Solution Phase Combinatorial Chemistry in Drug Discovery

Ischia Advanced School of Organic Chemistry
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Richard Storer, GlaxoWellcome Research and Development

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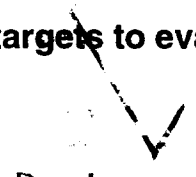
Industry Requirements

- First and best
- Reduced timescales
- More targets to evaluate



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Compound Libraries in Drug Discovery

- Primary libraries for hit generation
  - pools or discretes
- Hits to Leads
- Lead optimisation
  - discretes

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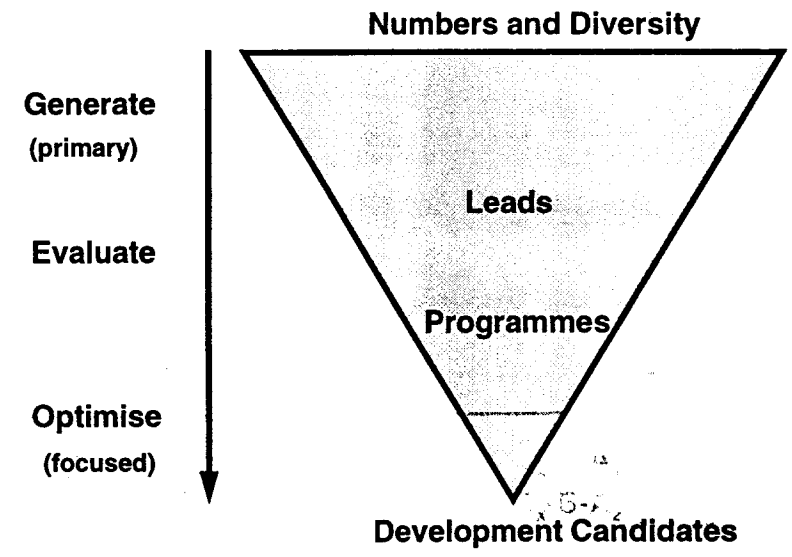

Solution Phase Chemistry

- Wide range of established chemistry
- Short lead-in time
- Ideal for short sequences
- No cleavage needed
- Direct link with screens
- High throughput
- Quantity

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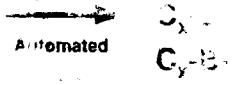
Library Size

Dimer ----------Trimer----------Tetramer

increasing numbers
increasing diversity

but: increasing steps
increasing M.Wt.



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Amide Trimer Synthesis

Carboxylic acid-------Aminoacid-------Amine

80 50 40

Amide bond chemistry
160,000 compounds
Pool size of 40
Quantity: 25 micromoles
Semi-automated synthesis

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Manual/Automated Approach

- Manual preparation of feedstock dimers
- Automated synthesis of final trimers

$A_{mix} + B \xrightarrow[\text{manual}]{} A_{mix}\text{-}B \xrightarrow[\text{Automated}]{} A_{mix}\text{-}B\text{-}C_1$, $A_{mix}\text{-}B\text{-}C_2$, :

- Decoding - reverse direction synthesis
- Maintain automated synthesis of final trimers

$C_x + B \xrightarrow[\text{manual}]{} C_x\text{-}B \xrightarrow[\text{Automated}]{} C_x\text{-}B\text{-}A_1$, $C_x\text{-}B\text{-}A_2$

Chemistry Development

- Discrete synthesis
  - all steps, full analysis
  - monomer selection
- Pooled synthesis
  - nmr, hplc, ms, lc-ms

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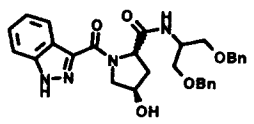
Screening Controls

- Standards using automated procedure
- Inclusion of known lead / active compounds



- By-product screening

Robotic Chemistry

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First Generation Robotics

- Solution dispensing
- Multiple reaction vessels
- Variable reagent addition
  - order
  - volume
- Heating capacity
- Solvent removal

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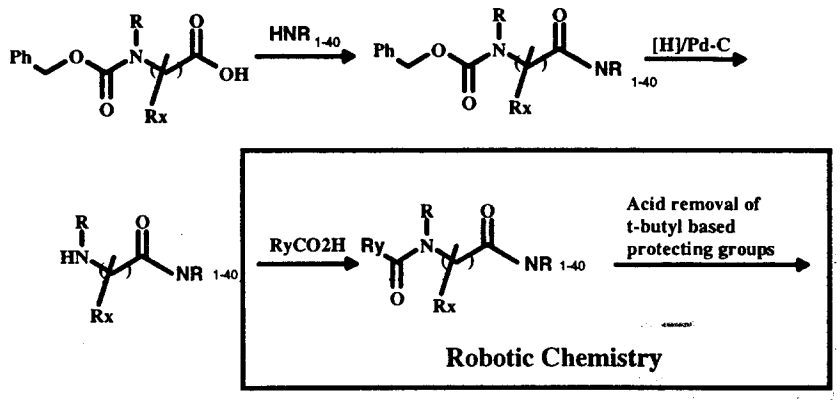
Library Synthesis



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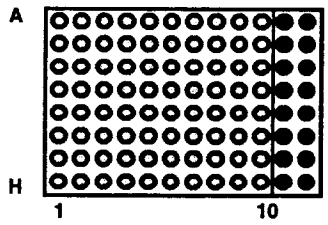
Synthetic plate design

- Direct parallel to screening mtp - 80 well plate
- Single aminoacid component on plate
- 80 acid array on each plate
- 40 amine components in each well
- Compound identity by plate/well address



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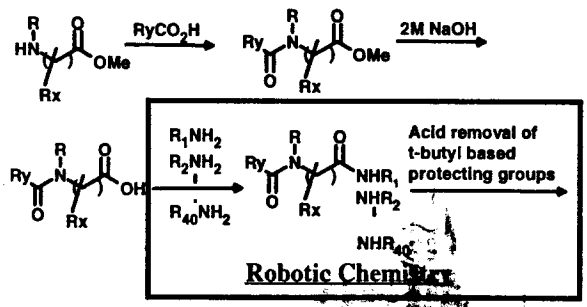
Decode Synthesis



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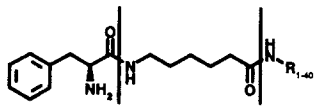
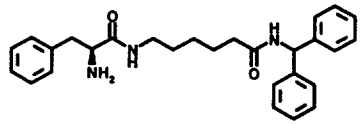
HIV Proteinase Inhibitor



IC_{50} = 130 μg/ml

Sample decoded to individual compounds



GR204887X IC_{50} = 10 μg/ml

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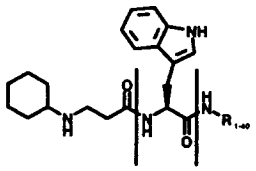
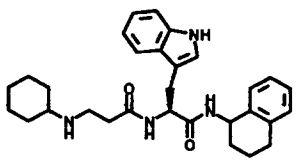
NK1 Antagonist



IC_{50} = 8 μg/ml

Sample decoded to individual compounds



GR 217869X pKi 7.3

Profiling of libraries

- Descriptor based
  - Charges, H-bonds, size, rings, flexibility
- Applications
  - Diversity within libraries
  - Comparison between libraries
  - "Hole filling" in collections
  - Target profiling

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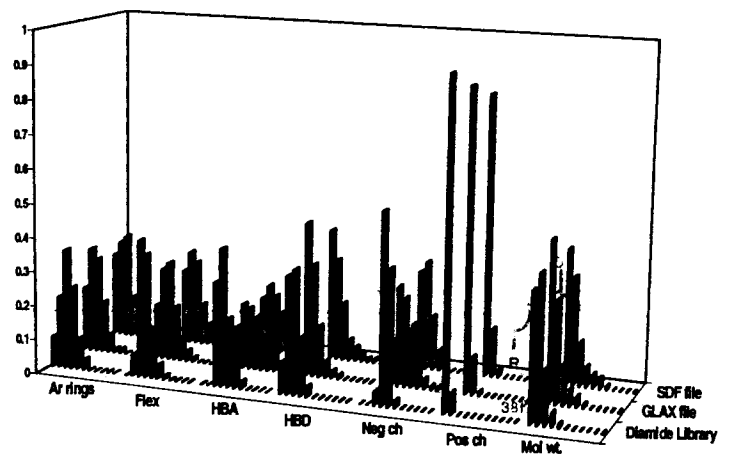
Library comparison with drug files



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Conclusions

- Highly successful exercise
- Leads generated in many areas
- Projects established
- Long-term screening resource generated
- General trend information without decoding
- Decoding causes problems
  - success rate
  - timescales

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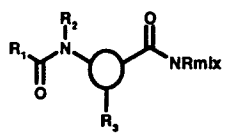
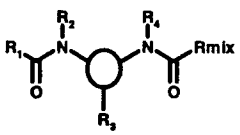
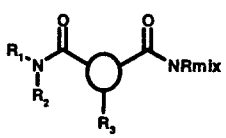
Future Directions



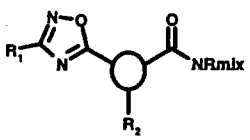




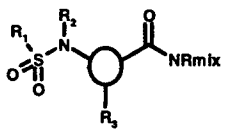
Total compounds: 400K

58K

182K



96K



38K

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Future Directions

- Extend range of chemistries
  - dimer formation / trimer formation
- Discrete synthesis / pooling option
- Extend robotic capability

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Chemistry Requirements

- Clean and high yielding
  - one major pathway
  - few (no) by-products
- Versatile and robust
- Combinatorial (A + B ⟶ C)
- Mild conditions
- Availability of building blocks
- Suitable products

Other Developed Solution Chemistry

- 1,4 Additions
- Aldols
- Cycloadditions
- Heteroaryl chloride displacement
- 5,6,7 ring heterocycles
- Hydrazones
- N-alkylation
- Oximes
- Reductive amination
- S-alkylation

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Heterocycle Libraries

- Chemically efficient
- Provide good templates
- Ubiquitous in drug molecules

Benzimidazoles	Pyrazolones
Benzodiazepines	Pyrimidines
Imidazopyridines	Thiazoles
Oxadiazoles	Triazoles

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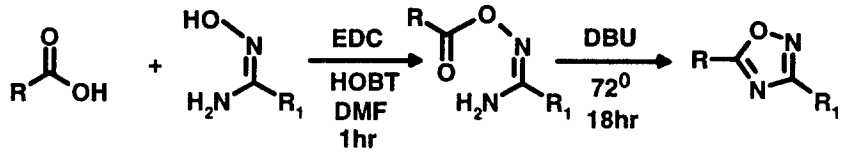
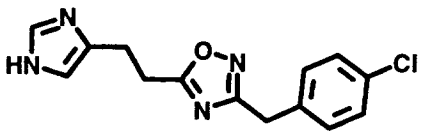
Oxadiazole Libraries





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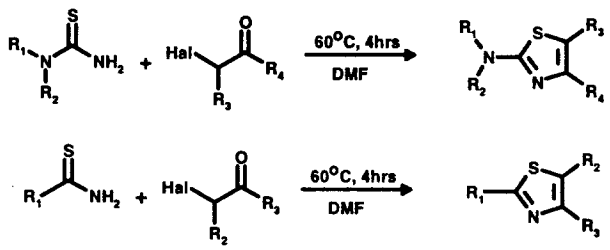
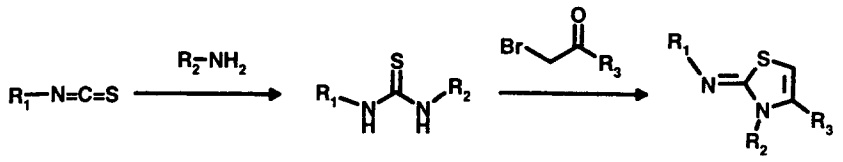
Thiazole Dimer Libraries



1440 discrete compounds in each series

S.P. Watson et al., Biorg Med Chem Lett, 1996, 6, 1406

Three Component Libraries



12 80 12

- Large libraries from modest monomer numbers
- 11,520 products from 104 monomers
- Lipophilic, H-bonding, acidic and basic substituents

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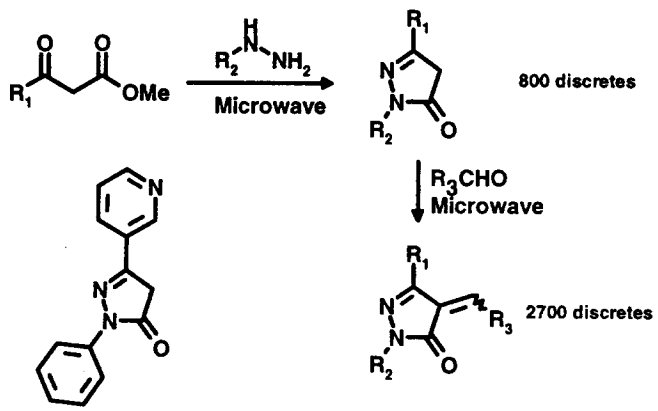
Pyrazolone Condensation Trimers



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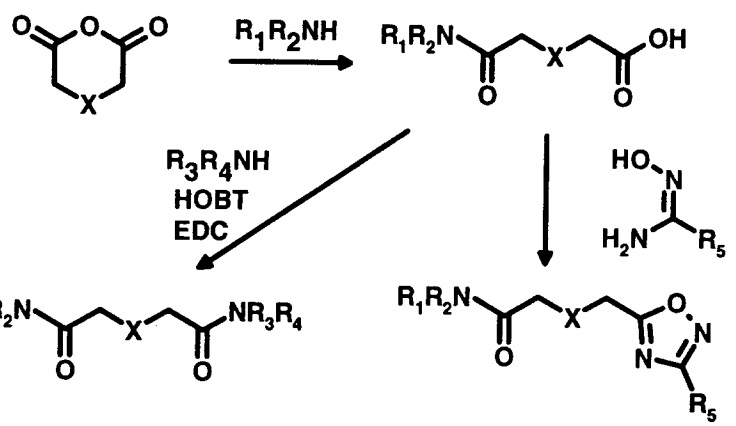
Anhydride Trimers



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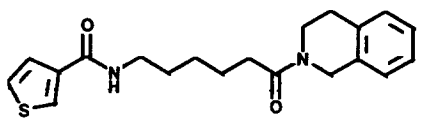
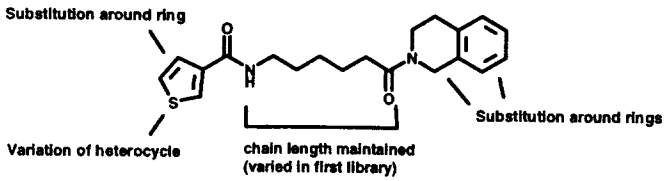
Bradykinin Diamide Hit

- One hit from 4000 mixture library
- Decoded to single active component



GR213548X pKi = 5.8

Hit to Lead Focused Library



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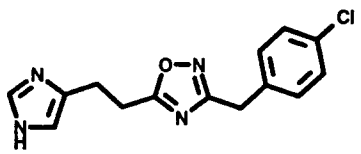
Histamine H3

- Project Lead
- Potential metabolic problem - imidazole



GR175737

J.W.Clitherow et al., Biorg Med Chem Lett, 1996, 6, 833

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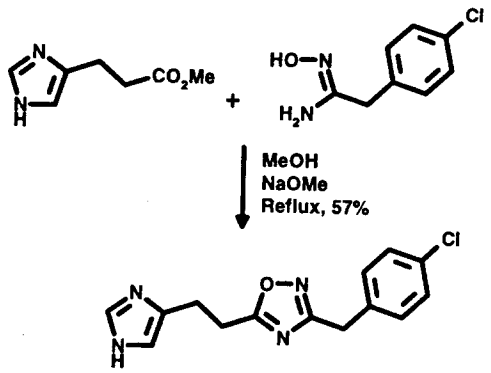
Project Route



GR175737

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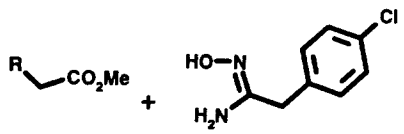
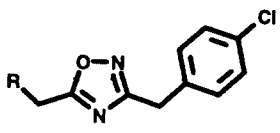
Initial Robotic Route

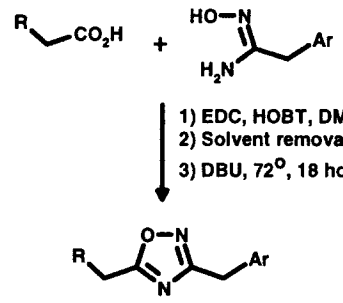


1) DBU, MeOH, DMF, 50° 1 hour
2) Solvent removal
3) 72°, 18 hours



- Reaction failed when tertiary amines in R group

Modified Robotic Route



- Extended to discrete library of 1600 samples

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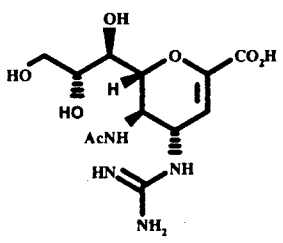
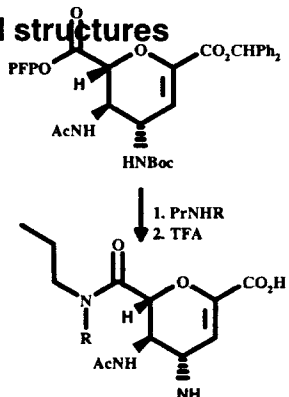
Influenza Sialidase

- GG167 - Treatment for influenza A and B
- Follow up - simplified structures



GG167



PW Smith et al., Biorg Med Chem Lett, 1996, 6, 1805

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New Generation Robotics

- Microtitre blocks
- Agitation
- Heating
  - conventional oven
  - microwave oven
- Vacuum centrifugation
- Solution phase purification
  - aqueous extraction
  - filtration

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Future Directions

- Low-tech equipment for modest numbers
- Equipment for each laboratory
- Array synthesis of larger (gm) quantities
- Parallel purification
- Solid phase arrays in lead optimisation
- Supported reagents
- Effective use of the technologies

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Project Considerations

- Wider choice of leads available
- Generate leads at the appropriate time
- Define preferred series
- Screen capacity must parallel chemical capacity
- Arrays for optimisation and evaluation
- Capacity to make simultaneous changes
- Results on x80 give better strategic view
- Less justification for individual compounds

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Future Issues

- Solution or solid phase
  - as appropriate in a particular case
- Libraries
  - smarter not bigger
  - expandable chemistry
- Monomer availability
- Process chemistry

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Acknowledgements

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Mark Ness
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Nigel Parr
Neil Pegg
Adrian Pipe
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