ROLLING SMARTS:
YOU DON'T ALWAYS FIND WHAT YOU WANT, BUT IF YOU TRY SOMETIMES, YOU FIND WHAT YOU NEED

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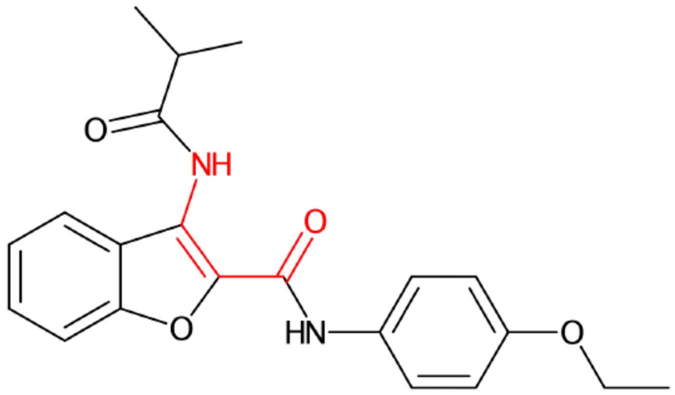
For the younger generation…

- “We need a president with tremendous… SMARTS…”
  - Donald J. Trump

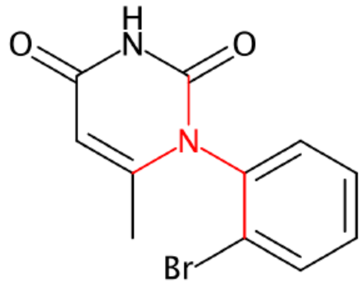
WHAT IS SMARTS?

- SMARTS is a line notation for specifying substructural patterns in (or queries on) chemical substructures.
- SMARTS are to SMILES, as regular expressions (regex) are to strings, and Biovia query files are to Mol files.



`O=[C,N]aa[N,O;!H0]`

intramolecular H Bonds



`[aD3]a!@-a([aD3])[aD3]`

biaryl atropisomers

SMARTS ATOM PRIMITIVES

- The portable subset of atom primitives include:

Symbol	Name	Definition	Default
<symbol>	(arom)element	IUPAC symbol (upper=A, lower=a)	(no default)
*	wildcard		(no default)
#n	atomic number	atomic number <n>	(no default)
A	aliphatic	aliphatic	(no default)
a	aromatic	aromatic	(no default)
R<0>	ring membership	in ring	any ring atom
X<n>	connectivity	<n> total connections	exactly one
D<n>	degree	<n> explicit connections	
H<n>	total H count	<n> attached hydrogens	
h<n>	Implicit H count	<n> implicit hydrogens	at least one
v<n>	valence	total bond order <n>	exactly one
x<n>	ring connectivity	<n> total ring connections	any ring atom
r<n>	smallest ring size	in smallest ring of size <n>	any ring atom
+<n>	positive charge	+<n> formal charge	+1 charge
-<n>	negative charge	-<n> formal charge	-1 charge

SMARTS ATOM PRIMITIVE EXTENSIONS

- Additional atom primitives include:

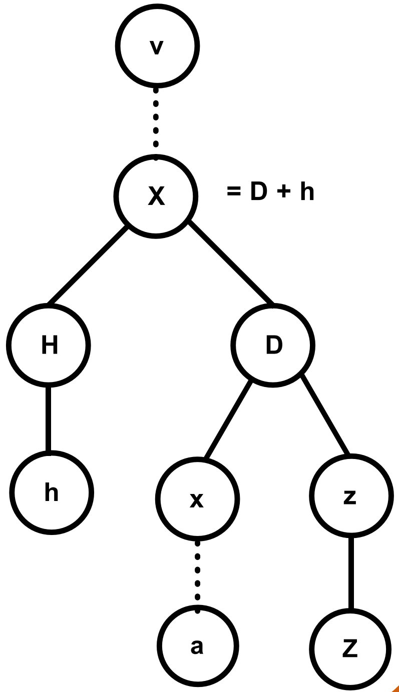
Symbol	Definition	Toolkits
R<n>	Input order dependent SSSR membership	Daylight
R<n>	Symmetrized SSSR membership	RDKit
R<n>	Number of ring bonds	OpenEye (NextMove)
z<n>	Heteroatom neighbor count	RDKit, CACTVS
Z<n>	Aliphatic heteroatom neighbor count	RDKit, CACTVS
Z<n>	In Ring of size <n>	NextMove
G<n>	Group <n> element	CCG MOE
a<n>	<n> explicit connections	CACTVS, NextMove
i<0>	Saturated or unsaturated atom	Lilly, CACTVS, NextMove
^<n>	<n> attached hydrogens	RDKit, OpenEye

- Several toolkits support ranges: X{m-n}, X{m-}, X{-n}
- Several toolkits support bounds: X>m, X<n

SMARTS ALGEBRA: X = D + h

- The most important axiom of SMARTS algebra is that X, the connectivity, is the degree (D) plus the implicit hydrogen count (h).

v	valence
X	connectivity
H	total hcount
h	implicit hcount
D	degree
x	ring bonds
a	aromatic bonds
z	hetero neighbors (RDKit)
Z	aliphatic hetero neighbors (RDKit)



LOGICAL OPERATORS

- SMARTS primitives can be negated with ! prefix.
- Primitives can be combined by conjunction (AND) and disjunction (OR).
- The (often optional) & operator has the highest priority, and binds tighter than OR.
- Atom lists are implemented by the "," disjunction operator, for example the familiar "[F,Cl,Br,I]".
- The low priority AND operator ";" can be used for constraining disjunctive lists.

De Morgan's Laws

- Arbitrarily complex Boolean expressions can be expressed in SMARTS, thanks to De Morgan's laws.
- e.g. The negation of "[F,Cl,Br,I]" is "[!F!Cl!Br!I]".
- The stable isotopes of hydrogen are "[0#1,1#1,2#1]", so unstable H isotopes "[#1;!0,!#1;!1,!#1;!2,!#1]".

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,!#4
6;!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,!#
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#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,!#5
3;!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,!#
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8;!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;!1
59,!#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;!16
4,!#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;!1
74,!#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,!
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;!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,!#8
2;!208,!#82]
```

STYLISH SMARTS

- Like programming languages, the formal specification or grammar defines what is acceptable, but often provide no guidance on preferred forms.
- Good style improves readability.
  - SMILES: [13CH3-]
  - SMARTS1? [#6&13;H3-1A]
  - SMARTS2? [!c13-#6H3]
  - SMARTS3? [13&C;H3&-]
- Good style sometimes benefits performance
  - [C,c] -> [#6]   [X0D0R0h0A] -> [X0]   [#26] -> [Fe]

ROBOCHEMISTRY AND THE BLACK SWAN

- A common source of “poor” SMARTS is observational bias, where an author makes assumptions about chemistry based on limited sampling.
- These SMARTS patterns are “good enough for government work”.
- An author may use the SMARTS “C” when they probably intended “[Cv4+0]”, after all aren’t all carbons neutral and four valent.
- Transformation rules misfiring on unanticipated input data leads to what PubChem calls “robochemistry”.

Pop Quiz: Find Benzene

- Consider the challenge of finding benzene and only benzene in a SMARTS search.
- c1ccccc1 is a substructure.
- c:1:c:c:c:c:c:1 just ensures the bonds are aromatic.
- [0cv4+0]:1:[0cv4+0]:[0cv4+0]:[0cv4+0]:[0cv4+0]:…
- [0cD2h1+0]:1:[0cD2h1+0]:[0cD2h1+0]:[0cD2h1+0]:…
- [0cX3H1+0]:1:[0cX3H1+0]:[0cX3H1+0]:[0cX3H1+0]:…
- [0c+0;D2h1,D3h0$(*-[0#1D1h0+0])]:1:…

POP QUIZ: MATCH NITRO GROUPS

- Likewise, if we assume RDKit has normalized nitro groups to *[N+](=O)[O-]
- [NX3v4+0](=[OD1h0+0])[OD1h0-1])
- [ND3h0v4+0](=[OD1h0+0])[OD1h0-1]

- For carboxylic acids and carboxylates
- [CX3v4+0](=[OD1h0+0])[OD1;h0-1,h1+0]
- And esters
- [CX3v4+0](=[OD1h0+0])[O+0;D1h1,X2v2]

RECURRING IDIOMS

- Degree, implicit hydrogen count and formal charge are often specified together: D?h?+?
- Connectivity and valence and formal charge are often specified together: X?v?+?

SKETCH SEMANTICS

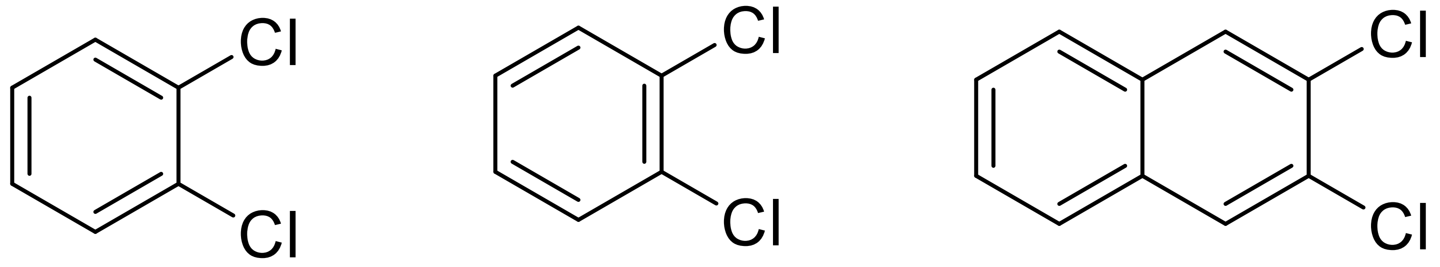
- SMARTS (mostly) has rigorous semantics that retrieve exactly what a cheminformatician asks for; unfortunately <1% of chemists can write SMARTS.

- The universal way of entering a substructure query is via a sketcher/structure editor such as JSME, Marvin, ChemDraw, Biovia Draw.

- Matching what a chemist believes they are asking for is a tricky challenge.

THE ROOT OF ALL EVIL: AROMATICITY

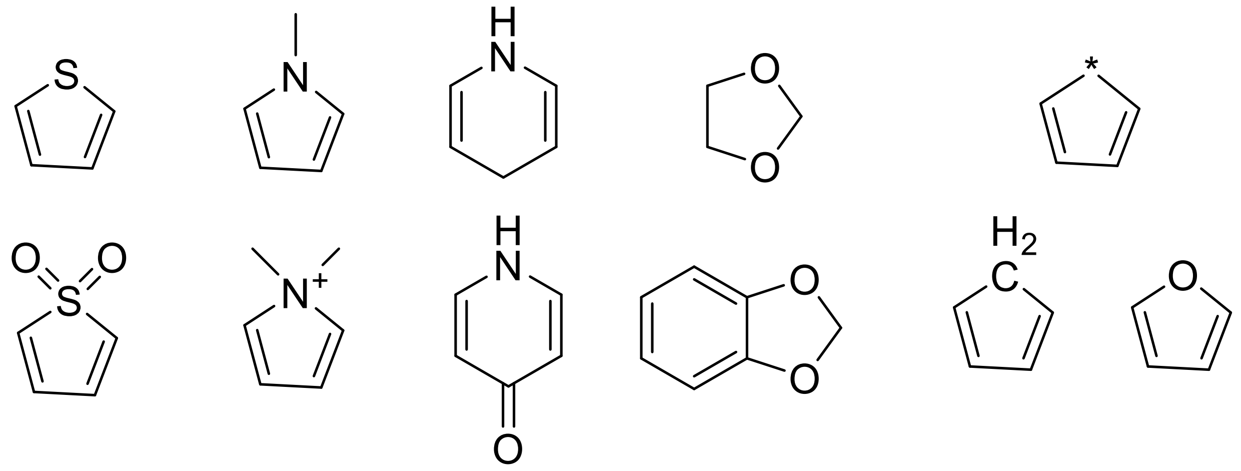
- The classic challenge of chemical search is that 1,2-dichlorobenzene should match itself independent of the Kekule form used to represent it.



- In theory, chemists could mark bonds aromatic.
- Take home #1: Sketch bonds may be aromatic.

THINGS ARE RARELY THAT SIMPLE

- These queries should(?) match the targets below.



- Queries drawn as aromatic may match aliphatic substructures, queries drawn as aliphatic may match aromatic substructures, and sometimes both.

Sketch Semantics: 2nd Attempt

- Allow atoms and bonds that could be aromatic, to be aromatic.
  - Benzene: [#6]1:,=[#6][#6]:,=[#6][#6]:,=[#6]1
  - Cyclohexane: [#6]1[#6][#6][#6][#6][#6]1
  - Cubane: [#6]12[#6]3[#6]4[#6]1[#6]5[#6]4[#6]3[#6]25

Sketch Semantics: 3rd Attempt

- An atom that is unsaturated in the query, must be unsaturated in the target.
  - Benzene: [#6i]1:,=[#6i][#6i]:,=[#6i][#6i]:,=[#6i]1
- Saturated atoms drawn with 2 neighbors may only be aromatic if saturated or unsaturated degree 3.
  - Cyclohexane: [#6;A,!i,D3]1[#6;A,!i,D3][#6;A,!i,D3][#6;A,!i,D3][#6;A,!i,D3][#6;A,!i,D3]1
- Saturated atoms drawn with 3 neighbors may only be aromatic if they remain saturated.
  - Cubane: [#6;A,!i]12[#6;A,!i]3[#6;A,!i]4[#6;A,!i]1[#6;A,!i]5[#6;A,!i]4[#6;A,!i]3[#6;A,!i]25

Features for Power Users

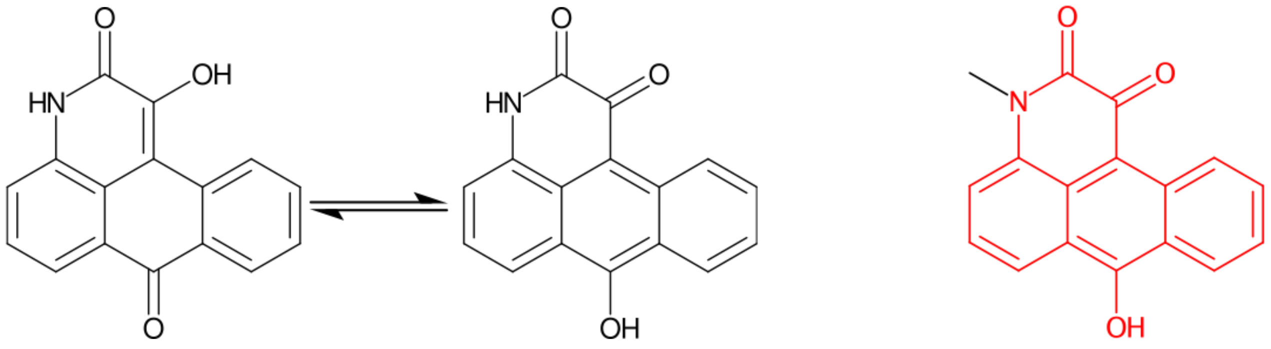
- Biovia query conversion should also support all of the expected features: atom lists, halogens, ring/chain topology, substitution count, bond logic,ring bond count, saturation/unsaturation etc.
- One cool feature supported by RDKit (and NextMove Software) is support for ChemAxon’s “M MRV SMA” field, which allows arbitrary SMARTS to be associated with an atom in a Biovia query.

SKETCH INTERPRETATION "SETTINGS"

- Lock Ring systems
  - A ring in a query always has to match a ring in the target. Locking ring systems prevents rings from forming parts of larger rings systems, i.e. benzene match naphthalene. Implemented by adding x2 constraints to ring atoms.
- Lock Chains
  - Acyclic query atoms must be acyclic in target.
- Lock Properties
  - Atoms without charge/isotope require no charge/isotope in target.
- Ignore stereochemistry/isotopes/charges.
  - Default behaviour of PubChem/CACTVS search.

THE PROBLEM WITH TAUTOMERS

- Tautomerism causes problems for SMARTS matching.



quinone_C filter

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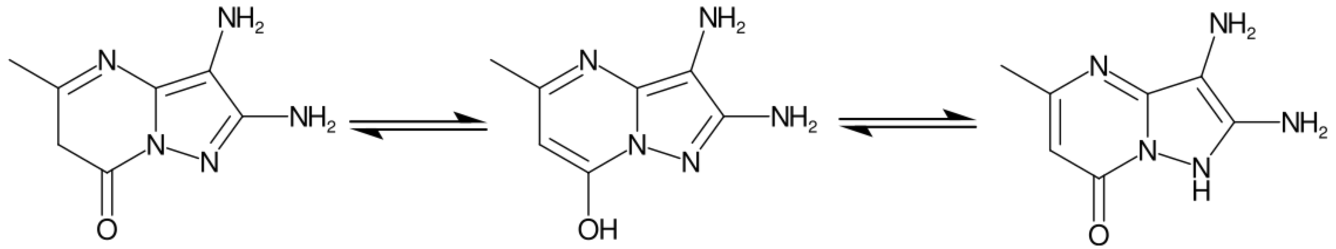

het_65_G filter

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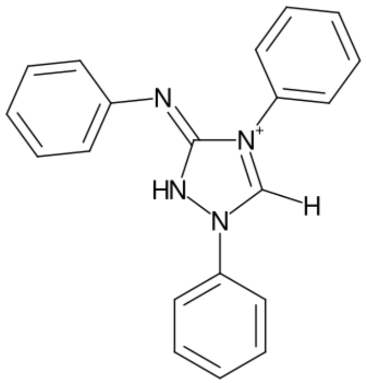
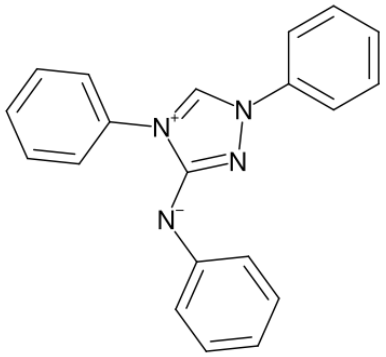
AND WITH RESONANCE FORMS

- As do resonance forms (and nitro representation &.)



het_5_inium filter



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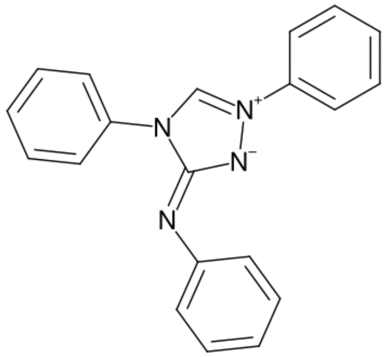
(Oct 2018)



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(Feb 2019)

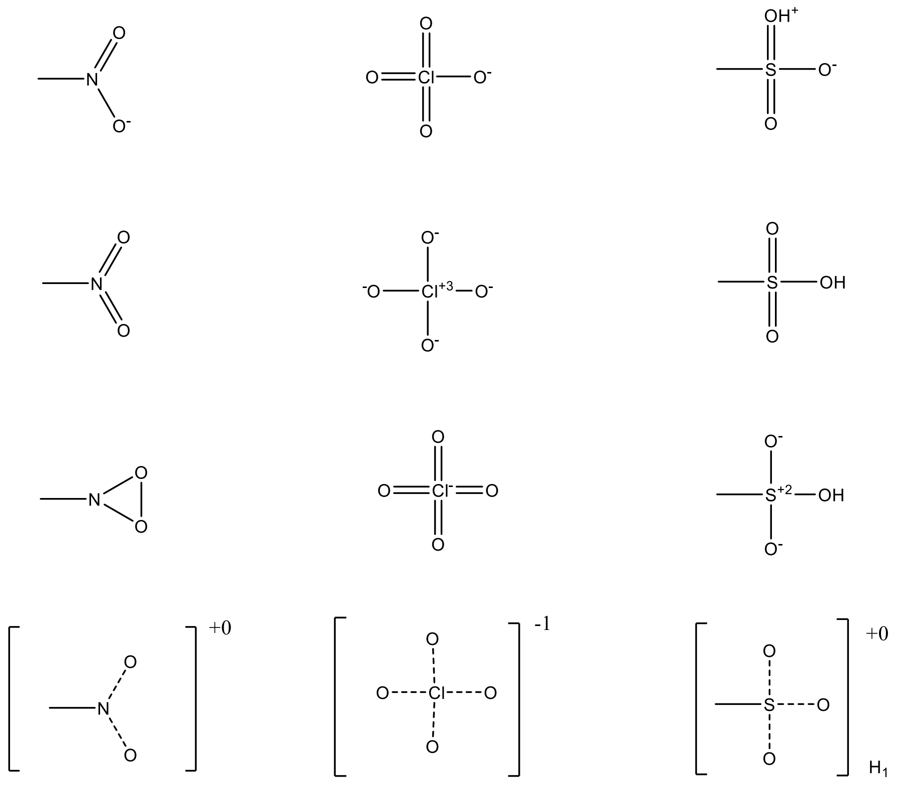
One way of solving this

- Is to enumerate all possible (tautomeric/resonance) forms, and then search for each of them.
- This is the approach used by RDKit::TautomerQuery which uses MolStandardize::TautomerEnumerator.
- Something similar could in theory be implemented using RDKit::ResonanceMolSupplier.

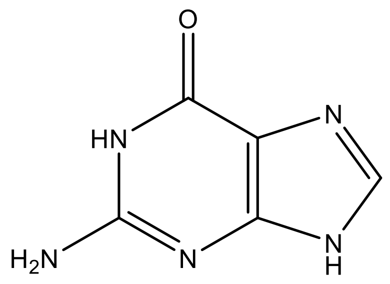
- This extremely powerful technique can also solve the aromaticity problem (by enumerating Kekulé forms) and canonicalization (by enumerating SMILES paths).

DEMOCRITUS TO BORN-OPPENHEIMER

"All that exists are atoms in space all else is conjecture"

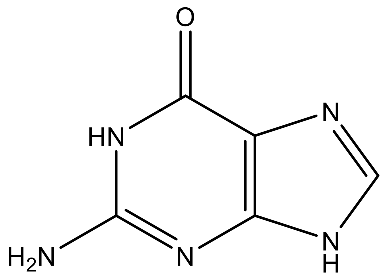


GUANINE TAUTOMERS SMARTS



- Carbons are constrained to be sp2, heteroatoms to standard valences.
- (Non-triple) bonds become single, double or aromatic.
- [#7]1-,=,:[#6]-,=,:[#7]-,=,:[#6]2-,=.:[#6]-,=,:1-,=,:[#7]-,=,:[#6](-,=,:[#7]) -,=,:[#7]-,=,:[#6] -,=,:2-,=,:[#8]
- Carbons: [#6X3v4i+0,#6X3v3-1,#6X3v3+1]
- Nitrogens: [#7X2v3+0,#7X3v3+0,#7X3v4+1,#7X4v4+1]
- Oxygens: [#8X1v2+0,#8X1v1-1,#8X2v2+0,#8X2v3+1,#8X3v3+1]

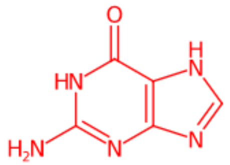
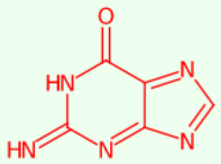
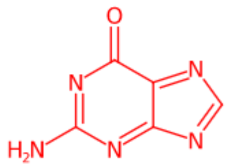
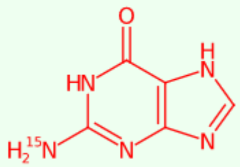
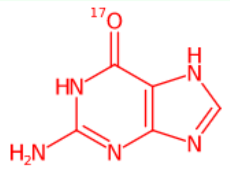
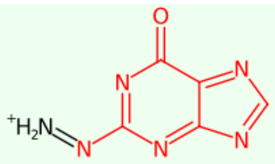
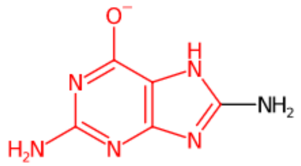
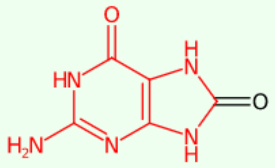
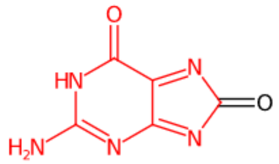
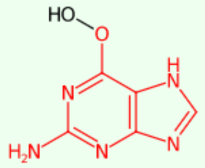
Guanine tautomers SMARTS



- [#7X2v3+0,#7X3v3+0,#7X3v4+1,#7X4v4+1]1-,=,: [#6X3v4i+0]-,=,: [#7X2v3+0,#7X3v3+0,#7X3v4+1,#7X4v4+1] -,=,: [#6X3v4i+0]2-,=,:[#6X3v4i+0]-,=,:1-,=,: [#7X2v3+0,#7X3v3+0,#7X3v4+1,#7X4v4+1]-,=,: [#6X3v4i+0](-,=,: [#7X2v3+0,#7X3v3+0,#7X3v4+1,#7X4v4+1]) -,=,: [#7X2v3+0,#7X3v3+0,#7X3v4+1,#7X4v4+1]-,=,: [#6X3v4i+0] -,=,:2-,=,: [#8X1v2+0,#8X1v1-1,#8X2v2+0,#8X2v3+1,#8X3v3+1]

GUANINE TAUTOMERS RESULTS

- Without post-processing, the raw results look like:

1		**135398634** $C_5H_5N_5O$ 151.126
2		**140355140** $C_5H_3N_5O$ 149.110
3		**504258** $C_5H_3N_5O$ 149.110
4		**135537618** $C_5H_3N_5O$ 150.104
5		**136689991** $C_5H_5N_5O$ 152.126
54		**101930028** C_5HN_6O 161.101
55		**102341194** $C_5H_5N_6O$ 165.133
56		**135420630** $C_5H_5N_5O_2$ 167.125
57		**135498233** $C_5H_3N_5O_2$ 165.109
58		**141357953** $C_5H_5N_5O_2$ 167.125

NetQ & TotX: Conservation of X

- Identifying/filtering relevant tautomers (perhaps via SubstructMatchParameters::extraFinalCheck)

```
int netq = 0;
unsigned int totx = 0;
for (unsigned int idx : match) {
  Atom *atm = mol->getAtomWithIdx(idx);
  netq += atm->getFormalCharge();
  totx += atm->getTotalDegree();
}
// Gaunine tautomers have totx of 29, and 0 netq.
return totx+netq >= 29;
```

- Under reasonable valence constraints $\Sigma(X_i + q_i)$ is a conserved quantity of substituted tautomers/protomers.

NEXT GEN. SMARTS OPTIMIZATION

- A significant development in the field of SMARTS optimization has been the development of next generation search engines.
  1. Uniform performance of all non-recursive atom expressions through the use of atom typing.
     - No penalty for [I,Br,F,Cl,C,c,#6,C]
  2. Atom and bond ordering in SMARTS patterns is now irrelevant.
     - BrCCC is no longer faster than CCCBr.
  3. Complex/distinctive expressions are now optimal.
     - [CD>3v4Z5Z6i0+0]

(PATSY) SMARTS OPTIMIZATION 2020

- Intramolecular H Bonds
  - Input: O=[C,N]aa[N,O;!H0]
  - Internal: [O&i]=[C,N;D>1v>2i]-[aD3]:[aD3]-[N,O;!H0!D0]
- Biaryl atropisomers
  - Input: [aD3]a!@-a([aD3])[aD3]
  - Internal: [aD3]:[aD3x2]!@-[aD3x2](:[aD3]):[aD3]
- Cubane
  - Input: C12C3C4C1C5C4C3C25
  - Internal: [CZ4Z6Z8x>2]12-@[CZ4Z6Z8x>2]3-@[CZ4Z6Z8x>2]4-@[CZ4Z6Z8x>2]-@1-@[CZ4Z6Z8x>2]5-@[CZ4Z6Z8x>2]-@4-@[CZ4Z6Z8x>2]-@3-@[CZ4Z6Z8x>2]-@2-@5

SUMMARY & CONCLUSIONS

- SMARTS is incredibly expressive.
- Writing SMARTS well is challenging.
- Divergence in implementations doesn’t help.
- The situation is (hopefully) improving.
- Significant recent technical advances.
- Sketch semantics lowers the barrier to entry.
- But opens up new opportunities/challenges.

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FOR GREG #1: FASTER ATOM MATCHING

- Current code

```
static inline int makeAtomType(int atomic_num, bool aromatic) {
  return atomic_num + 1000 * static_cast<int>(aromatic);
}
static inline void parseAtomType(int val, int &atomic_num, bool &aromatic) {
  if (val > 1000) {
    aromatic = true;
    atomic_num = val - 1000;
  } else {
    aromatic = false;
    atomic_num = val;
  }
}
```

- Suggestion

```
static inline int makeAtomType(int atomic_num, bool aromatic) {
  return (atomic_num<<1) + (aromatic?1:0);
}
static inline void parseAtomType(int val, int &atomic_num, bool &aromatic) {
  atomic_num = val >> 1;
  aromatic = val & 1;
}
```

FOR GREG #2: FASTER ATOM METHODS

```
namespace RDKit {
struct FastAtom : public Atom {
  ROMol &fast_getOwningMol() const { return *dp_mol; }
};
}

RDKit::ROMol &Atom_getOwningMol_old(const RDKit::Atom *at) {
  return at->getOwningMol();
}
RDKit::ROMol &Atom_getOwningMol_new(const RDKit::Atom *at) {
  return ((const RDKit::FastAtom*)at)->fast_getOwningMol();
}
unsigned int Atom_getDegree_new(const RDKit::Atom *at) {
  unsigned int idx = at->getIdx();
  const RDKit::MolGraph &graph = at->getOwningMol().getTopology();
  return (unsigned int)graph.m_vertices[idx].m_out_edges.size();
}
unsigned int Atom_getDegree_newer(const RDKit::Atom *at) {
  unsigned int idx = at->getIdx();
  const RDKit::FastAtom *fat = (const RDKit::FastAtom *)at;
  const RDKit::MolGraph &graph = fat->fast_getOwningMol().getTopology();
  return (unsigned int)graph.m_vertices[idx].m_out_edges.size();
}
```