS RING BITS

- A significant fraction of time is spent on the ring bits
  - BITS 22 (3M RING), 11 (4M RING), 96 (5M RING), 163 (6M RING), 19 (7M RING) and 101 (8M RING).
- How a ring SMARTS is expressed affects performance
  - *~1~*~*~*~1 Poor
  - *@1@*@*@*@1 Good
  - [R]~1~[R]~[R]~[R]~1 Better
  - [R]@1@*@*@*@1 Best
- However the most significant improvements come from matching these ring patterns simultaneously.

FPCC CHEMAXON BACKEND

```
public class FPGenerator
  extends chemaxon.descriptors.MDGenerator {
  …
  public String[]
  generate(chemaxon.struc.Molecule mol,
           chemaxon.descriptors.MolecularDescriptor md) {
    chemaxon.descriptors.CustomDescriptor fp =
      (chemaxon.descriptors.CustomDescriptor)md;
    fp.clear();
    …
    return null;
  }
}
```

BIT 125: 2+ AROMATIC RINGS

```
// BIT 125
int[][][] arings = mol.getAromaticAndAliphaticRings(
                      chem.struc.MoleculeGraph.AROM_BASIC,
                      true, true, 6, 0);
if (arings[0].length >= 2)
  fp.set(124,1);
```

BIT 145: 2+ 6M RINGS

```
// BIT 145
int count = 0
int[][] sssr = mol.getSSSR();
for (int r=0; r<sssr.length; r++)
  if (sssr[r].length == 6) {
    if (count == 1) {
      fp.set(144,1);
      break;
    } else count++;
  }
```

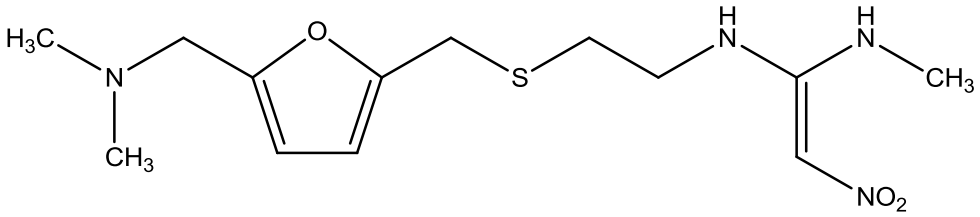
CHEMAXON MACCS FINGERPRINTING

Implementation	Total	Match
File I/O	32s	
Original Impl	8120s	8088s
Parse SMARTS once	1195s	1163s
Generated Impl	1066s	1034s
Speed-up	7.6x	7.8x

DERWENT CPI CODES

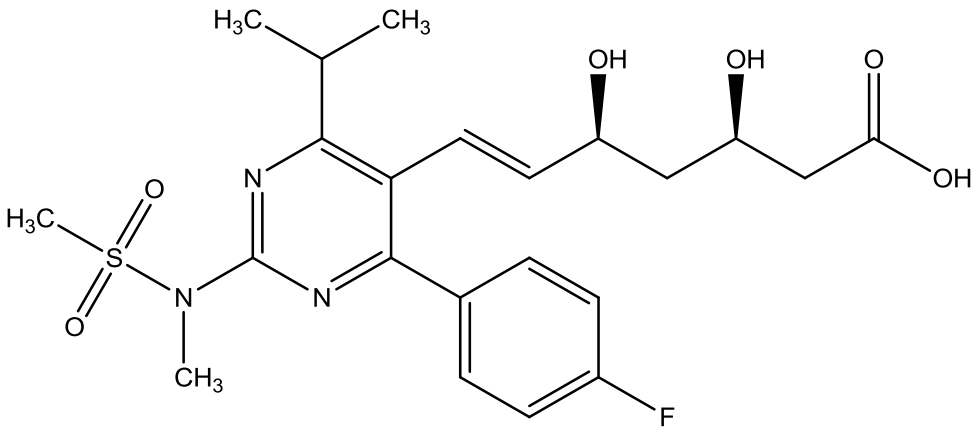
- A far more complex “fragment fingerprint” are the CPI codes used by Derwent/Thompson Reuters to index the “World Patent Index”.
- These codes form the basis of WPI structure searching in STNExpress.
- CPI uses about 1080 substructure/fragment codes that can be assigned automatically.

CPI INDEXING EXAMPLE: RANITIDINE



F012 – Mono-heterocycle substituted at 2-position
F015 – Mono-heterocycle substituted at 5-position
F111 – 5-Membered mono-heterocycle with 1 oxygen: C_4H_40; furan
H102 – Secondary amine (N-atom not in a ring)
H103 – Tertiary amine (N-atom not in a ring)
H183 – > 2 Amino groups bonded to C-atom of aliphatic group
H381 – 1 Nitro group bonded to non-cyclic (aliphatic) C-atom
H598 – S-atom of thioether group bonded to C-atom of acyclic group (no ring atoms)
H721 – 1 Unconjugated acyclic C=C
L640 – N-C-U group (U is N, O, S, Se or Te)
M211 – Methane or methyl group
M413 – Organic with >=1 unfused heterocycles, but no fused heterocycles
M521 – Organic containing 1 unfused heterocyclic ring
M540 – Organic containing no non-aromatic carbocyclic rings.

CPI INDEXING EXAMPLE: ROSUVASTATIN



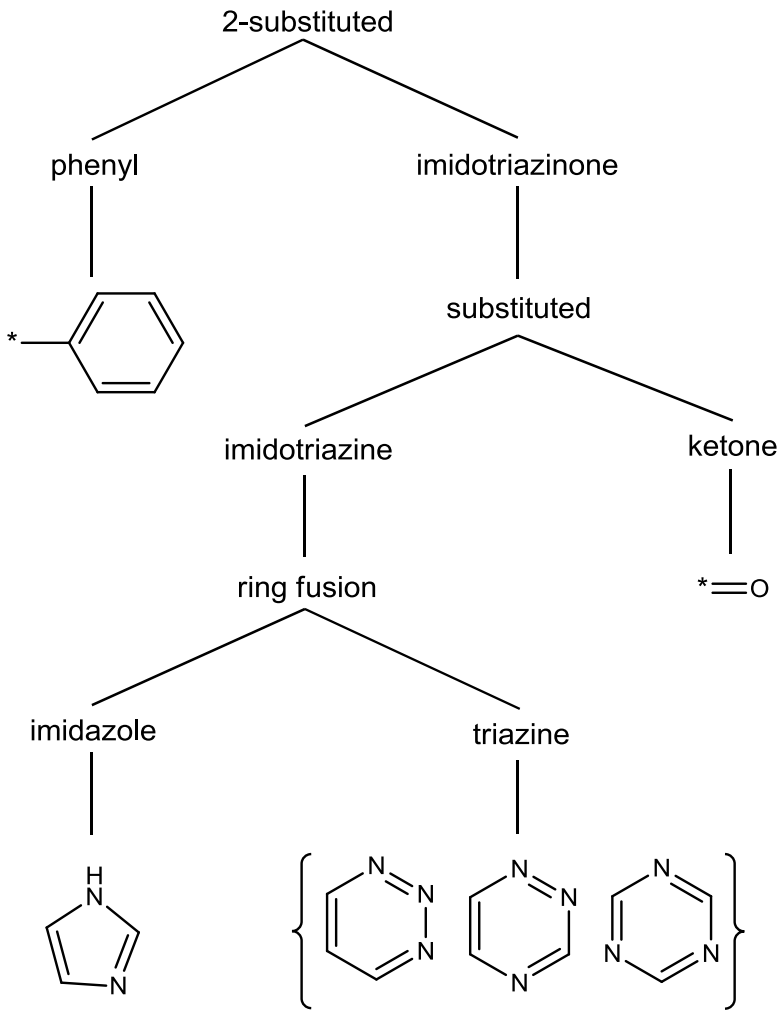
C316 – Inorganic sulphur, selenium or tellurium present with valency > 5
F012 – Mono-heterocycle substituted at 2-position
F541 – 6-membered mono-heterocycle with 2N; C_4H_4N2 (pyrimidine)
G013 – 2 positions substituted on unfused benzene; 1,4- (para)
G100 – 1 or more uncondensed benzenes with no other carbocycles
H482 – 2 -OH groups bonded to C-atoms of acyclic groups
H601 – Fluorine present [except in C(=[O,S])X or trifluoromethyl]
H641 – 1 Halogen bonded to carbocyclic aromatic ring
J011 – Total number of carboxylic acids, esters and amides = 1
J171 – 1 C(=O)OH group bonded to C-atom of acyclic group or formic acid
K353 – Other organic S-N groups

PATENT TEXT MINING

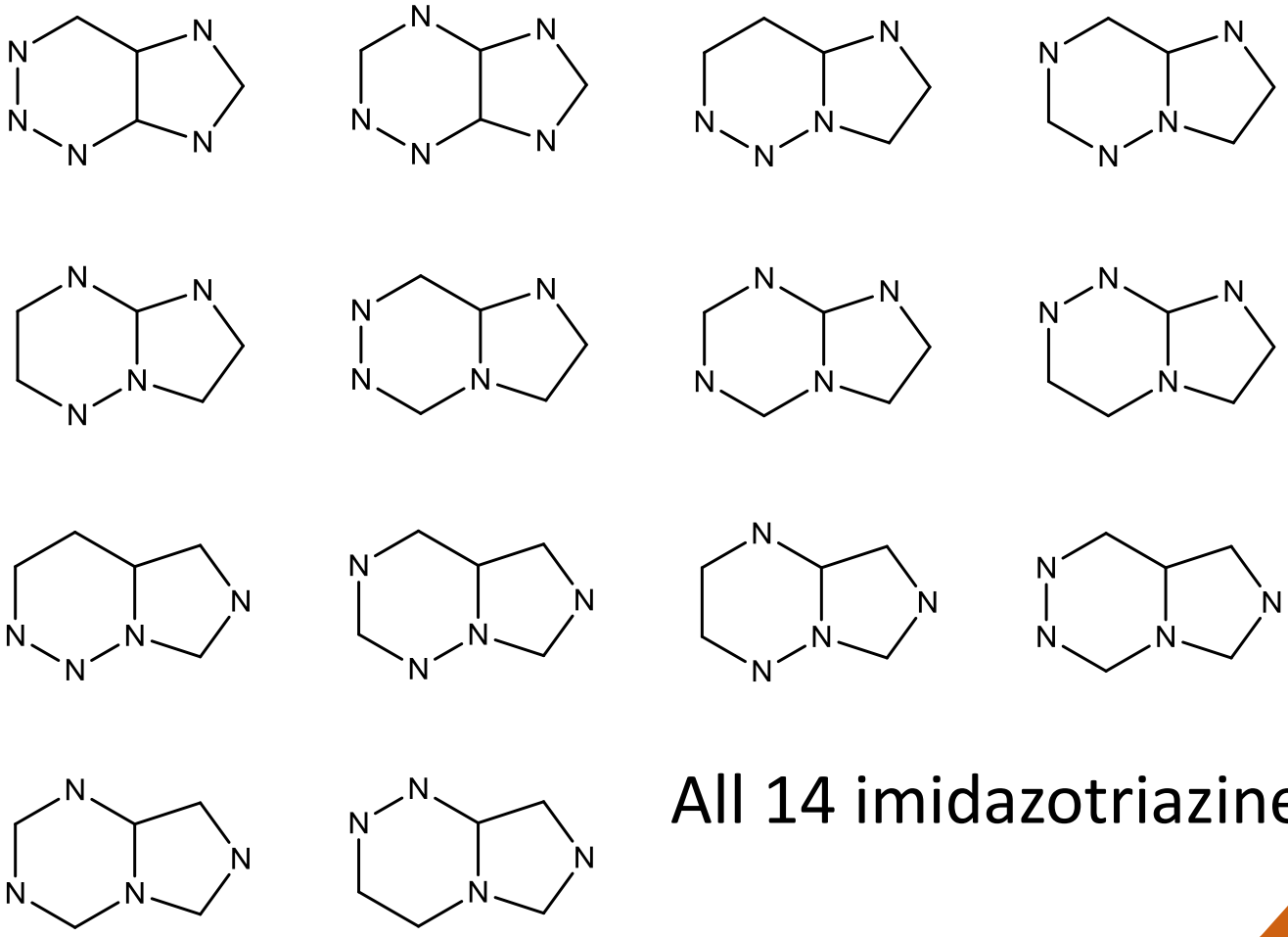
- The classic example of pharmaceutical patent busting is the 2009 Bayer patent for Vardenafil (Levitra), entitled "**2-phenyl substituted imidazotriazinones as phosphodiesterase inhibitors**", US patent number 7,696,206(B2).

- How much information can/could be mined from the title alone?

2-PHENYL SUBSTITUTED TRIAZINONES

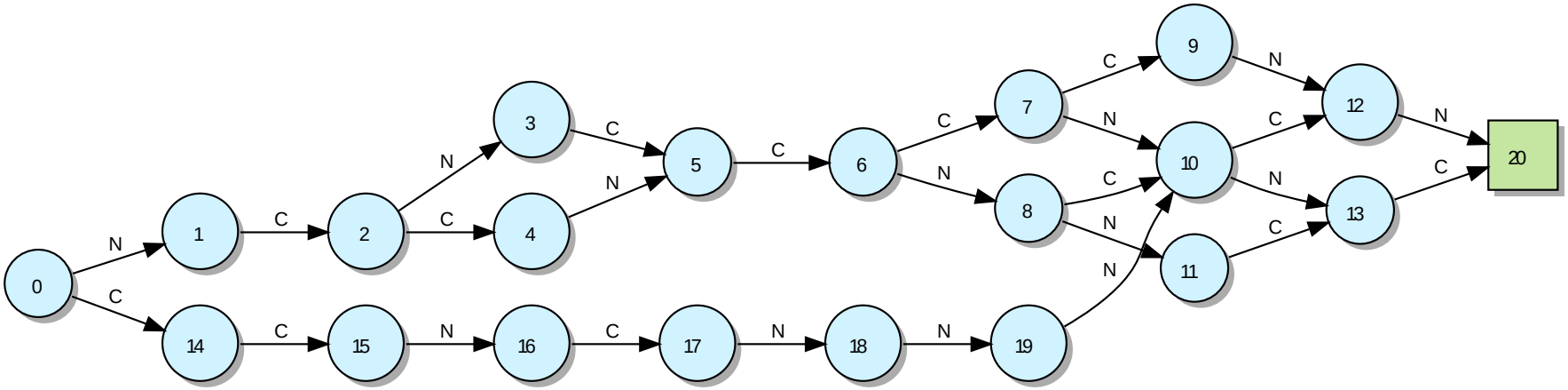


IMIDAZOTRIAZINES



All 14 imidazotriazines

BACKTRACKING STATE MACHINE



Simultaneously matching all 14 imidazotriazine SMARTS can be accomplished by the above finite state machine (FSM). A single SMARTS match is conceptually a linear state sequence.

CONCLUSIONS

- The “compilation” of SMARTS patterns, Patsy, is shown to dramatically improve the run-time performance of subgraph matching.
- The biggest gains are seen when matching multiple patterns, as compilation allows some patterns to be matched simultaneously.
- Increasing speed leads to improvements in expressive power, enabling previously impossible/prohibitive applications/queries.

APPLICATIONS/FUTURE WORK

- Reaction Informatics
  - Matching of a potentially large number of transformations for both normalization and synthetic/retrosynthetic analysis.
- Markush Representation
  - Capturing the semantics/scope of pharmaceutical patent claims.

THANK YOU FOR YOUR TIME

- Thanks again to the Alex Allardyce and the folks at ChemAxon for allowing me to present.
- Thanks to Vertex Pharmaceuticals for funding.
- And thank you for your questions.