Supporting Information

Enumeration of Ring-Chain Tautomers Based on SMIRKS Rules

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Breaking Bond	Geometry Carbon	Size of ring	Rule	SMIRKS
exo	trig	3	RC1	[#1:1][O,N,S,Se,Te:2][#6R1;!c;z2:3]1[#6;!c;R1:4][O,N,S,Se,Te;R1:5]1>>[O,N,S,Se,Te:2]=[C;!R;z1:3][#6;!R:4][O,N,S,Se,Te;!R:5][#1:1]
		4	RC2	[#1:1][O,N,S,Se,Te:2][#6R1;!c:3]1[#6;R1:4]~[C;R1:6][O,N,S,Se,Te;R1:5]1>>[O,N,S,Se,Te:2]=[C;!R:3][C;!R:4][C;!R:6][O,N,S,Se,Te;!R:5][#1:1]
		5	RC3	[#1:1][O,N,S,Se,Te:2][#6R1;!c:3]1[*:4]~[*:7]~[R1:6][O,N,S,Se,Te;R:5]1>>[O,N,S,Se,Te:2]=[C;!R:3][R{0-1}:4]~[R{0-1}:7][!R:6][O,N,S,Se,Te:5][#1:1]
			RC3'	[#1:1][O,N,S,Se,Te:2][#6R1;!c:3]1[*;R1:4]~[*:7]~[R:6][O,N,S,Se,Te;R1:5]1>>[O,N,S,Se,Te:2]=[C;!R:3][!R:4]~[R{0-1}:7][R{0-1}:6][O,N,S,Se,Te;!R:5][#1:1]
			RC3''	[#1:1][O,N,S,Se,Te:2][#6R1;!c:3]1[*;R1:4]~[*:7]~[R:6][N:5]1>>[O,N,S,Se,Te:2]=[C;!R:3][!R:4]~[!R:7][R{0-1}:6][N:5][#1:1]
		6	RC4	[#1:1][O,N,S,Se,Te:2][#6R1;!c:3]1[*:4]~[*:7]~[*;R1:8]~[C;R1:6][O,N,S,Se,Te;R:5]1>>[O,N,S,Se,Te:2]=[C;!R:3][R{0-1}:4]~[R{0-1}:7]~[!R:8]~[!C:6][O,N,S,Se,Te:5][#1:1]
			RC4'	[#1:1][O,N,S,Se,Te:2][#6R1;!c:3]1[*;R1:4]~[*:7]~[*:8]~[R1:6][O,N,S,Se,Te;R:5]1>>[O,N,S,Se,Te:2]=[C;!R:3][!R:4]~[R{0-1}:7]~[R{0-1}:8]~[!R:6][O,N,S,Se,Te:5][#1:1]
			RC4''	[#1:1][O,N,S,Se,Te:2][#6R1;!c:3]1[*;R1:4]~[*;R1:7]~[*:8]~[R:6][O,N,S,Se,Te;R1:5]1>>[O,N,S,Se,Te:2]=[C;!R:3][!R:4]~[!R:7]~[R{0-1}:8]~[R{0-1}:6][O,N,S,Se,Te;!R:5][#1:1]
			RC4'''	[#1:1][O,N,S,Se,Te:2][#6R1;!c:3]1[*;R1:4]~[*;R1:7]~[*;R1:8]~[R:6][N:5]1>>[O,N,S,Se,Te:2]=[C;!R:3][!R:4]~[!R:7]~[!R:8]~[R{0-1}:6][N:5][#1:1]
		7	RC5	[#1:1][O,N,S,Se,Te:2][#6R1;!c:3]1[*:4]~[*:7]~[*;R1:8]~[*;R1:9]~[R1:6][O,N,S,Se,Te;R:5]1>>[O,N,S,Se,Te:2]=[C;!R:3][R{0-1}:4]~[R{0-1}:7]~[!R:8]~[!R:9]~[!R:6][O,N,S,Se,Te:5][#1:1]
			RC5'	[#1:1][O,N,S,Se,Te:2][#6R1;!c:3]1[*;R1:4]~[*:7]~[*:8]~[*;R1:9]~[R1:6][O,N,S,Se,Te;R:5]1>>[O,N,S,Se,Te:2]=[C;!R:3][!R:4]~[R{0-1}:7]~[R{0-1}:8]~[!R:9]~[!R:6][O,N,S,Se,Te:5][#1:1]
			RC5''	[#1:1][O,N,S,Se,Te:2][#6R1;!c:3]1[*;R1:4]~[*;R1:7]~[*:8]~[*:9]~[R1:6][O,N,S,Se,Te;R:5]1>>[O,N,S,Se,Te:2]=[C;!R:3][!R:4]~[!R:7]~[R{0-1}:8]~[R{0-1}:9]~[!R:6][O,N,S,Se,Te:5][#1:1]
			RC5'''	[#1:1][O,N,S,Se,Te:2][#6R1;!c:3]1[*;R1:4]~[*;R1:7]~[*;R1:8]~[*:9]~[R:6][O,N,S,Se,Te;R1:5]1>>[O,N,S,Se,Te:2]=[C;!R:3][!R:4]~[!R:7]~[!R:8]~[R{0-1}:9]~[R{0-1}:6][O,N,S,Se,Te;!R:5][#1:1]
			RC5''''	[#1:1][O,N,S,Se,Te:2][#6R1;!c:3]1[*;R1:4]~[*;R1:7]~[*;R1:8]~[*;R1:9]~[R:6][N:5]1>>[O,N,S,Se,Te:2]=[C;!R:3][!R:4]~[!R:7]~[!R:8]~[!R:9]~[R{0-1}:6][N:5][#1:1]
	dig	5	RC6	[#1:1][N:2]=[#6R1;!c:3]1[*:4]~[*:7]~[#6R1:6][O,N,S,Se,Te;R:5]1>>[N;X1:2]#[C;!R:3][R{0-1}:4]~[R{0-1}:7]~[#6;!R:6][O,N,S,Se,Te:5][#1:1]
			RC6'	[#1:1][N:2]=[#6R1;!c:3]1[*;R1:4]~[*:7]~[#6R:6][O,N,S,Se,Te;R1:5]1>>[N;X1:2]#[C;!R:3][!R:4]~[R{0-1}:7]~[#6;R{0-1}:6][O,N,S,Se,Te;!R:5][#1:1]
			RC6''	[#1:1][N:2]=[#6R1;!c:3]1[*;R1:4]~[*;R1:7]~[#6R:6][N:5]1>>[N;X1:2]#[C;!R:3][!R:4]~[!R:7]~[#6;R{0-1}:6][N:5][#1:1]
		6	RC7	[#1:1][N:2]=[#6R1;!c:3]1[*:4]~[*:7]~[*;R1:8]~[#6R1:6][O,N,S,Se,Te;R:5]1>>[N;X1:2]#[C;!R:3][R{0-1}:4]~[R{0-1}:7]~[*;!R:8]~[#6;!R:6][O,N,S,Se,Te:5][#1:1]
			RC7'	[#1:1][N:2]=[#6R1;!c:3]1[*;R1:4]~[*:7]~[*:8]~[#6R1:6][O,N,S,Se,Te;R:5]1>>[N;X1:2]#[C;!R:3][!R:4]~[R{0-1}:7]~[*;R{0-1}:8]~[#6;!R:6][O,N,S,Se,Te:5][#1:1]
			RC7''	[#1:1][N:2]=[#6R1;!c:3]1[*;R1:4]~[*;R1:7]~[*:8]~[#6R:6][O,N,S,Se,Te;R1:5]1>>[N;X1:2]#[C;!R:3][!R:4]~[!R:7]~[*;R{0-1}:8]~[#6;R{0-1}:6][O,N,S,Se,Te;!R:5][#1:1]
			RC7'''	[#1:1][N:2]=[#6R1;!c:3]1[*;R1:4]~[*;R1:7]~[*;R1:8]~[#6R:6][N:5]1>>[N;X1:2]#[C;!R:3][!R:4]~[!R:7]~[!R:8]~[#6;R{0-1}:6][N:5][#1:1]
		7	RC8	[#1:1][N:2]=[#6R1;!c:3]1[*:4]~[*:7]~[*;R1:8]~[*;R1:9]~[#6R1:6][O,N,S,Se,Te;R:5]1>>[N;X1:2]#[C;!R:3][R{0-1}:4][R{0-1}:7][*;!R:8][*;!R:9][#6;!R:6][O,N,S,Se,Te:5][#1:1]
			RC8'	[#1:1][N:2]=[#6R1;!c:3]1[*;R1:4]~[*:7]~[*:8]~[*;R1:9]~[#6R1:6][O,N,S,Se,Te;R:5]1>>[N;X1:2]#[C;!R:3][!R:4][R{0-1}:7][*;R{0-1}:8][*;!R:9][#6;!R:6][O,N,S,Se,Te:5][#1:1]

			RC8''	[#1:1][N:2]=[#6R1;!c:3]1[*;R1:4]~[*;R1:7]~[*:8]~[*:9]~[#6R1:6][O,N,S,Se,Te;R:5]1>>[N;X1:2]#[C;!R:3][!R:4][!R:7][*;R{0-1}:8][*;R{0-1}:9][#6;!R:6][O,N,S,Se,Te:5][#1:1]
			RC8'''	[#1:1][N:2]=[#6R1;!c:3]1[*;R1:4]~[*;R1:7]~[*;R1:8]~[*:9]~[#6R:6][O,N,S,Se,Te;R1:5]1>>[N;X1:2]#[C;!R:3][!R:4][!R:7][*;!R:8][*;R{0-1}:9][#6;R{0-1}:6][O,N,S,Se,Te;!R:5][#1:1]
			RC8''''	[#1:1][N:2]=[#6R1;!c:3]1[*;R1:4]~[*;R1:7]~[*;R1:8]~[*;R1:9]~[#6R:6][N:5]1>>[N;X1:2]#[C;!R:3][!R:4][!R:7][*;!R:8][*;!R:9][#6;R{0-1}:6][N:5][#1:1]
endo	trig	5	RC9	[#1:1][N;R1;X3:3]1[!a:4]~[R:6][O,N,S,Se,Te;R:5][#6R;z2;X4:2]1>>[C;!R;z1;X3:2]=[N;!R,X2;+0:3][*:4]~[*:6][O,N,S,Se,Te;!R:5][#1:1]
			RC9'	[#1:1][N;R1;X3:3]1[!a;R1:4]~[R:6][N:5][#6R;z2;X4:2]1>>[C;!R;z1;X3:2]=[N;!R,X2;+0:3][!R:4]~[*:6][N:5][#1:1]
			RC9''	[#1:1][O:7][N;R1:3]1[!a:4]~[R:6][O,N,S,Se,Te;R:5][#6R;z2;X4:2]1>>[C;!R;z1;X3:2]=[N+;!R:3]([O-:7])[*:4]~[*:6][O,N,S,Se,Te;!R:5][#1:1]
		6	RC10	[#1:1][N;R1;X3:3]1[!a:4]~[*:7]~[*;R1:6][O,N,S,Se,Te;R:5][#6R;z2;X4:2]1>>[C;!R;z1;X3:2]=[N;!R;+0:3][R{0-1}:4]~[*;R{0-1}:7]~[!R:6][O,N,S,Se,Te:5][#1:1]
			RC10'	[#1:1][N;R1;X3:3]1[!a;R1:4]~[*:7]~[*:6][O,N,S,Se,Te;R1:5][#6R;z2;X4:2]1>>[C;!R;z1;X3:2]=[N;!R;+0:3][!R:4]~[*;R{0-1}:7]~[R{0-1}:6][O,N,S,Se,Te;!R:5][#1:1]
			RC10''	[#1:1][N;R1;X3:3]1[!a;R1:4]~[*;R1:7]~[*:6][N:5][#6R;z2;X4:2]1>>[C;!R;z1;X3:2]=[N;!R;+0:3][!R:4]~[*;!R:7]~[R{0-1}:6][N:5][#1:1]
			RC10'''	[#1:1][O:8][N;R1;X3:3]1[!a:4]~[*:7]~[*;R1:6][O,N,S,Se,Te;R:5][#6R;z2;X4:2]1>>[C;!R;z1;X3:2]=[N+;!R:3]([O-:8])[R{0-1}:4]~[*;R{0-1}:7]~[!R:6][O,N,S,Se,Te:5][#1:1]
		7	RC11	[#1:1][N;R1;X3:3]1[!a:4]~[*:7]~[*;R1:8]~[R1:6][O,N,S,Se,Te;R:5][#6R;z2;X4:2]1>>[C;!R;z1;X3:2]=[N;!R;+0:3][R{0-1}:4]~[*;R{0-1}:7]~[*;!R:8]~[!R:6][O,N,S,Se,Te:5][#1:1]
			RC11'	[#1:1][N;R1;X3:3]1[!a;R1:4]~[*:7]~[*:8]~[R1:6][O,N,S,Se,Te;R:5][#6R;z2;X4:2]1>>[C;!R;z1;X3:2]=[N;!R;+0:3][!R:4]~[*;R{0-1}:7]~[*;R{0-1}:8]~[!R:6][O,N,S,Se,Te:5][#1:1]
			RC11''	[#1:1][N;R1;X3:3]1[!a;R1:4]~[*;R1:7]~[*:8]~[R:6][O,N,S,Se,Te;R:5][#6R;z2;X4:2]1>>[C;!R;z1;X3:2]=[N;!R;+0:3][!R:4]~[*;!R:7]~[*;R{0-1}:8]~[R{0-1}:6][O,N,S,Se,Te;!R:5][#1:1]
			RC11'''	[#1:1][N;R1;X3:3]1[!a;R1:4]~[*;R1:7]~[*;R1:8]~[R:6][N:5][#6R;z2;X4:2]1>>[C;!R;z1;X3:2]=[N;!R;+0:3][!R:4]~[*;!R:7]~[*;!R:8]~[R{0-1}:6][N:5][#1:1]
			RC11''''	[#1:1][O:9][N;R1;X3:3]1[!a:4]~[*:7]~[*:8]~[*;R1:6][O,N,S,Se,Te;R:5][#6R;z2;X4:2]1>>[C;!R;z1;X3:2]=[N+;!R:3]([O-:9])[R{0-1}:4]~[*;R{0-1}:7]~[*:8]~[!R:6][O,N,S,Se,Te:5][#1:1]

Table SI2 - Bibliographic examples of ring-chain tautomerism together with predicted tautomers.

Ref	SMILES (**input molecule** / tautomer(s))	Ring-chain rule applied	#experimentally identified ring-chain tautomers	#predicted ring-chain tautomers	#predicted prototropic tautomers	#predicted tautomers for both types
1	**C1=CC(=CC=C1)C=NC(CC(=O)N)C(=O)O** C1=CC(=CC=C1)C2NC(CC(N2)=O)C(O)=O	6_endo_trig	1	18	2	149
2	**C1(=C(C2=C(C(=C1Cl)O)C(C(C(C2=O)C3CCCC(C3)=O)O)=O)O)Cl** C1(=C(C2=C(C(=C1Cl)O)C(C4C(C2=O)C3CCCC(C3)(O)O4)=O)O)Cl	Not covered	1	0	86	0
3	**C1=CC=CC(=C1C)N2[C@H](C(OC2=O)(C)C)O** C1=CC=CC(=C1C)NC(OC(C=O)(C)C)=O	5_exo_trig	1	1	0	3
4	**C1[N+](CC[CH2]C1)=[C](C)CCC(=[N+]([O-])[O-])C**	Not applicable				
5	**c1cccc(c12)Sec3c(cccc3)C=NCCNCCN=Cc4c(cccc4)Sec5c(cccc5)C=NCCNCCN=C2** c1cccc(c1[CH]23)Sec4c(cccc4)C=NCCNCCN=Cc5c(cccc5)Sec6c(cccc6)C=NCCN2CCN3 c1cccc(c1[CH]23)Sec4c(cccc4)C=NCCN5[CH](NCC5)c6c(cccc6)Sec7c(cccc7)C=NCCN2CCN3	Not covered	2	0	0	0
6	**C1(NC(OC1)C2=CC=C(C=C2)Cl)C3=CC=CC=C3** C(N=CC1=CC=C(C=C1)Cl)(CO)C2=CC=CC=C2	5_endo_trig	1	1	0	1
7	**N1=C(C=CC=C1)C(C2=C(CC(CC2=O)(C)C)O)C3=C(CC(CC3=O)(C)C)O** N1=C(C=CC=C1)C3C2=C(CC(CC2(O)OC4=C3C(CC(C4)(C)C)=O)(C)C)O	Not covered	1	0	74	74
8	**C13(N(C(OC1)C2=CC=CC=C2)C(SC3)C4=CC=CC=C4)CO**	Not applicable				
9	**C1CCC(C(=C1)N2CCCCC2)C(C[N](=O)=O)C(Cl)(Cl)Cl**	Not applicable				
10	**C1(=CC(=CC=C1)C2OCCCN2)C3NCCCO3** C1(=CC(=CC=C1)C=NCCCO)C2NCCCO2 C1(=CC(=CC=C1)C=NCCCO)C=NCCCO	6_endo_trig	2	2	0	2
11	**C3=C(C(C1=C(OC2=C(C1=O)C=CC=C2)O)CC(=O)C)C=CC=C3** C4=C(C3C1=C(OC2=C(C1=O)C=CC=C2)OC(C3)(O)C)C=CC=C4	6_exo_trig	1	1	8	10
12	**C1=CC2=C(C=C1)C(NNC(S2)C3=CC=C(C=C3)[N](=O)=O)=O** C1=CC(=C(C=C1)C(NN=CC2=CC=C(C=C2)[N](=O)=O)=O)S	7_endo_trig	1	1	1	14
13	**C1=CC=CC(=C1)NC(OC(C=O)(C)C)=O** C1=CC=CC(=C1)N2C(OC(C2O)(C)C)=O	5_exo_trig	1	1	1	3
14	**C1(=C(SC=C1)C(C2=C(C=CS2)C)=CCCO)C**	Not applicable				
15	**C1=CC=CC(=C1)C2C(NC(O2)C3=C(C=CS3)C)C** C1=CC=CC(=C1)C(C(N=CC2=C(C=CS2)C)C)O	5_endo_trig	1	1	0	1
16	**N1(C(N(C(C1)C2=CC=CC=C2)O)C3=CC=CC=C3)C** N(CC([N+](=CC1=CC=CC=C1)[O-])C2=CC=CC=C2)C	5_endo_trig	1	1	0	1
17	**C1=CC(=C(C=C1)C([P](O)(=O)OC)=O)C(O)=O** C1=CC2=C(C=C1)C([P](O)(=O)OC)(O)OC2=O	5_exo_trig	1	2	0	2
18	**C1=CC=CC=C1C2OCC(N2)C** C1=CC=CC=C1C=NC(CO)C	5_endo_trig	1	1	0	1
19	**C1=C(C=C(C=C1)C2OCCC(N2)C)C** C1=C(C=C(C=C1)C=NC(CCO)C)C	6_endo_trig	1	1	0	1
20	**C1=CC2=C(C=C1)C(NNC(S2)(C)C)=O** C1=CC(=C(C=C1)C(NN=C(C)C)=O)S	7_endo_trig	1	1	1	41
21	**C1N(C(N(C1C2=CC=CC=C2)O)C3=CC=C(C=C3)Cl)C4=CC=C(C=C4)C** C(NC1=CC=C(C=C1)C)C([N+](=CC2=CC=C(C=C2)Cl)[O-])C3=CC=CC=C3	5_endo_trig	1	1	0	1
22	**C1=CC2C(=CN1C)C(NC2(C3=CC=CC=C3)O)=O** C1=CC(C(=CN1C)C(N)=O)C(C2=CC=CC=C2)=O	5_exo_trig	1	1	1	7
23	**C1(NC(OCC1)C2=CC=CC=C2)C**	6_endo_trig	1	1	0	1

	C(N=CC1=CC=CC=C1)(CCO)C					
24	**C1C=C(C(CC1)C(C[N](=O)=O)C2=CC=CC=C2)OC**	Not applicable				
25	**C1=CC2=C(C=C1)C3=C(C=C2)OC(NC3)C4=CC=CC=C4**	6_endo_trig	1	1	0	1
	C1=CC2=C(C=C1)C(=C(C=C2)O)CN=CC3=CC=CC=C3					
26	**C1=CC2=C(C=C1)C3=C(C=C2)OC(NC3)C4=CC=CC=C4**	6_endo_trig	1	1	0	1
	C1=CC2=C(C=C1)C(=C(C=C2)O)CN=CC3=CC=CC=C3					
27	**C1=CC(=C(C=C1)N)C(N=CCC(=O)C2=CC=C(C=C2)C)=O**	6_endo_trig	1	1	70	126
	C1=CC3=C(C=C1)NC(CC(=O)C2=CC=C(C=C2)C)NC3=O					
28	**C1=CC=C(C=C1)C=NC2=C(C=CC=C2)CO**	6_endo_trig	1	1	0	1
	C1=CC=C(C=C1)C3NC2=C(C=CC=C2)CO3					
29	**C1(=CC2=C(C=C1OC)CCN3C2CCNC3C4=CC=C(C=C4)[N](=O)=O)OC**	6_endo_trig	1	1	0	1
	C1(=CC2=C(C=C1OC)CCNC2CCN=CC3=CC=C(C=C3)[N](=O)=O)OC					
30	**S1CCNC1C(=C)OC**	5_endo_trig	1	1	0	1
	SCCN=CC(=C)OC					
31	**N1C(NCCC1C)C2=CC=CC=C2**	6_endo_trig	2	2	0	2
	NC(CCN=CC1=CC=CC=C1)C					
	N(=CC1=CC=CC=C1)C(CCN)C					
32	**C1=CC2=C(C=C1)C3=C(C=C2)OC(NC3C4=CC=C(C=C4)[N](=O)=O)C5=CC=C(C=C5)Cl**	6_endo_trig	1	1	0	1
	C1=CC2=C(C=C1)C(=C(C=C2)O)C(N=CC3=CC=C(C=C3)Cl)C4=CC=C(C=C4)[N](=O)=O					
33	**C(C(N(C)C)=O)CCBr**	Not applicable				
34	**C(C(N(C)C)=O)CCCl**	Not applicable				
	C1(OCCN1)C(OCC)=C	5_endo_trig	1	1	0	1
	C(=NCCO)C(OCC)=C					
35	**C1CC2(C(C1)COC(N2)C3=CC=C(C=C3)[N](=O)=O)C**	6_endo_trig	1	1	0	1
	C1CC(C(C1)CO)(N=CC2=CC=C(C=C2)[N](=O)=O)C					
	C1CC2(C(C1)CNC(O2)C3=CC=C(C=C3)[N](=O)=O)C	6_endo_trig	1	1	0	1
	C1CC(C(C1)CN=CC2=CC=C(C=C2)[N](=O)=O)(O)C					
	C1=CC2=C(C=C1)C3=C(C=C2)C(NC(O3)C4=CC=C(C=C4)Cl)C5=CC=C(C=C5)Br	6_endo_trig	1	1	0	1
	C1=CC2=C(C=C1)C(=C(C=C2)C(N=CC3=CC=C(C=C3)Cl)C4=CC=C(C=C4)Br)O					
	C1(=CC=CC(=C1)Br)C2OCC(CN2)O	6_endo_trig	2	2	0	2
	C1(=CC=CC(=C1)Br)C=NCC(CO)O	5_endo_trig				
	C1(=CC=CC(=C1)Br)C2NCC(CO)O2					
	C1CC(C2(CC1)CNC(O2)C3=CC=C(C=C3)Cl)O	5_endo_trig	2	2	0	2
	C1CC(C(CC1)(CN=CC2=CC=C(C=C2)Cl)O)O	6_endo_trig				
	C1CC3C(CC1)(CNC(C2=CC=C(C=C2)Cl)O3)O					
	C1(=CC=C(C=C1)C(C2COC(N2)C3=CC=CC=C3)O)[N](=O)=O	5_endo_trig	2	2	0	2
	C1(=CC=C(C=C1)C(C(CO)N=CC2=CC=CC=C2)O)[N](=O)=O					
	C1(=CC=C(C=C1)C3C(CO)NC(C2=CC=CC=C2)O3)[N](=O)=O					
	C1=CC=C(C=C1)C2OC3C(CN2)OC(NC3)C4=CC=CC=C4	6_endo_trig	2	4	0	4
	C1=CC=C(C=C1)C=NCC2C(O)CNC(O2)C3=CC=CC=C3					
	C1=CC=C(C=C1)C=NCC(C(O)CN=CC2=CC=CC=C2)O					
	C1(=CC=C(C=C1)C2OCC(N2)(C)CO)C3OCC(N3)(C)CO	5_endo_trig	2	2	0	2
	C1(=CC=C(C=C1)C=NC(CO)(C)CO)C2OCC(N2)(C)CO					
	C1(=CC=C(C=C1)C=NC(CO)(C)CO)C=NC(CO)(C)CO					
	O2CCOC1=C(C=CC=C1)C=NC(C(N=CC3=CC=CC=C23)CO)CO	Not covered	2	0	0	0
	O2CCOC1=C(C=CC=C1)C4NC(C(N=CC3=CC=CC=C23)CO4)CO					
	O2CCOC1=C(C=CC=C1)C5NC4C(NC(C3=CC=CC=C23)OC4)CO5					
	C1(NC(OC1)C(C)=O)(CO)CO	5_endo_trig	3	2	1	5
	C(N=CC(C)=O)(CO)(CO)CO	6_exo_trig				
	C1(N=CC(C)(O)OC1)(CO)CO					

	C12(NC(C(C)(O)OC1)OC2)CO					
	C1C(N(COC1C2=CC=CC=C2)O)C	6_endo_trig	1	1	0	1
	C(C([N+](=C)[O-])C)C(O)C1=CC=CC=C1					
	S1C(NCC1)C(C(C(C(CO)O)O)O)O	5_endo_trig	2	6	0	6
	SCCN=CC(C(C(C(CO)O)O)O)O	6_exo_trig				
	SCCNC1C(C(C(C(CO)O1)O)O)O					
	C1=C(C=CC=C1)NCCN=CC2=CC=CC=C2	5_endo_trig	1	1	0	1
	C1=C(C=CC=C1)N2CCNC2C3=CC=CC=C3					
	C1=CC2=C(C=C1)CC3N(C2)C(NC3)C4=CC=CC=C4	5_endo_trig	1	1	0	1
	C1=CC2=C(C=C1)CC(NC2)CN=CC3=CC=CC=C3					
	N1C(NCCC1)C(C(C(C(CO)O)O)O)O	6_endo_trig	2	6	0	6
	N(=CC(C(C(C(CO)O)O)O)O)CCCN	6_exo_trig				
	N(C1C(C(C(C(CO)O1)O)O)O)CCCN					
	C1=CC2=C(C=C1)CNC(N2)(CC(N(O)C3=CC=CC=C3)=O)C	6_endo_trig	2	2	1	9
	C1=CC(=C(C=C1)CN=C(CC(N(O)C2=CC=CC=C2)=O)C)N	5_exo_trig				
	C1=CC(=C(C=C1)CNC2(CC(N(O2)C3=CC=CC=C3)=O)C)N					
	C1(NNC(SC1)(C)C)=O	6_endo_trig	1	1	2	6
	C(NN=C(C)C)(CS)=O					
	C1=CC2=C(C=C1)C(N(NC(N2)C)C)=O	7_endo_trig	1	1	3	12
	C1=CC(=C(C=C1)C(N(N=CC)C)=O)N					
36	**C(C(C)=O)CCN**	5_exo_trig	1	1	2	3
	C1C(C)(O)NCC1					
37	**Erythromycin A**	Not covered	2	0	5	5
38	**C1OC(CC1)(O)C(OC(C)(C)C)=O**	5_exo_trig	1	2	0	4
	C(O)CCC(=O)C(OC(C)(C)C)=O					
39	**C1COC(NC1C2=CC=CC=C2)C3=CC=CC=C3**	6_endo_trig	1	1	0	1
	C(CO)C(N=CC1=CC=CC=C1)C2=CC=CC=C2					
40	**C1=CC2=C(C=C1)CNC(N2)C3=CC=C(C=C3)Cl**	6_endo_trig	1	1	0	1
	C1=CC(=C(C=C1)CN=CC2=CC=C(C=C2)Cl)N					
41	**C1=CC2=C(C=C1)C(N3N(C2=O)C(CC3)O)=O**	5_exo_trig	1	1	0	4
	C1=CC2=C(C=C1)C(N(NC2=O)CCC=O)=O					
42	**C1CC2C(CC1)COC(N2)C3=CC=CC=C3**	6_endo_trig	1	1	0	1
	C1CC(C(CC1)CO)N=CC2=CC=CC=C2					
	C1(C(CCCC1)CNC(C)(C)C)N=CC2=CC=CC=C2	6_endo_trig	1	1	0	1
	C12C(CCCC1)CN(C(C)(C)C)C(N2)C3=CC=CC=C3					
43	**C1=CC(N2N(C1=O)C(CC2)NNC=O)=O**	5_exo_trig	1	1	1	11
	C1=CC(N(NC1=O)CCC=NNC=O)=O					
44	**C(C(CC(CC(C)(C)C)C)=O)(C)ON)=O)(C)(C)C**	5_exo_trig	1	1	2	5
	C(C1(CC(CC(C(C)(C)C)C)=O)(C)ON1)O)(C)(C)C					
45	**C1=CC(=CC=C1O)C4(C2=CC=C(C=C2)O)C3=CC=CC=C3C(O4)=O**	Not applicable				
46	**C1=C(C=CC(=C1)C=NC(CO)(C)CO)C=NC(CO)(C)CO**	5_endo_trig	2	2	0	2
	C1=C(C=CC(=C1)C2NC(CO2)(C)CO)C=NC(CO)(C)CO					
	C1=C(C=CC(=C1)C2NC(CO2)(C)CO)C3NC(CO3)(C)CO					
47	**C1NC(N(CC1)C)C2=CC=C(C=C2)Br**	6_endo_trig	1	1	0	1
	C(N=CC1=CC=C(C=C1)Br)CCNC					
48	**C12(SCC(CO1)(C)C)C(C(C(CC2)C3=CC=CC=C3)C)C**	Not applicable				
49	**C1(NC(OC1C2=CC=CC=C2)C3=CC=CC=C3)C**	5_endo_trig	1	1	0	1
	C(N=CC1=CC=CC=C1)(C(O)C2=CC=CC=C2)C					
50	**C3(=NC1(C2(CCC(C1(C)C)C2)C)SC(=N3)C)C**	6_endo_trig	1	0	4	9
	C(N=C1C2(CCC(C1(C)C)C2)C)(=NC(=S)C)C					

51	**C(C(O)=O)=CC(=O)C1=CC=CC=C1** C2=CC(O)(C1=CC=CC=C1)OC2=O	5_exo_trig	1	1	0	1
52	**C(=O)\C=C/C(=O)O** C1(O)\C=C/C(=O)O1	5_exo_trig	1	1	0	1

This table shows the SMILES for 71 molecules extracted from the literature with the corresponding number of experimentally identified ring-chain tautomers, predicted ring-chain tautomers (by our ring-chain rules), predicted prototropic tautomers (by CACTVS tautomerism rules) and predicted tautomers of either type (by combined application of ring-chain and CACTVS tautomerism rules). The column "Ring-chain rule applied" shows the ring-chain rule that transforms the input molecule to the documented ring-chain tautomer. The SMILES in bold denote the input molecules. The plain SMILES (below the bold ones) are the corresponding documented ring-chain tautomers; they are in red if the ring-chain rules do not cover that particular transformation.

(1) Ershov, A. Y.; Nasledov, D. G.; Nasonova, K. V.; Sezyavina, K. V.; Susarova, T. V.; Lagoda, I. V.; Shamanin, V. V. Ring-Chain Tautomerism of 2-Aryl-6-Oxohexahydropyrimidine-4-Carboxylic Acid Sodium Salts. *Chem. Heterocycl. Compd.* **2013**, *49*, 598–603.

(2) Balaneva, N. N.; Radchenko, O. S.; Glazunov, V. P.; Novikov, V. L. 1,4-Conjugate Addition of 2-Hydroxynaphthazarins to Acyclic and Cyclic Alpha,beta-Unsaturated Ketones. Prototropic Ring-Chain Tautomerism of the Adducts. *Russ. Chem. Bull.* **2012**, *61*, 1900–1908.

(3) Yildirim, A.; Konuklar, F. A. S.; Catak, S.; Van Speybroeck, V.; Waroquier, M.; Dogan, I.; Aviyente, V. Solvent-Catalyzed Ring-Chain-Ring Tautomerization in Axially Chiral Compounds. *Chem.- Eur. J.* **2012**, *18*, 12725–12732.

(4) Korotaev, V. Y.; Barkov, A. Y.; Sosnovskikh, V. Y. Reactions of (E)-3,3,3-Trichloro(trifluoro)-1-Nitropropenes with Enamines Derived from Cycloalkanones. A New Type of Ring-Chain Tautomerism in a Series of Cyclobutane Derivatives and Stereochemistry of the Products. *Russ. Chem. Bull.* **2012**, *61*, 1736–1749.

(5) Bucsa, M.; Pollnitz, A.; Varga, R. A.; Pirnau, A.; Silvestru, A.; Vlassa, M. The Ring-Chain Tautomeric Equilibria of Selenium Macrocyclic Compounds: The Isolation of the Ring Tautomer. *Dalton Trans.* **2012**, *41*, 4506–4510.

(6) Juhasz, M.; Lazar, L.; Fueloep, F. Substituent Effects in Ring-Chain Tautomerism of the Condensation Products of Non-Racemic 1,2-Aminoalcohols with Aromatic Aldehydes. *Tetrahedron-Asymmetry* **2011**, *22*, 2012–2017.

(7) Sigalov, M.; Shainyan, B.; Krief, P.; Ushakov, I.; Chipanina, N.; Oznobikhina, L. Intramolecular Interactions in Dimedone and Phenalen-1,3-Dione Adducts of 2(4)-Pyridinecarboxaldehyde: Enol–enol and Ring-Chain Tautomerism, Strong Hydrogen Bonding, Zwitterions. *J. Mol. Struct.* **2011**, *1006*, 234–246.

(8) Saiz, C.; Wipf, P.; Mahler, G. Synthesis and Ring-Chain-Ring Tautomerism of Bisoxazolidines, Thiazolidinyloxazolidines, and Spirothiazolidines. *J. Org. Chem.* **2011**, *76*, 5738–5746.
(9) Korotaev, V. Y.; Barkov, A. Y.; Slepukhin, P. A.; Kodess, M. I.; Sosnovskikh, V. Y. Unusual Ring-Chain Tautomerism in bicyclo[4.2.0]octane Derivatives. *Tetrahedron Lett.* **2011**, *52*, 3029–3032.
(10) Nan, A.; David, L.; Tintas, M.; Lar, C.; Grosu, I. Synthesis, Stereochemistry and Ring-Chain Tautomerism of Some New Bis(1,3-Perhydrooxazin-2-Yl)benzene Derivatives. *Lett. Org. Chem.* **2011**, *8*, 16–21.
(11) Porter, W. R. Warfarin: History, Tautomerism and Activity. *J. Comput. Aided Mol. Des.* **2010**, *24*, 553–573.
(12) Chernitsa, B. V.; Ershov, A. Y.; Doroshenko, V. A.; Yakimovich, S. I.; Lagoda, I. V.; Zerova, I. V.; Pakal'nis, V. V.; Shamanin, V. V. Ring-Chain Tautomerism of 2-Mercaptobenzoylhydrazones of Aromatic Aldehydes. *Chem. Heterocycl. Compd.* **2010**, *46*, 1133–1137.
(13) Demir-Ordu, O.; Dogan, I. Axially Chiral N-(o-Aryl)-4-Hydroxy-2-Oxazolidinone Derivatives from Diastereoselective Reduction of N-(o-Aryl)-2,4-Oxazolidinediones: Thermally Interconvertible Atropisomers via Ring-Chain-Ring Tautomerization. *Chirality* **2010**, *22*, 641–654.
(14) Herbert, J. M.; Mathers, T. W. Ring-Chain Tautomerism in 2,2-bis(2-Thienyl)tetrahydrofurans: Preparation of [butene-H-2(5)]-Tiagabine. *J. Label. Compd. Radiopharm.* **2010**, *53*, 598–600.
(15) Talancon, D.; Bosque, R.; Lopez, C. Study of the Effect Induced by the Substituents on the Ring-Chain Tautomerism of Schiff Bases Derived from Norephedrine. *J. Org. Chem.* **2010**, *75*, 3294–3300.
(16) Coskun, N.; Aksoy, C. An Imidazolidin-1-Ol, Nitrone and Oxadiazinane Ring-Chain-Ring Tautomeric Dynamic Combinatorial Library. *Tetrahedron Lett.* **2009**, *50*, 3008–3012.
(17) Augner, S.; Kehler, J.; Szakacs, Z.; Breuer, E.; Haegele, G. Ring-Chain Tautomerism and Protolytic Equilibria of 3-Hydroxy-3-Phosphonoisobenzofuranone Studied by H-1, C-13 and P-31 and NMR-Controlled Titrations. *New J. Chem.* **2008**, *32*, 1608–1616.
(18) Pihlaja, K.; Juhasz, M.; Kivela, H.; Fueloep, F. Substituent Effects on the Ring-Chain Tautomerism of Some 1,3-Oxazolidine Derivatives. *Rapid Commun. Mass Spectrom.* **2008**, *22*, 1510–1518.
(19) Juhasz, M.; Lazar, L.; Fueloep, F. Substituent Effects in the Ring-Chain Tautomerism of 4-Alkyl-2aryl Substituted Oxazolidines and Tetrahydro-1,3-Oxazines. *J. Heterocycl. Chem.* **2007**, *44*, 1465–1473.
(20) Ershov, A. Y.; Lagoda, I. V.; Yakimovich, S. I.; Pakal'nis, V. V.; Shamanin, V. V. Ring-Chain Tautomerism of the Condensation Product of Acetone with 2-Sulfanylbenzohydrazide. *Russ. J. Org. Chem.* **2007**, *43*, 1745–1746.
(21) Coskun, N.; Asutay, O. Imidazolidin-1-Oles, N-2-Aminoethyl Nitrones and 1,2,5-Oxadiazinanes. A Novel Ring-Chain Tautomerism. *Tetrahedron Lett.* **2007**, *48*, 5151–5155.
(22) Delaine, T.; Bernardes-Genisson, V.; Stigliani, J.-L.; Gornitzka, H.; Meunier, B.; Bernadou, J. Ring-Chain Tautomerism of Simplified Analogues of Isoniazid-NAD(P) Adducts: An Experimental and Theoretical Study. *Eur. J. Org. Chem.* **2007**, 1624–1630.

(23) Juhasz, M.; Fulop, F.; Pihlaja, K. Substituent Effects on the Gas-Phase Ring-Chain Tautomerism of 3,4,5,6-Tetrahydro-2H-1,3-Oxazines. *Rapid Commun. Mass Spectrom.* **2007**, *21*, 3701–3710.
(24) Smirnov, V. O.; Khomutova, Y. A.; Tishkov, A. A.; Ioffe, S. L. Silylation of Bicyclic Six-Membered Nitronates. Ring-Chain Tautomerism of Intermediate N,N Bis(oxy)iminium Cations. *Russ. Chem. Bull.* **2006**, *55*, 2061–2070.
(25) Toth, D.; Szatmari, I.; Fulop, F. Substituent Effects in the Ring-Chain Tautomerism of 1-Alkyl-3-arylnaphth[1,2-e][1,3]oxazines. *Eur. J. Org. Chem.* **2006**, 4664–4669.
(26) Szatmari, I.; Toth, D.; Koch, A.; Heydenreich, M.; Kleinpeter, E.; Fueloep, F. Study of the Substituent-Influenced Anomeric Effect in the Ring-Chain Tautomerism of 1-Alkyl-3-Aryl-naphth[1,2-e][1,3]oxazines. *Eur. J. Org. Chem.* **2006**, 4670–4675.
(27) Maloshitskaya, O. A.; Sinkkonen, J.; Alekseyev, V. V.; Zelenin, K. N.; Pihlaja, K. A Comparison of Ring-Chain Tautomerism in Heterocycles Derived from 2-Aminobenzenesulfonamide and Anthranilamide. *Tetrahedron* **2005**, *61*, 7294–7303.
(28) Perez, S.; Lopez, C.; Caubet, A.; Roig, A.; Molins, E. Ring-Chain Tautomerism of the Novel 2-Ferrocenyl-2,4-Dihydro-1H-3,1-Benzoxazine. *J. Org. Chem.* **2005**, *70*, 4857–4860.
(29) Zalan, Z.; Hetenyi, A.; Lazar, L.; Fulop, F. Substituent Effects in the Ring-Chain Tautomerism of 4-Aryl-1,3,4,6,7,11b-Hexahydro-2H-pyrimido[6,1-A]isoquinolines. *Tetrahedron* **2005**, *61*, 5287–5295.
(30) Keiko, N. A.; Funtikova, E. A.; Stepanova, L. G.; Larina, L. I. Reaction of 2-Alkoxypropenals with 2-Aminoethanethiol and Ring-Chain Tautomerism of the Resulting 2-(1-Alkoxyvinyl)-1,3-Thiazolidines. *Russ. J. Org. Chem.* **2005**, *41*, 517–522.
(31) Maloshitskaya, O.; Sinkkonen, J.; Ovcharenko, V. V.; Zelenin, K. N.; Pihlaja, K. Chain-Ring-Chain Tautomerism in 2-Aryl-Substituted Hexahydropyrimidines and 1H-2,3-Dihydroperimidines. Does It Appear? *Tetrahedron* **2004**, *60*, 6913–6921.
(32) Szatmari, I.; Martinek, T. A.; Lazar, L.; Fulop, F. Synthesis of 2,4-Diaryl-3,4-Dihydro-2H-naphth[2,1-e][1,3]oxazines and Study of the Effects of the Substituents on Their Ring-Chain Tautomerism. *Eur. J. Org. Chem.* **2004**, 2231–2238.
(33) Zlokazov, M. V.; Lozanova, A. V.; Veselovsky, V. V. New Type of Ring-Chain Tautomerism. Direct Evidence from H-1 NMR Spectroscopy. *Russ. Chem. Bull.* **2004**, *53*, 547–550.
(34) Zlokazov, M. V.; Lozanova, A. V.; Veselovsky, V. V. New Examples of Ring-Chain Tautomeric Conversions. *Mendeleev Commun.* **2003**, 242–243.
(35) Lazar, L.; Fulop, F. Recent Developments in the Ring-Chain Tautomerism of 1,3-Heterocycles. *Eur. J. Org. Chem.* **2003**, 3025–3042.
(36) Struve, C.; Christophersen, C. Structural Equilibrium and Ring-Chain Tautomerism of Aqueous Solutions of 4-Aminobutyraldehyde. *Heterocycles* **2003**, *60*, 1907–1914.
(37) Iuliucci, R. J.; Clawson, J.; Hu, J. Z.; Solum, M. S.; Barich, D.; Grant, D. M.; Taylor, C. M. V. Ring-Chain Tautomerism in Solid-Phase Erythromycin A: Evidence by Solid-State NMR. *Solid State Nucl. Magn. Reson.* **2003**, *24*, 23–38.
(38) Wang, M. X.; Liu, Y.; Gao, H. Y.; Zhang, Y.; Yu, C. Y.; Huang, Z. T.; Fleet, G. W. J. Ring-Chain Tautomerism in Organic Synthesis: Synthesis of Heterocyclic Enamines from a Novel and Practical Formal Ring Transformation Reaction of Lactones. *J. Org. Chem.* **2003**, *68*, 3281–3286.

(39) Szatmari, I.; Martinek, T. A.; Lazar, L.; Fulop, F. Substituent Effects in the Ring-Chain Tautomerism of 1,3-Diaryl-2,3-Dihydro-1H-naphth[1,2-E] [1,3]oxazines. *Tetrahedron* **2003**, *59*, 2877–2884.
(40) Sinkkonen, J.; Zelenin, K. N.; Potapov, A. K. A.; Lagoda, I. V.; Alekseyev, V. V.; Pihlaja, K. Ring-Chain Tautomerism in 2-Substituted 1,2,3,4-Tetrahydroquinazolines A H-1, C-13 and N-15 NMR Study. *Tetrahedron* **2003**, *59*, 1939–1950.
(41) Sinkkonen, J.; Ovcharenko, V.; Zelenin, K. N.; Bezhan, I. P.; Chakchir, B. A.; Al-Assar, F.; Pihlaja, K. Stereoisomerism and Ring-Chain Tautomerism in 1-Hydroxy-2,3-Dihydro-1H-pyrazolo[1,2-A]pyridazine-5,8-Diones and 1-Hydroxy- and 1-Amino-2,3-Dihydro-1H-pyrazolo[1,2-B]phthalazine-5,10-Diones. *Eur. J. Org. Chem.* **2002**, 3447–3454.
(42) Lazar, L.; Goblyos, A.; Martinek, T. A.; Fulop, F. Ring-Chain Tautomerism of 2-Aryl-Substituted Cis- and Trans-Decahydroquinazolines. *J. Org. Chem.* **2002**, *67*, 4734–4741.
(43) Sinkkonen, J.; Ovcharenko, V.; Zelenin, K. N.; Bezhan, I. P.; Chakchir, B. A.; Al-Assar, F.; Pihlaja, K. H-1 and C-13 NMR Study of 1-Hydrazino-2,3-Dihydro-1H-pyrazolo[1,2-A]pyridazine-5,8-Diones and-1H-pyrazolo[1,2-B]phthalazine-5,10-Diones and Their Ring-Chain Tautomerism. *Eur. J. Org. Chem.* **2002**, 2046–2053.
(44) Uncuta, C.; Tudose, A.; Caproiu, M. T.; Udrea, S.; Roussel, C. Hydration of 2-Isoxazoline Leading to a Stable 3,5,5-Trisubstituted 3-Isoxazolidinol - N-Acylated Derivatives and Ring-Chain Tautomerism Study. *Eur. J. Org. Chem.* **2002**, 1919–1924.
(45) Kunimoto, K. K.; Sugiura, H.; Kato, T.; Senda, H.; Kuwae, A.; Hanai, K. Ring-Chain Tautomerism of Halogenated Phenolphthaleins: Vibrational Spectroscopic and Semiempirical MO Study. *Heterocycles* **2002**, *57*, 895–901.
(46) Maiereanu, C.; Darabantu, M.; Ple, G.; Berghian, C.; Condamine, E.; Ramondenc, Y.; Silaghi-Dumitrescu, I.; Mager, S. Ring-Chain Tautomerism and Other Versatile Behaviour of 1,4-Diimino- and 1,2-Phenylene Derivatives of Some C-Substituted Serinols. *Tetrahedron* **2002**, *58*, 2681–2693.
(47) Goblyos, A.; Lazar, L.; Fulop, F. Ring-Chain Tautomerism of 2-Aryl-Substituted-Hexahydropyrimidines and Tetrahydroquinazolines. *Tetrahedron* **2002**, *58*, 1011–1016.
(48) Terec, A.; Grosu, I.; Muntean, L.; Toupet, L.; Ple, G.; Socaci, C.; Mager, S. Synthesis, Stereochemistry and Ring-Chain Tautomerism of Some New Spiro-1,3-Oxathianes. *Tetrahedron* **2001**, *57*, 8751–8758.
(49) Neuvonen, K.; Fulop, F.; Neuvonen, H.; Koch, A.; Kleinpeter, E.; Pihlaja, K. Substituent Influences on the Stability of the Ring and Chain Tautomers in 1,3-O,N-Heterocyclic Systems: Characterization by C-13 NMR Chemical Shifts, PM3 Charge Densities, and Isodesmic Reactions. *J. Org. Chem.* **2001**, *66*, 4132–4140.
(50) Maier, O.; Frohlich, R.; Wurthwein, E. U. Polydonor-Substituted 1-Oxa- and 1-Thia-3,5-Diazahexatrienes: Synthesis, Structures, Ring-Chain Tautomerism and Theoretical Calculations. *Eur. J. Org. Chem.* **2001**, 83–92.
(51) Fabian, W. M. F.; Bowden, K. Ab Initio and Density Functional Calculations on the Ring-Chain Tautomerism of Gamma-Oxocarboxylic Acids. *Eur. J. Org. Chem.* **2001**, 303–309.
(52) Skrinarova, Z.; Bowden, K.; Fabian, W. M. F. An Ab Initio and Density Functional Study on the Ring-Chain Tautomerism of (Z)-3-Formyl-Acrylic Acid. *Chem. Phys. Lett.* **2000**, *316*, 531–535.