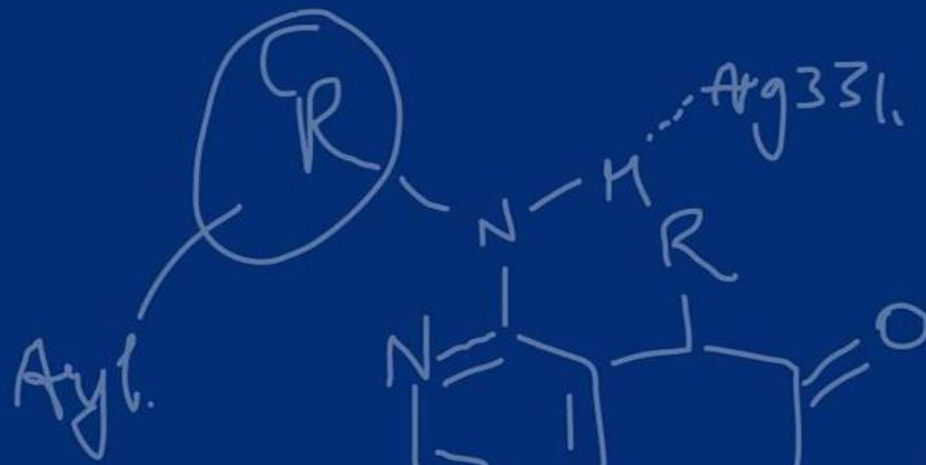
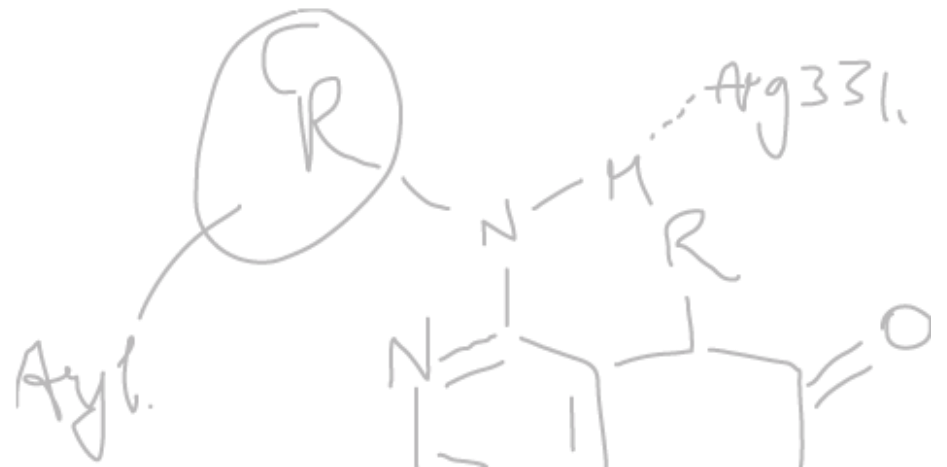

Instant JChem: Linking Chemistry & Biology

Creating integrated drug discovery
innovation alliances



Agenda

- **Overview**
- Project data flow
- Schemas
- Data model
- User security
- Deployment
- Integrating Oracle views
- Conclusion



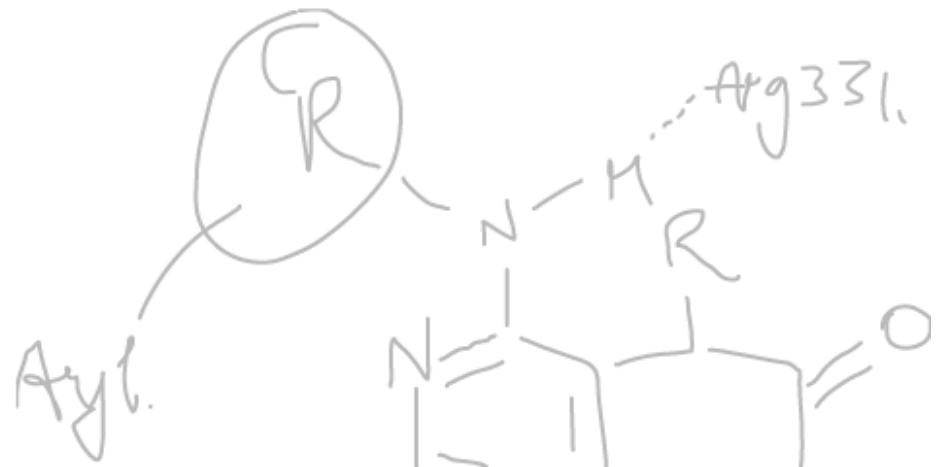
Overview

Shared IJC project database setup at Evotec

- Enterprise licenses for server use shared across Abingdon and Hamburg sites
- Dedicated IJC server at Abingdon with Oracle 10g and JChem cartridge
- One Oracle schema per drug discovery project containing project data (currently used 7 live IJC shared projects)
- A project IJC schema is connected to each Oracle schema
- Built-in IJC security & roles used for user management
- Deployment to project users via web server URLs

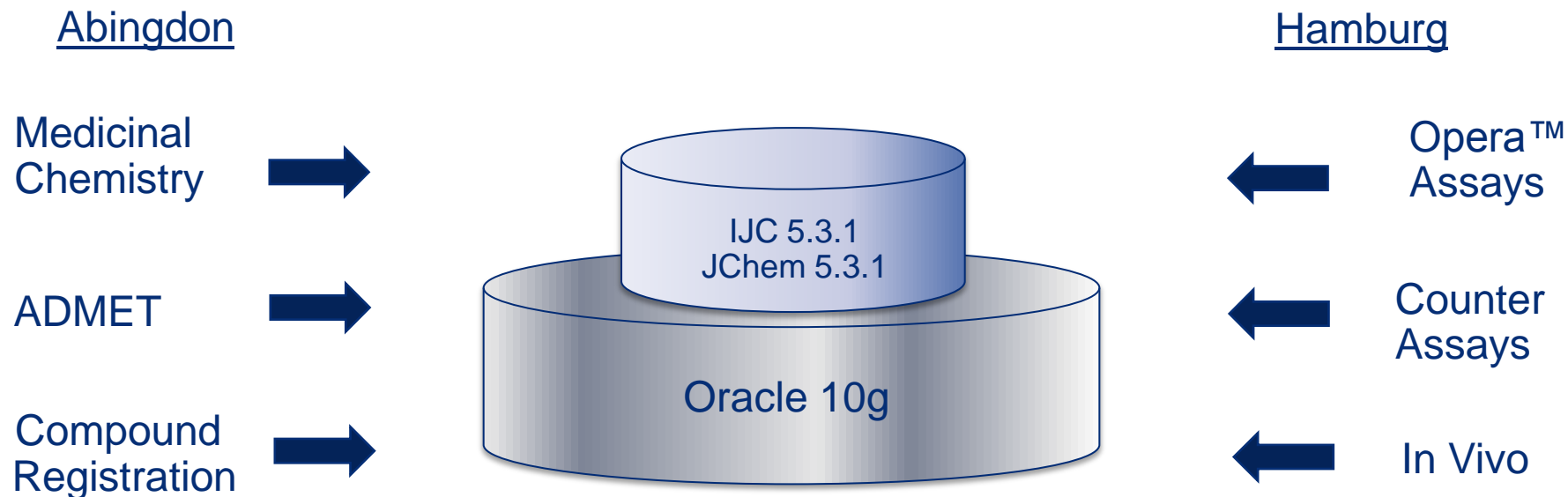
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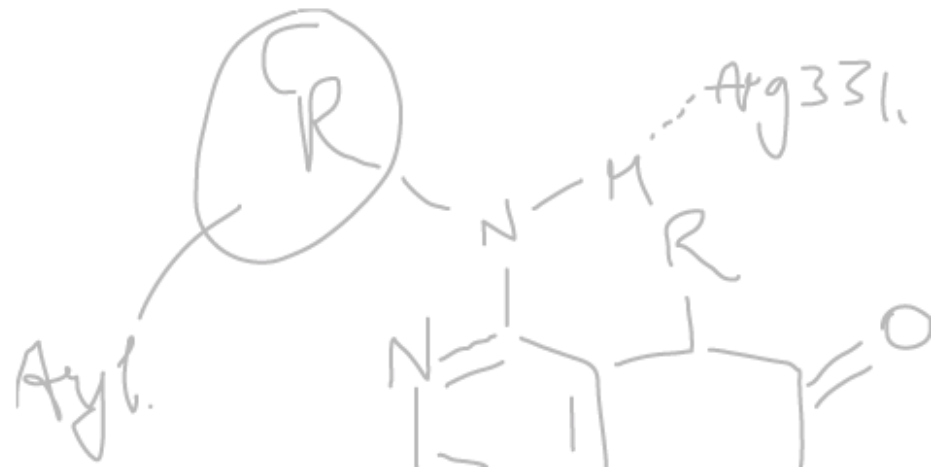
Project data flow

Drug discovery IJC project at Evotec



Agenda

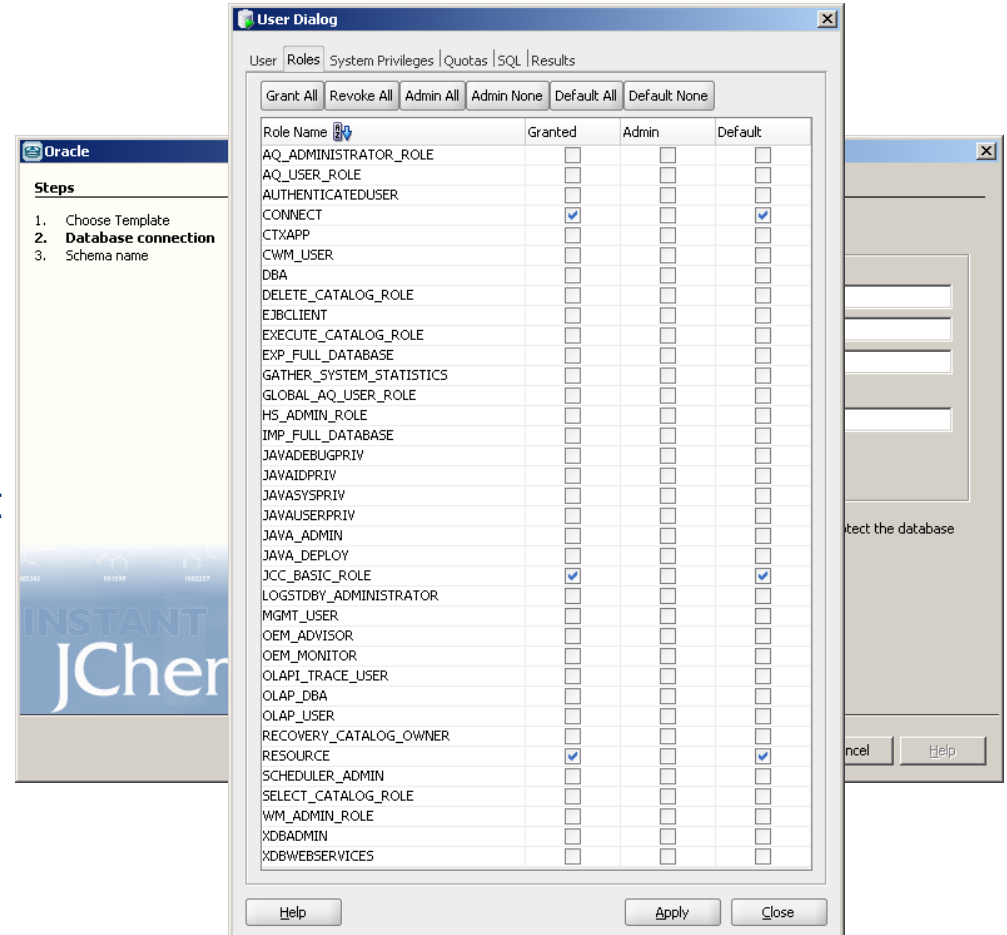
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Schemas

Create Oracle & IJC schemas

- Create project Oracle user
- Grant JCC_BASIC_ROLE to Oracle user
- Create a new empty IJC project
- Create a new schema in IJC & connect to the Oracle project schema



The screenshot shows the Oracle User Dialog window with the 'Roles' tab selected. The 'Grant All' button is active. The table below shows the roles and their status for the user.

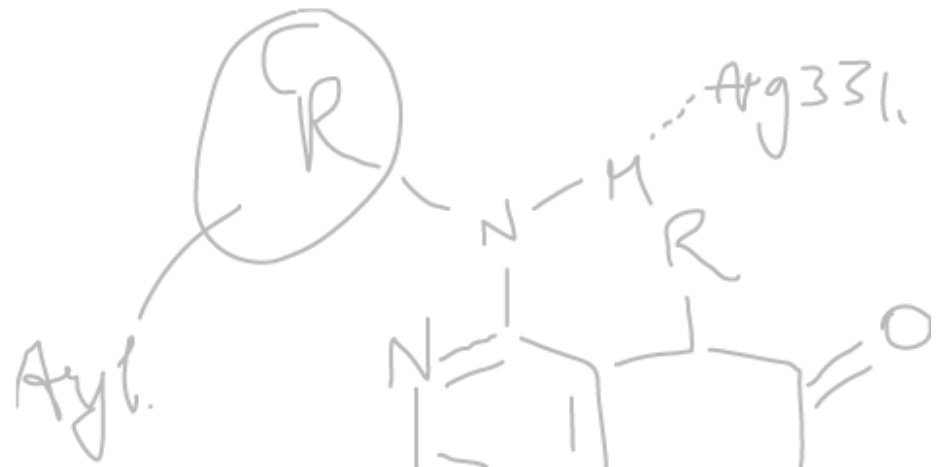
Role Name	Granted	Admin	Default
AQ_ADMINISTRATOR_ROLE	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
AQ_USER_ROLE	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
AUTHENTICATEDUSER	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
CONNECT	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
CTXAPP	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
CWM_USER	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
DBA	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
DELETE_CATALOG_ROLE	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
EJBCLIENT	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
EXECUTE_CATALOG_ROLE	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
EXP_FULL_DATABASE	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
GATHER_SYSTEM_STATISTICS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
GLOBAL_AQ_USER_ROLE	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
HS_ADMIN_ROLE	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
IMP_FULL_DATABASE	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
JAVADEBUGPRIV	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
JAVAIIDPRIV	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
JAVASYSPRIV	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
JAVAUERPRIV	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
JAVA_ADMIN	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
JAVA_DEPLOY	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
JCC_BASIC_ROLE	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
LOGSTDBY_ADMINISTRATOR	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
MGMT_USER	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
OEM_ADVISOR	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
OEM_MONITOR	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
OLAPI_TRACE_USER	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
OLAP_DBA	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
OLAP_USER	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
RECOVERY_CATALOG_OWNER	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
RESOURCE	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
SCHEDULER_ADMIN	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
SELECT_CATALOG_ROLE	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
WM_ADMIN_ROLE	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
XDBADMIN	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
XDBWEBSERVICES	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

The 'Instant JCher' interface on the left shows the 'Steps' section:

1. Choose Template
2. Database connection
3. Schema name

Agenda

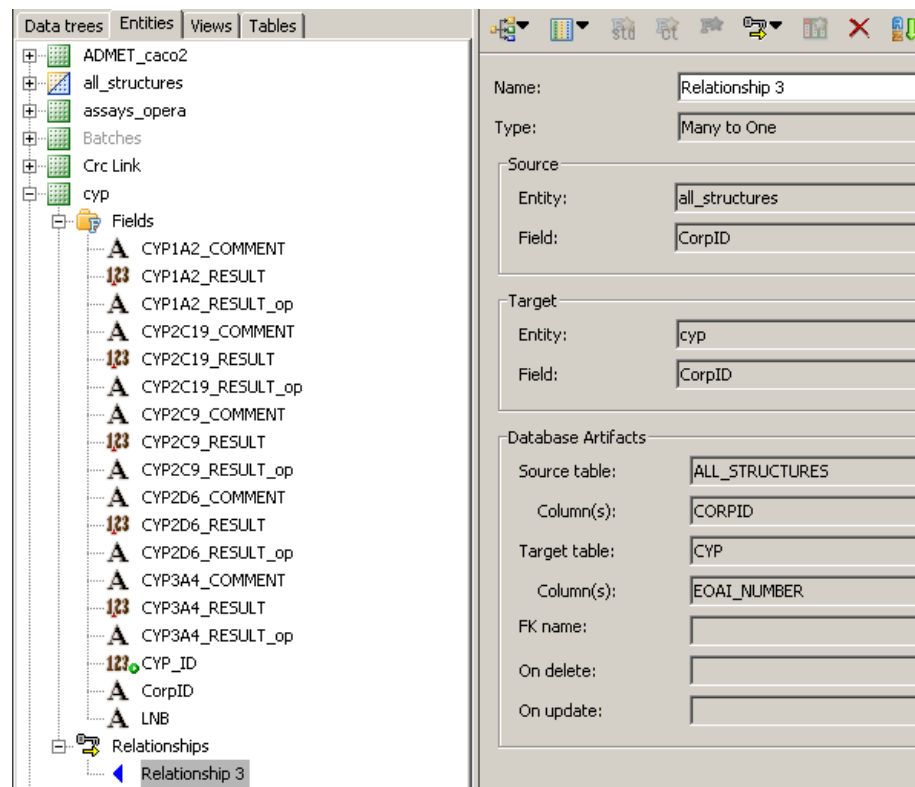
- Overview
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Data model

Build project databases in IJC

- Create tables
 - SDFFile import of existing data is a convenient method
 - Choose cartridge-indexed type for structure tables
- Create relationships, indexes, edges & datatrees
- Link tables on CorpID field
- Set constraints on tables & fields
- Create grid & form views
- Create project users and assign roles



The screenshot displays the IJC data model interface. On the left, a tree view shows the following structure:

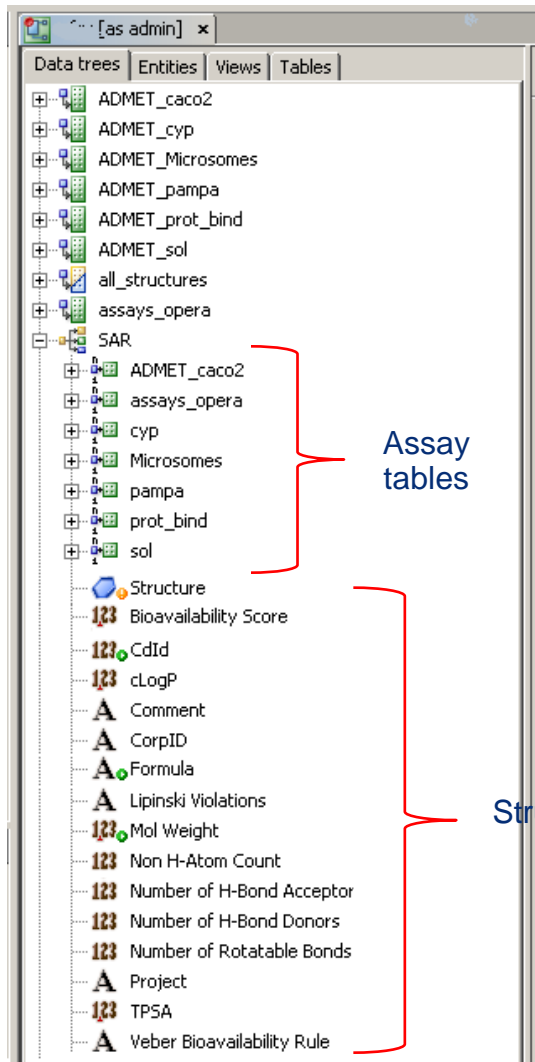
- ADMET_caco2
- all_structures
- assays_opera
- Batches
- Crc Link
- cyp
 - Fields
 - CYP1A2_COMMENT
 - CYP1A2_RESULT
 - CYP1A2_RESULT_op
 - CYP2C19_COMMENT
 - CYP2C19_RESULT
 - CYP2C19_RESULT_op
 - CYP2C9_COMMENT
 - CYP2C9_RESULT
 - CYP2C9_RESULT_op
 - CYP2D6_COMMENT
 - CYP2D6_RESULT
 - CYP2D6_RESULT_op
 - CYP3A4_COMMENT
 - CYP3A4_RESULT
 - CYP3A4_RESULT_op
 - CYP_ID
 - CorpID
 - LNB
 - Relationships
 - Relationship 3

On the right, the configuration panel for 'Relationship 3' is shown:

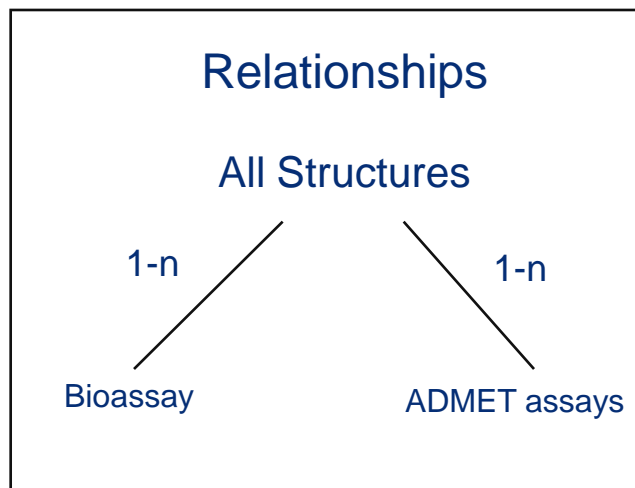
- Name: Relationship 3
- Type: Many to One
- Source
 - Entity: all_structures
 - Field: CorpID
- Target
 - Entity: cyp
 - Field: CorpID
- Database Artifacts
 - Source table: ALL_STRUCTURES
 - Column(s): CORPID
 - Target table: CYP
 - Column(s): EOAI_NUMBER
 - FK name:
 - On delete:
 - On update:

Data model

Schema Editor view: Data trees

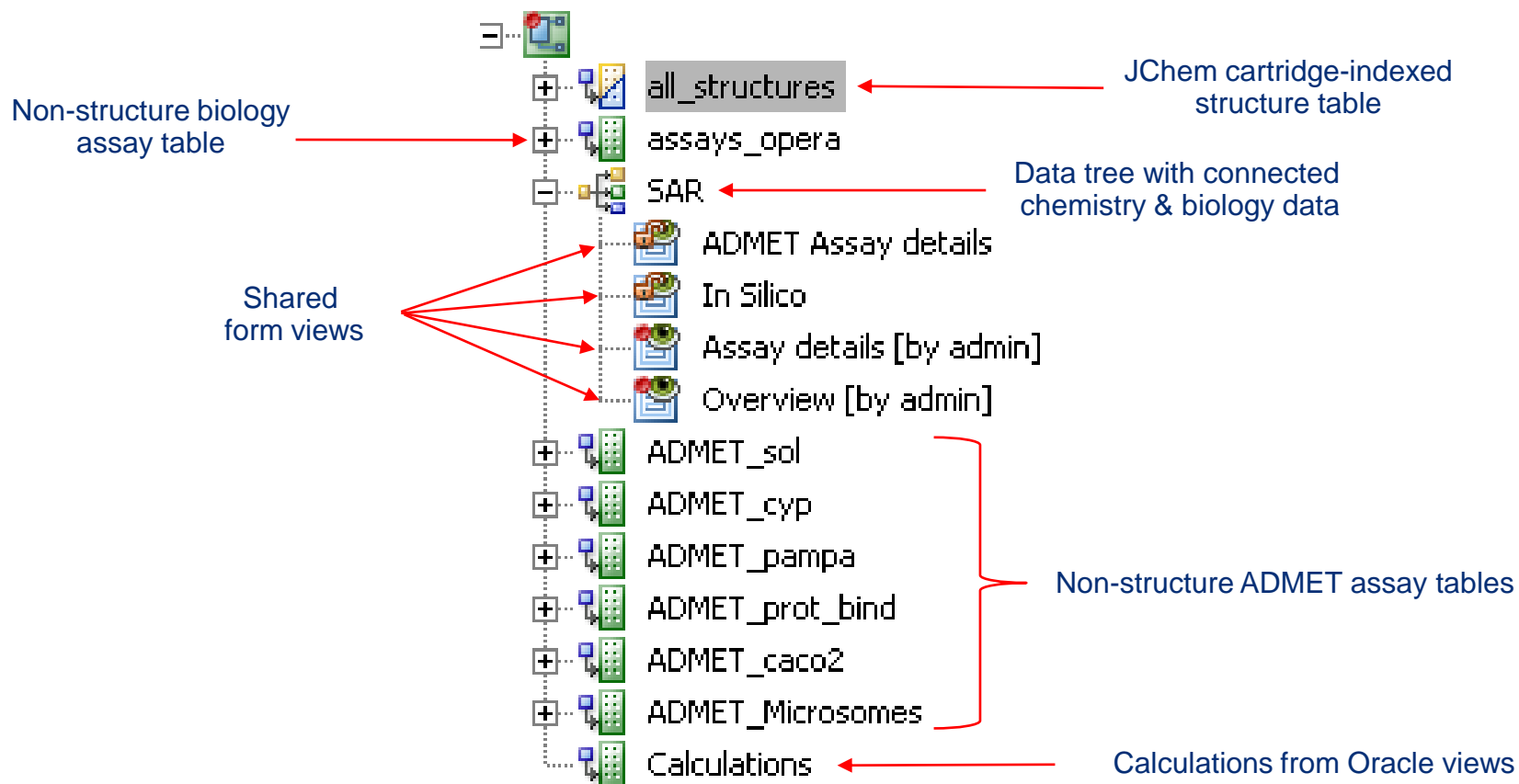


- SAR data tree contains joined chemistry & biology tables, allowing many assay results for each assay type per compound structure



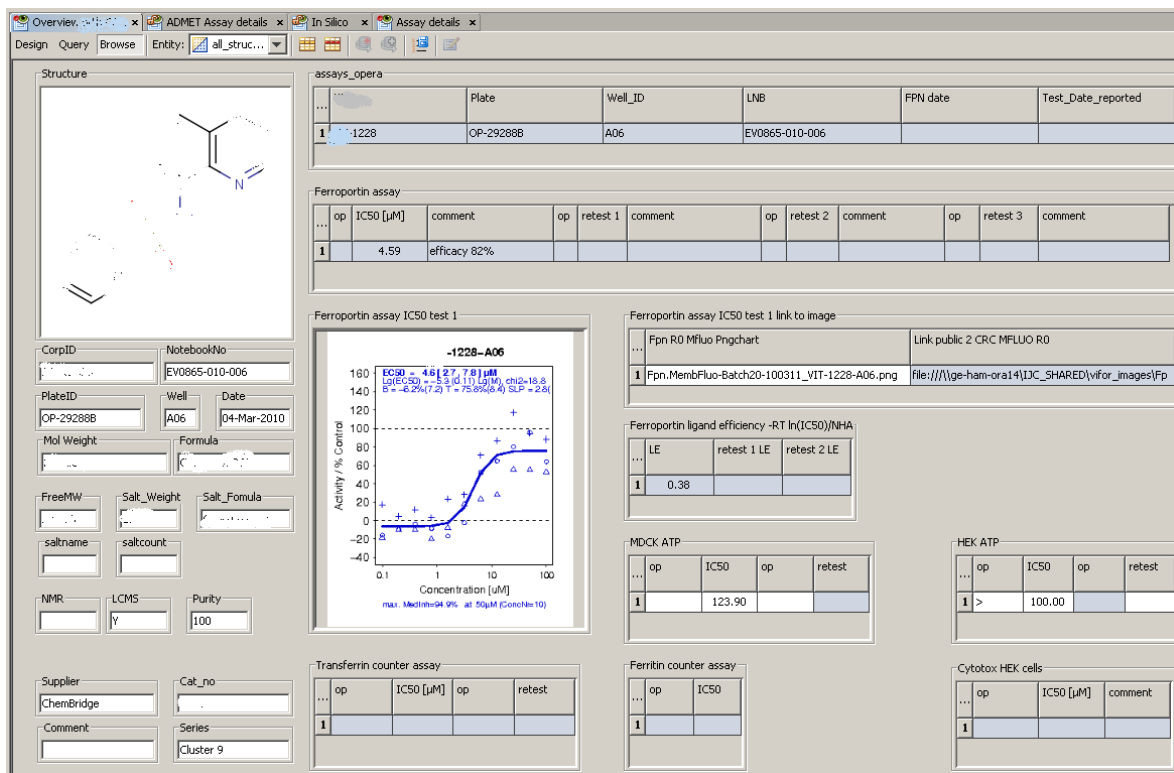
Data model

User view



Data model

User view



The screenshot displays a comprehensive data model for assays. It includes a chemical structure viewer, a table of assay operations, and a graph of assay results.

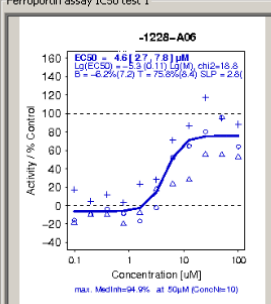
assays_opera

...	Plate	Well_ID	LNB	FPN date	Test_Date_reported
1	OP-29288B	A06	EV0865-010-006		

Ferroportin assay

op	IC50 [µM]	comment	op	retest 1	comment	op	retest 2	comment	op	retest 3	comment
1	4.59	efficacy 82%									

Ferroportin assay IC50 test 1



Ferroportin assay IC50 test 1 link to image

...	FPN R0 Mfluo Pngchart	Link public 2 CRC MFLUO R0
1	Fpn.MembFluo-Batch20-100311_VIT-1228-A06.png	file:///\\ge-ham-ora14\DC_SHARED\vfior_images\Fp

Ferroportin ligand efficiency -RT ln(IC50)/NHA

...	LE	retest 1 LE	retest 2 LE
1	0.38		

MDCK ATP

op	IC50	op	retest
1	123.90		

HEK ATP

op	IC50	op	retest
1	>	100.00	

Transferrin counter assay

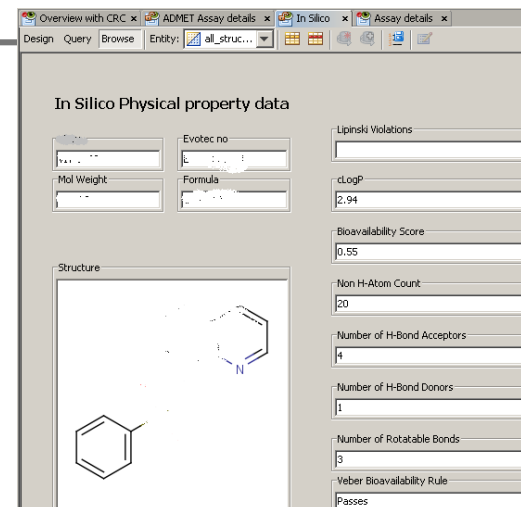
op	IC50 [µM]	op	retest
1			

Ferritin counter assay

op	IC50
1	

Cytotox HEK cells

op	IC50 [µM]	comment
1		

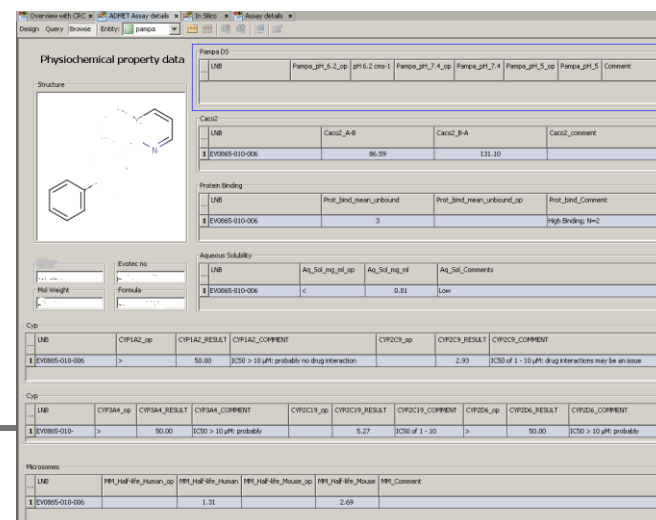


The 'In Silico Physical property data' window displays various physicochemical parameters for a molecule. It includes a chemical structure viewer and a table of Lipinski violations.

In Silico Physical property data

Evotec no: []
 Mol Weight: []
 Formula: []

Lipinski Violations: []
 cLogP: 2.94
 Bioavailability Score: 0.55
 Non H-Atom Count: 20
 Number of H-Bond Acceptors: 4
 Number of H-Bond Donors: 1
 Number of Rotatable Bonds: 3
 Veber Bioavailability Rule: Passes



The 'Physicochemical property data' window provides a detailed view of a molecule's properties, including a chemical structure and a table of CYP interactions.

Physicochemical property data

Structure: []

CYP

LNB	CYP3A4_op	CYP3A4_RESULT	CYP3A4_COMMENT	CYP3C_op	CYP3C_RESULT	CYP3C_COMMENT
1	>	50.00	IC50 > 10 µM probably no drug interaction	2.93	IC50 of 1 - 10 µM drug interactions may be an issue	

CYP

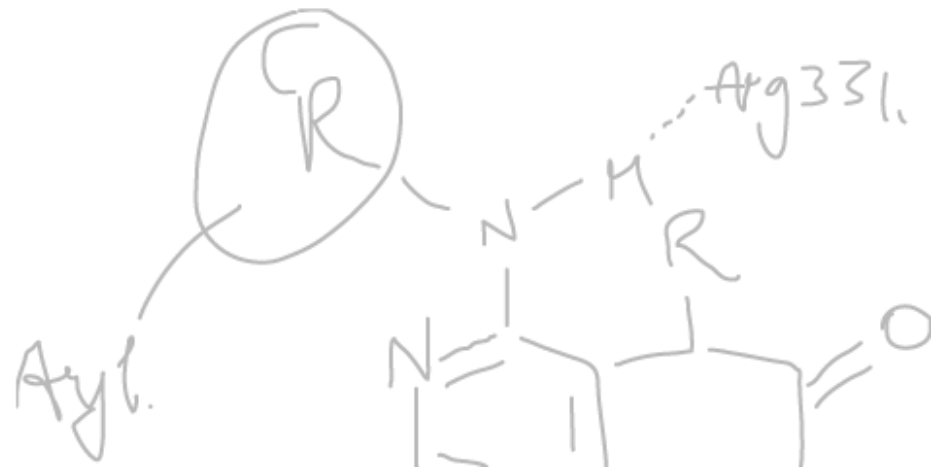
LNB	CYP3A4_op	CYP3A4_RESULT	CYP3A4_COMMENT	CYP3C_op	CYP3C_RESULT	CYP3C_COMMENT	CYP3D_op	CYP3D_RESULT	CYP3D_COMMENT
1	>	50.00	IC50 > 10 µM probably	5.27	IC50 of 1 - 10	>	50.00	IC50 > 10 µM probably	

Microsomes

LNB	HEP_Haf_Hfe_Human_op	HEP_Haf_Hfe_Human	HEP_Haf_Hfe_House_op	HEP_Haf_Hfe_House	HEP_Comment
1		1.31		2.69	

Agenda

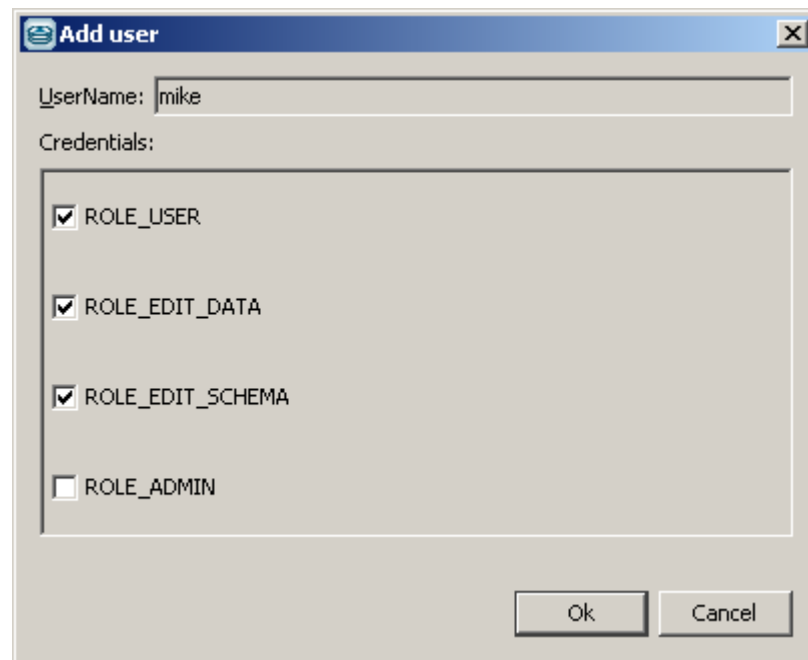
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User security

Typical IJC setup for a small drug discovery project

- 4 Scientists with Edit Data Role (2 in Abingdon & 2 in Hamburg)
- Updates made via SDfile (Edit Data Role) with auto mapping (SDfiles for loading formatted in the Evotec CCD)
- 14 Scientists with Read Only Role (ROLE USER) across Abingdon and Hamburg
- 2 Administrators (1 in Abingdon & 1 in Hamburg) with Edit Schema Role
- Built in Admin user used for rebuilding JChem tables after software updates & managing users and roles



Add user

UserName: mike

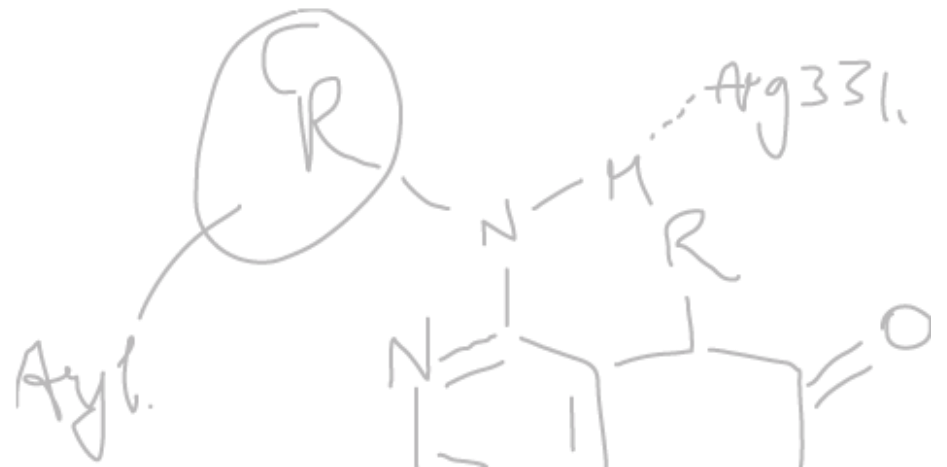
Credentials:

- ROLE_USER
- ROLE_EDIT_DATA
- ROLE_EDIT_SCHEMA
- ROLE_ADMIN

Ok Cancel

Agenda

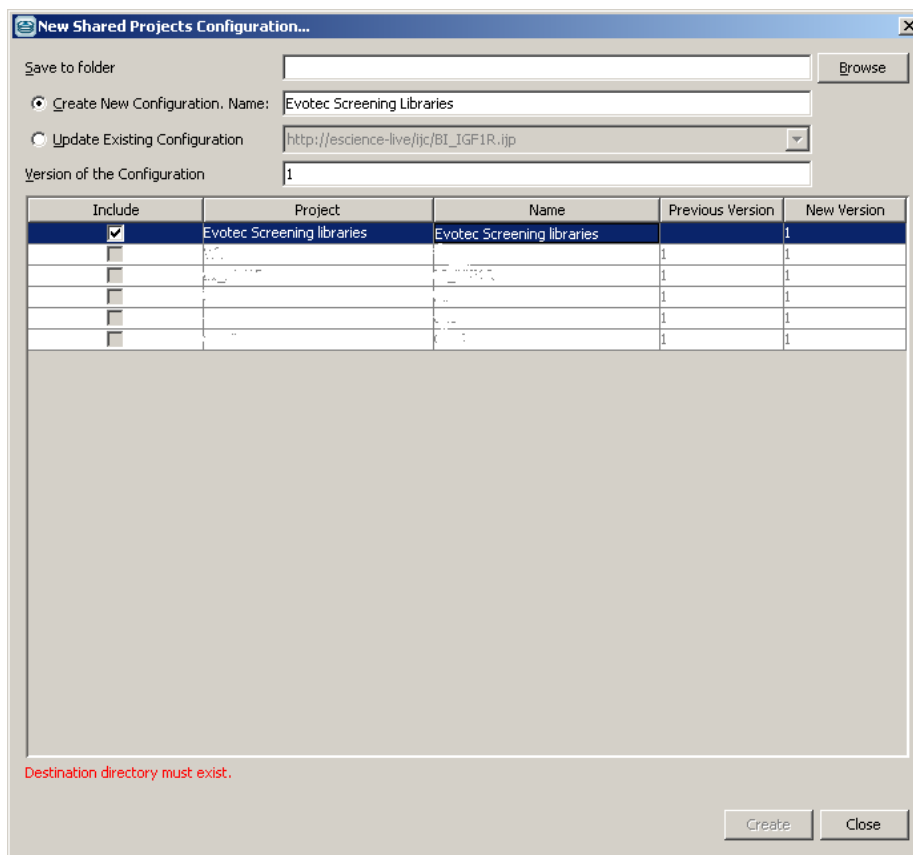
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Deployment

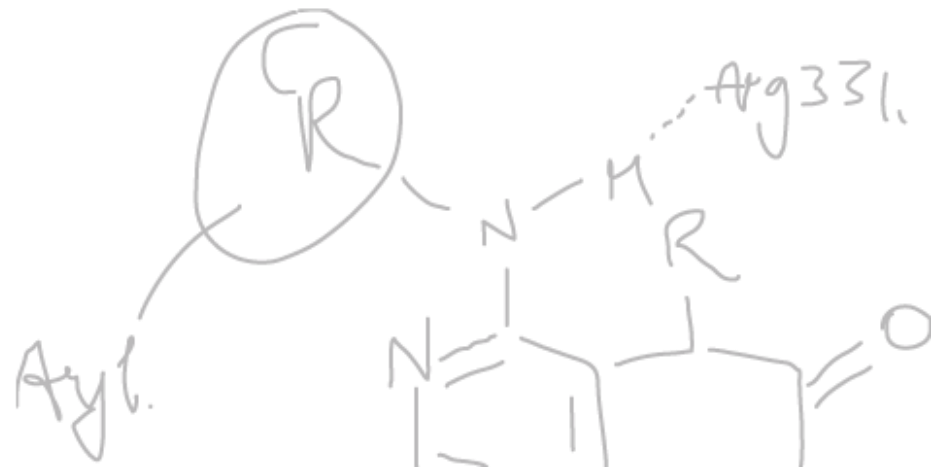
Via shared URLs

- Create users and roles & make all views you want to deploy shared
- Use Create Shared Projects wizard to generate new configuration files (.ijp and .zip files)
- Place configuration files on a web server: <http://escience/ijc/>
- Provide user account with initial password and URL e.g. <http://escience/ijc/project.ijp> to all of the users



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Integrating Oracle views

Useful for calculations across multiple tables

e.g. Ligand Efficiency of a compound = $RT \ln(\text{IC}_{50})/\text{NHA}$

Where:

R = molar gas constant = 0.0019859 kcal K⁻¹ mol⁻¹

T = Assay temperature in Kelvin = 273.15+37

IC₅₀ in Molar units → Database field in **assays opera** table

NHA = Non-H atom count → Database field in **structure** table

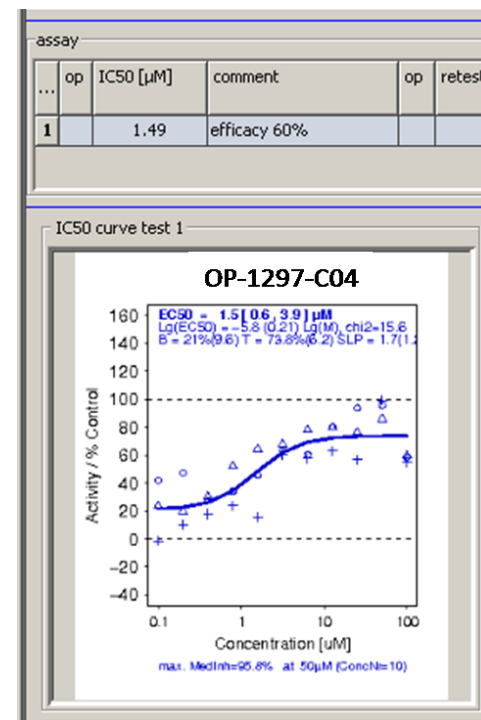
- Create or replace view Calculations as select **a.compound_id**, **b.IC50**, **a.NHA**, ... from **all_structures a**, **assays_opera b** where **a.compound_id = b.compound ID**
- Promote the Oracle view Calculations to a new entity in the IJC schema. Add relationships & data edges and integrate the Ligand Efficiency field into the IJC form for viewing and querying.

ligand efficiency -RT ln(IC50)/NHA			
...	LE	retest 1 LE	retest 2 LE
1	0.45	0.32	0.46

Integrating Oracle views

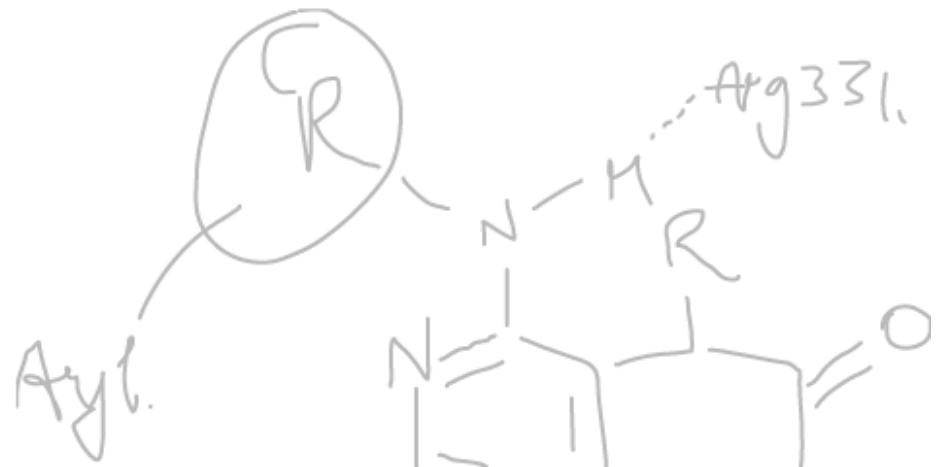
Useful for viewing Dynamic URLs when the related table needs to be updated

- Data imports into tables containing dynamic URL fields is not yet possible. A workaround is with Oracle views:
 - The data is updated in table A, e.g. IC50, ID's, Filename etc.
 - Create the Oracle view selecting the Compound ID & Filename
 - Promote the Oracle view to a new entity in the IJC schema -> table B
 - Define a dynamic link on table B, e.g. root path + table B.filename
 - Create a 1-1 relationship on tables A & B in IJC and incorporate into the data tree
 - Integrate the dynamic link into the IJC form
 - Can now do IJC imports into table A and get the dynamically linked images of concentration response curves from table B



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Conclusion

Overview and future

- IJC is providing Evotec a valuable resource for storing and sharing Chemistry and Biology data for our client projects
- We are using IJC as a replacement for ISIS/Base databases with positive feedback from the users
- We are still finding new uses for it!

Future Plans

- Integrate our own calculators & methods into Marvin / IJC
 - Integrate more ways of displaying results (graphing, etc.)
 - Implement user dependent permissions on viewing & editing entities would be nice
 - Improved ways of sharing IJC data with our clients
-

Thank yous

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