Dynamic combinatorial chemistry with hydrazones: libraries incorporating heterocyclic and steroidal motifs†

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We expand the possibilities in hydrazone based dynamic combinatorial chemistry with a series of new building blocks incorporating heterocyclic motifs. The synthetic procedure allows efficient access to building blocks with the general structure $(MeO)_2CH$-Heterocycle-$C(O)NHNH_2$, originating from heterocycles with an amine and an ester functionality. The equilibrium distribution of macrocyclic *N*-acyl hydrazones formed upon deprotection of the building blocks with TFA in organic solvents is reported. The mixing behaviour of these heterocycle-based building blocks with our cholate-based building blocks is described, particularly the observation of kinetic intermediates that disappear following 'proof-reading'.

Introduction

Dynamic combinatorial chemistry has emerged as an important strategy in the search for selective hosts in supramolecular chemistry.[1,2] Several reversible chemistries have been explored, one of the most successful being exchange of hydrazones. This has especially been explored with amino acid and steroid based building blocks.[3–10] Herein we describe the synthesis and properties of a range of new hydrazone building blocks for dynamic combinatorial libraries (DCLs) based on heterocyclic scaffolds. The building blocks have the general structure $(MeO)_2CH$-Heterocycle-$C(O)NHNH_2$ with varying recognition abilities (Fig. 1).

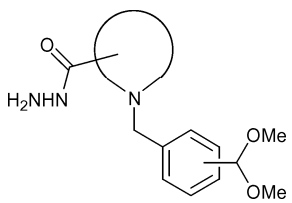
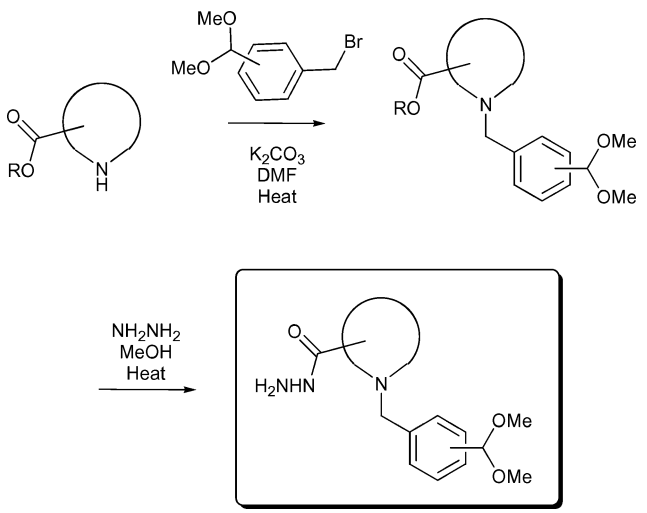


Fig. 1 General structure of heterocyclic building blocks for hydrazone based dynamic combinatorial chemistry.

Knowledge about the effects of changes in the heterocyclic building block geometry on the distribution of the macrocyclic *N*-acyl hydrazones formed and how this compares with cholate building blocks was sought.[8] The main goal, however, was to determine the outcome of mixing heterocyclic with cholate based building and to isolate and characterise the products. In the course of this work we have uncovered macrocyclic kinetic intermediates and remarkable proof-reading effects in the DCLs.

Results and discussion

A series of heterocycle based building blocks (**15**, **16**, **21**, **22**, **25**, **28**, **31** and **38**) was assembled in a slightly different fashion to their steroidal and amino acid counterparts, to enable introduction of a hydrazide under forcing conditions.[8] The introduction of the dimethyl acetal was achieved by means of *N*-alkylation of the amine of the methyl or ethyl ester derivative of the heterocycle with a *meta*- or *para*-substituted bromomethylbenzyl dimethyl acetal. The hydrazide was then introduced by hydrazinolysis of the ester under forcing conditions (Scheme 1).



Scheme 1 General synthetic strategy for heterocyclic based building blocks.

Synthesis

The dimethyl acetals **5** and **6** were synthesised in quantitative yield by treating the aldehydes **3** and **4** with a catalytic amount of *p*TsOH

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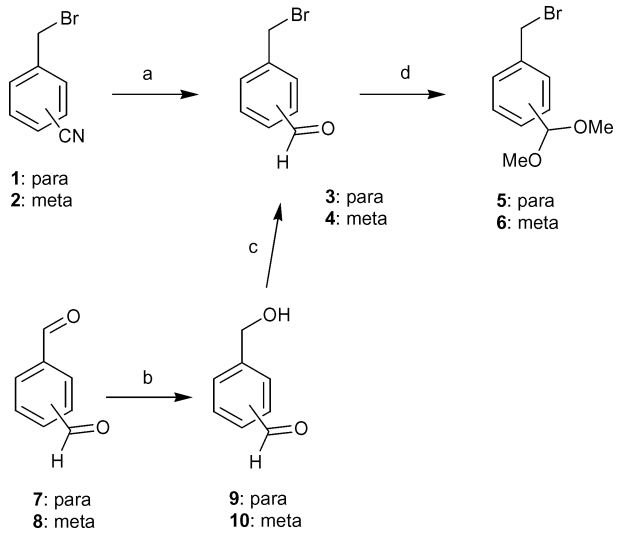
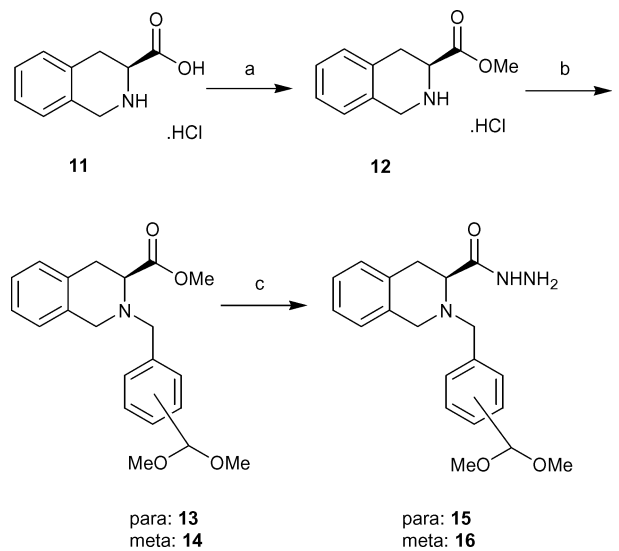
in MeOH at room temperature.[11] The bromomethyl benzaldehydes (**3** and **4**) were synthesised from the respective α-bromo tolunitriles (**1** and **2**) by means of a modification of the procedure of Schlenoff *et al.* (Scheme 2).[12] Alternatively, **3** and **4** were synthesised on a larger scale from the symmetrical dialdehydes (**7** and **8**) by mono reduction using $NaBH_4$ in MeOH to give the benzylic alcohols (**9** and **10**), followed by bromination with aqueous HBr.[13,14]



Scheme 2 Syntheses of acetal aromatic linkers. Reaction conditions: a) DIBAL, Toluene (72–80%), H^+. b) $NaBH_4$, MeOH (65–68%). c) HBr (aq), toluene (82–85%). d) *p*TsOH, MeOH (quant.).

The ester **12** was synthesised from (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**11**) by the procedure of Nakamura *et al.*[15] and then alkylated with **5** or **6** utilising K_2CO_3 in DMF to form **13** and **14**. Hydrazinolysis was accomplished with 10 equivalents of hydrazine monohydrate in boiling MeOH (Scheme 3) to give the hydrazides **15** and **16**.



Scheme 3 Synthesis of tetrahydroisoquinoline (THIQ) building blocks **15** and **16** illustrated by the (*S*)-stereoisomer. Reaction conditions: a) $SOCl_2$, MeOH (82%). b) **5** or **6**, K_2CO_3, DMF, 100 °C (90%). c) $NH_2NH_2{\times}H_2O$, MeOH, reflux (90–92%).

An identical methodology was used to synthesise the (*R*)-stereoisomers of the THIQ building blocks (**21** and **22**) *via* the methyl esters (**19** and **20**) (Fig. 2.). The intermediates **19** and **20** were prepared from (*R*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**17**) and its methyl ester (**18**).

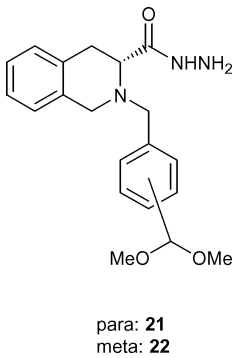
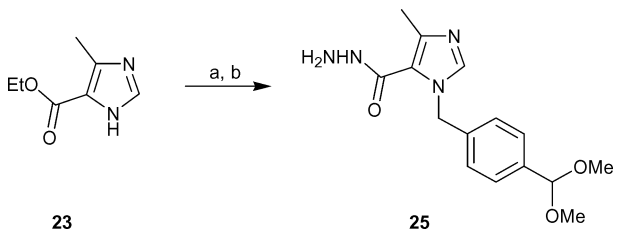


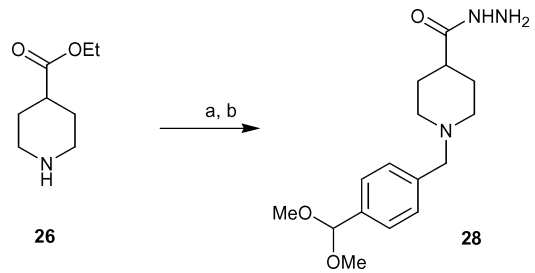
Fig. 2 (*R*)-Stereoisomer of tetrahydroisoquinoline (THIQ) building blocks **21** and **22**.

For further studies on the effect of the heterocycle structure on product distributions in DCLs, ethyl-4-methyl-5-imidazolecarboxylate (**23**) was alkylated with **5** utilising K_2CO_3 in DMF to afford **24** (only one isomer isolated). Hydrazinolysis of **24** with a large excess of hydrazine monohydrate in boiling MeOH afforded the hydrazide (**25**, Scheme 4).



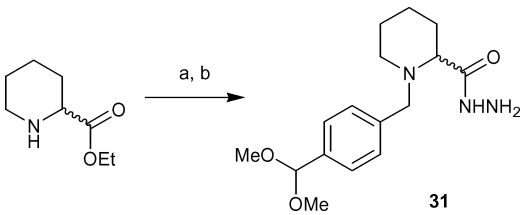
Scheme 4 Synthesis of imidazole (Imid) based building block **25**. Reaction conditions: a) **5**, K_2CO_3, DMF, heat (43%). b) $NH_2NH_2{\times}H_2O$, MeOH, reflux (63%).

The building blocks **28** and **31** were synthesised from ethyl piperidine-4-carboxylate (**26**, *via* the acetal **27**) and ethyl piperidine-2-carboxylate (**29**, *via* the acetal **30**) respectively (Schemes 5 and 6).



Scheme 5 Synthesis of a piperidine (Pip4) based building block (**28**). Reaction conditions: a) **5**, K_2CO_3, DMF, heat. b) $NH_2NH_2{\times}H_2O$, MeOH, reflux (50%, 2 steps).

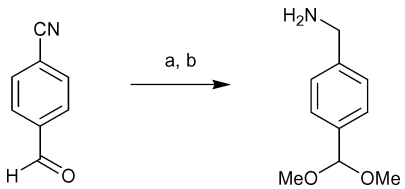
The indole-based building block **38** was synthesised from indole-3-carboxylic acid (**34**, Scheme 8). In this case the dimethyl



Scheme 6 Synthesis of a piperidine (Pip2) based building block (**31**). Reaction conditions: a) **5**, K_2CO_3, DMF, heat. b) $NH_2NH_2{\times}H_2O$, MeOH, reflux (53%, 2 steps).

acetal was introduced *via* EDC mediated amide coupling of the amino dimethyl acetal **33**.

The *p*-methylamino-benzaldehydedimethylacetal (**33**) was synthesised from 4-cyanobenzaldehyde (**32**). The aldehyde was protected as its dimethyl acetal (**32**) by means of NH_4Cl in MeOH,[16] and the nitrile was reduced with $LiAlH_4$ in THF (Scheme 7).[17]



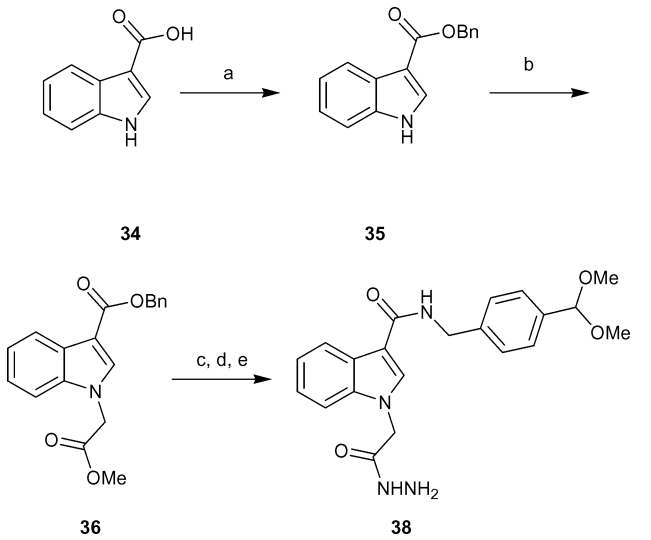
Scheme 7 Reaction conditions: a) NH_4Cl, MeOH, heat. b) $LiAlH_4$, THF (91%).

The carboxylic acid (**34**) was transformed into its benzyl ester (**35**) by treatment with trifluoroacetic anhydride and benzyl alcohol in CH_2Cl_2. *N*-Alkylation of the indole (**35**) with methyl bromoacetate and K_2CO_3 in DMF gave **36**. Hydrogenation using 10% Pd/C afforded the carboxylic acid, which was reacted with the amine (**33**) by means of EDC and a catalytic amount of DMAP in CH_2Cl_2 to afford the amide (**37**).

Hydrazinolysis of the ester (**37**) was accomplished with 10 equivalents of hydrazine monohydrate in MeOH at room temperature to produce the hydrazide (**38**, Scheme 8).

Cyclisation of heterocyclic building blocks

Deprotection of the dimethyl acetal moieties of the building blocks was carried out using the previously reported conditions:[8,10] the building block was dissolved to give a 5 mM solution, TFA (5% v/v) was then added and the reaction mixture stirred at room temperature. The acid has two functions i) it removes the dimethyl acetal to form the aldehyde, and ii) it catalyses the formation of macrocyclic *N*-acyl hydrazones. The solvents used were anhydrous CH_2Cl_2 for monomers **15**, **16**, **21**, **22**, **25**, **28** and **31**, and DMSO for **38**, for solubility reasons. The results of deprotecting these dimethyl acetal hydrazides are given in Table 1, as determined by HPLC-MS. At a monomer concentration of 5 mM **15**, **16**, **21** and **22** initially gave rise to a series of CH_2Cl_2-soluble macrocyclic *N*-acyl hydrazones, from dimer through to hexamer. There was no difference in distribution between the enantiomers **15** and **21**; the cyclic dimer $[THIQ]_2$ was the most favoured macrocycle initially and grew in abundance with time. After seven days the cyclic dimer was virtually the only product present. In contrast **16** and **22** gave



Scheme 8 Synthesis of an indole (Ind) based building block (**38**). Reaction conditions: a) TFA anhydride, BnOH, CH_2Cl_2 (68%). b) Methyl bromoacetate, K_2CO_3, DMF, heat (76%). c) Pd/C, H_2, THF (70%). d) **33**, EDC, DMAP, CH_2Cl_2 (59%). e) $NH_2NH_2{\times}H_2O$, MeOH, room temperature (70%).

Table 1 Distribution of libraries for the eight new building blocks described in this work. For (**38**) the experiment was carried out in DMSO, all others in CH_2Cl_2. The monomer concentration was 5 mM and TFA was used as the acid

Monomer[a]	Initial distribution	Equilibrium distribution
15 or **21**	$[THIQ]_{2-6}$	$[THIQ]_2$
16 or **22**	$[THIQ]_{2-6}$	$[THIQ]_2$
25	$[Imid]_{2-3}$	$[Imid]_2$
28	$[pip4]_2$	$[pip4]_2$
31	$[pip2]_2$	$[pip2]_2$
38	$[Ind]_{2-4}$	$[Ind]_{2-4}$

[a] [THIQ]: **15** or **21**, [Imid]: **25**, [pip4]: **28**, [pip2]: **31**, [Ind]: **38**.

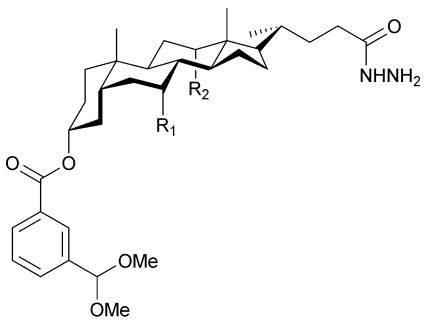
rise to a slightly different initial distribution of products (compared to **15** and **21**) in which the cyclic trimer was the dominant species. Over a period of seven days, however, this too exchanged to form cyclic dimer as the overwhelmingly favoured product. Increasing the concentration of **15** and **21** to 10 mM led to the formation of significant amounts of precipitate after the addition of TFA.

Dilute solutions (5 mM) of **25**, **28** and **31** in CH_2Cl_2 generated significant amounts of precipitate 10 min after the addition of the TFA. Filtering the precipitate off and analysing the filtrate by LC-MS indicated that the only cyclic products from **25** were the cyclic dimer and trimer. Only cyclic dimer could be observed in the filtrate obtained after adding TFA to 5 mM solutions of **28** and **31**. Repeating the deprotection using DMSO as the solvent avoided formation of precipitate on TFA addition but did not lead to a wider distribution of products: in all cases the only product at equilibrium was the cyclic *N*-acyl hydrazone dimer. The deprotection of a 5 mM solution of **38** led to the formation of cyclic dimer, trimer and tetramer, according to LC-MS, with the dimer once again the most favoured macrocycle. The distribution of products in this case did not collapse and drift towards the cyclic dimer. It is important to note that the equilibration in DMSO is much slower that in CH_2Cl_2.

The consistency of the observations concerning product distribution is perhaps not too surprising, given that the structures of **15**, **21**, **25** and **31** are superficially, rather similar. What is a little surprising is the effect of the structure of the building block on the solubility of the macrocyclic *N*-acyl hydrazone formed in CH_2Cl_2. Thus, *N*-acyl hydrazones derived from **15** are freely soluble in CH_2Cl_2 where those derived from **31** are only sparingly soluble. The fact that changing the orientation of the aldehyde in **16** to *meta* did not lead to a significantly different product distribution at equilibrium was disappointing, given the success of this strategy in our previous work with steroidal building blocks.[8] Similarly the lack of effect of changing the position of the dimethyl acetal with respect to the hydrazide in **28**. The marked stability of the cyclic *N*-acyl hydrazone dimer seems to be a common factor in this.

Mixing steroidal and heterocyclic hydrazides and hydrazones

In an attempt to generate more diverse DCLs we investigated the mixing of the new heterocyclic building blocks with the cholate building blocks shown in Fig. 3.[8]



39: R_1 = H, R_2 = pyridine-4-carboxylate

40: R_1 = H, R_2 = pyridine-3-carboxylate

41: R_1 = H, R_2 = benzoate

42: R_1 = H, R_2 = OH

43: R_1 = H, R_2 = H

44: R_1 = pyridine-4-carboxylate, R_2 = H

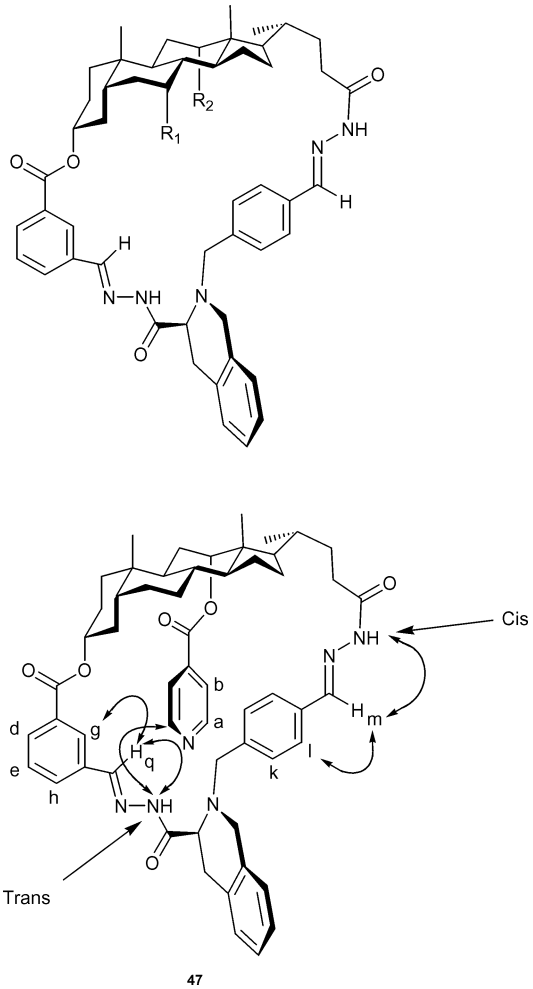
45: R_1 = pyridine-3-carboxylate, R_2 = H

46: R_1 = OH, R_2 = H

Fig. 3 Structures of steroid based building blocks **39–46**.[8]

All the mixing experiments were carried out at the same concentration in CH_2Cl_2 to facilitate isolation of the macrocyclic products by conventional preparative thin layer chromatography.

Combining a 5 mM CH_2Cl_2 solution of the library derived from **15** with an equimolar 5 mM solution of the cyclic *N*-acyl hydrazone dimer[8] derived from **39** in CH_2Cl_2 slowly led to the formation of the heterodimer **47** (Fig. 4), according to LC-MS. Equilibrium was attained after 7 days and **47** was isolated in 60% yield following neutralisation of the reaction mixture with triethylamine. The remainder of the material consisted of the homodimers derived from **15** and **39**, together with a trace amount of the heterotrimer derived from two heterocycle and one steroid unit.



47

Fig. 4 Top: General structure of mixed dimeric macrocycles between **15** and the steroidal building blocks. Bottom: Structure of **47** showing some nOe connections that define the overall conformation of the structure.

Under identical conditions of concentration and solvent essentially the same outcome was observed at equilibrium by deprotecting the building blocks **15** and **39** in *one pot*. The initial distribution of products was quite different, however, in that the dominant product was the heterotrimer previously observed by LC-MS. Furthermore higher oligomers, such as mixed tetramers and pentamers could also be observed. The trimers, tetramers and pentamers were all ephemeral kinetic products that recycled to form the heterodimer over a period of three days. This is an example of proof-reading which can be observed with macrocyclic *N*-acyl hydrazones (Fig. 5).[8]

Isolation of the heterodimer **47** allowed us to show, importantly, that its formation was reversible. Thus, when a 2.5 mM solution of **47** in CH_2Cl_2 was treated with TFA (5% v/v), LC-MS showed the formation of the homodimers derived from **15** and **39** after 24 h, as well as a trace amount of the heterotrimer. The equilibrium distribution of products was comparable to that obtained from deprotecting the building blocks **15** and **39** in one pot and from combining the separately preformed *N*-acyl hydrazones. This confirms that the system is under thermodynamic control.

Since such mixed macrocyclic hydrazones had not been previously reported we studied their structures in some detail. The

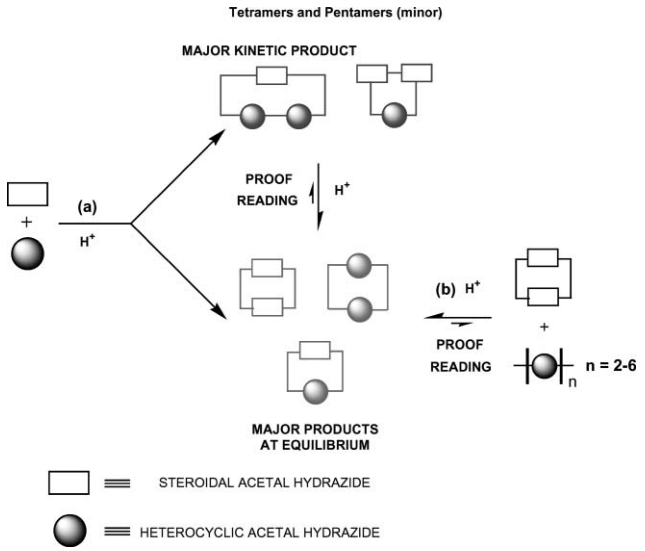


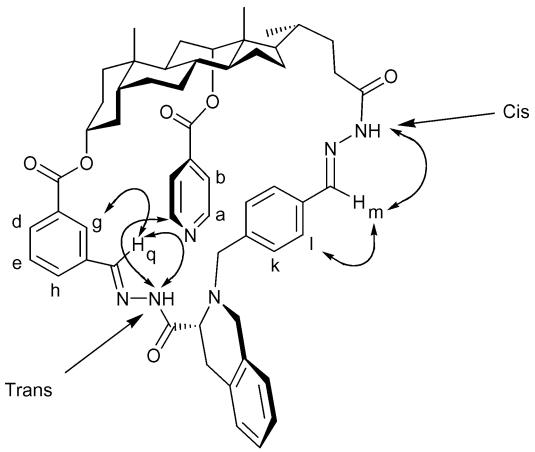
Fig. 5 Schematic representation of the proof-reading process.

^{1}H NMR spectrum of **47** in $CDCl_3$ has the simplicity one would associate with a rigid macrocycle, existing in a single well-defined conformation. Perhaps the most striking feature of the spectrum is the *N*-acyl hydrazone NH resonance downfield shifted to 11.60 ppm. The COSY and NOESY spectra of **47** in $CDCl_3$ allowed both *cis E* and *trans E N*-acyl hydrazone geometries to be identified. These geometries have been identified in steroid-based *N*-acyl hydrazone macrocycles previously but in separate molecules. The *cis E* geometry was identified by virtue of an nOe connectivity between the *N*-acyl hydrazone NH at 8.59 ppm with the azamethine proton, H_μ, at 7.58 ppm. As anticipated the azamethine proton, H_μ, has an nOe connectivity with H_λ at 7.22 ppm.

The *trans E* geometry was assigned by virtue of the nOe connectivity between the *N*-acyl hydrazone NH resonance at 11.60 ppm and the azamethine proton, H_θ, at 9.00 ppm. H_θ also exhibits an nOe cross-peak with H_γ, at 7.67 ppm. In addition nOe connectivities could be observed between the *N*-acyl hydrazone NH at 11.60 ppm, H_κ, at 7.32 ppm and the α-pyridyl proton, at 9.10 ppm. This last nOe connectivity strongly suggests that the downfield shift of the *N*-acyl hydrazone NH at 11.60 ppm is due to a hydrogen-bond between the *trans N*-acyl hydrazone NH and the 12-pyridine substituent. In a variable temperature NMR experiment conducted with **47** in $CDCl_3$ the *trans N*-acyl hydrazone NH did not shift significantly downfield as the temperature was lowered to –60 °C. In contrast the *cis N*-acyl hydrazone NH moved downfield from 8.82 ppm to 10.50 ppm on lowering the temperature from ambient to –60 °C.

Furthermore when the pyridine-4-carboxylate substituent was replaced with a benzoate group in heterodimer **49** the *trans N*-acyl hydrazone NH was shifted upfield to 10.41 ppm. Notably, no nOe connectivities could be observed between the *trans N*-acyl hydrazone NH and the benzoate protons (**49**, Table 2).

When these mixing experiments were repeated with the enantiomer **21** and **39** no significant effect on the yield of the heterodimer **55** formed at equilibrium was found (Fig. 6). The ^{1}H NMR spectrum of **55** was slightly different to that of **47** but not sufficiently to merit further discussion. COSY and NOESY indicated that the two *N*-acyl hydrazone geometries were again present as was the significant downfield shift of the *N*-acyl hydrazone NH resonance; this signal appears at 11.50 ppm.



55

Fig. 6 Structure of **55** and some nOe correlations confirming the geometrical arrangement around the *N*-acyl hydrazone bond.

The yields, at equilibrium, of the heterodimers derived from **15** and the various steroids employed (Table 2) range from 10 to 90%, indicating that the substituent at the 7 or 12-position of the steroid controls the extent to which the heterodimer is formed instead of a self-sorted mixture of homodimers.

The explanation for this difference in behaviour is not clear. It seems most likely that the pyridine-3-carboxylate is situated such that under acidic conditions it can be protonated and assist in

Table 2 Yields of heterodimers from **15** and various steroid building blocks. The structure of the steroids are shown in Fig. 4 (top)

Heterodimer	R^1	R^2	Yield of heterodimer (%)
47	H	pyridine-4-carboxylate	62
48	H	pyridine-3-carboxylate	10
49	H	benzoate	55
50	H	trifluoroacetate	40
51	H	H	48
52	pyridine-4-carboxylate	H	88
53	pyridine-3-carboxylate	H	90
54	OH	H	45

ring opening of the *cis N*-acyl hydrazone of the heterodimer. This would then lead to kinetic instability of the heterodimer compared to the parent homodimers. Thermodynamic arguments would, however, seem to be more appropriate when accounting for the difference in behaviour of the pyridine substituted deoxycholate and chenodeoxycholate-based monomers.

The unexpected trifluoroacylation of the 12-OH, leading to heterodimer **50**, is a function of the position of the hydroxyl group in the molecule. It is observed in the formation of **50** but not **54** so it would seem reasonable to link this with the closer proximity of the *cis N*-acyl hydrazone in the former heterodimer. One can envisage that a hydrazone could assist in the trifluoroacylation of the 12-position either through general acid catalysis, whereby the protonated imine nitrogen protonates TFA and so activates it to nucleophilic attack by the 12-OH, or through nucleophilic acid catalysis, whereby the imine nitrogen is acylated by self-protonated TFA, which then undergoes intramolecular nucleophilic attack by the 12-OH group to transfer the trifluoroacetyl group.

Since a combination of a *meta* substituted cholate and a *para* substituted THIQ favours formation of heterodimer, the next step was to mix a *meta* substituted steroid with a *meta* substituted THIQ (**16**). In the initial distribution of products formed from deprotecting a 2.5 mM solution of **16** and **39** in CH_2Cl_2 with the standard amount of TFA in *one pot* a whole series of mixed macrocycles (heterodimer, trimers and tetramers) could be observed by LC-MS. These were proof-read, however, the result being that at equilibrium only a trace of the heterodimer was present. No higher mixed macrocycles were present and the homodimers derived from **16** and **39** were the only other products. The outcome was the same when the preformed macrocyclic *N*-acyl hydrazones derived from **16** and **39** were combined under the same conditions.

Mixing 5 mM solutions of the other heterocycle-based monomers **25**, **28** and **31** in CH_2Cl_2 in the presence of steroid **39** led, uninformatively, to the formation of precipitates.

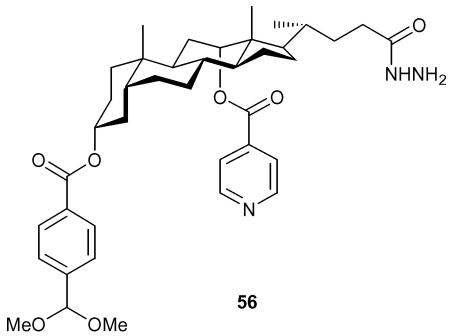
Mixing experiments were carried out between the *para* substituted steroid (**56**, Fig. 7) the *meta* substituted glycine extended steroid (**57**) and the *para* substituted THIQs (**15** and **21**). In the case of mixing experiments between **56** and **15** and **21**, a range of macrocycles were formed, including mixed trimers and tetramers. The same was observed when **57** and **15** were mixed; the heterodimer was not the major product and at equilibrium other mixed macrocycles were also present as shown in Table 3.

This is an encouraging result, as diversity in parent libraries might facilitate templating in DCLs.

Table 3 Equilibrium distributions of mixed libraries and structures of extended steroid building blocks

Monomer[a]	Equilibrium distribution
56 + (**15** or **21**)	$[St]_2$, $[THIQ]_2$, [St][THIQ], $[St]_3$, $[THIQ][St]_2$, $[THIQ]_2[St]$, $[THIQ]_2[St]_2$, $[THIQ][St]_3$
57 + (**15** or **21**)	$[St]_2$, $[THIQ]_2$, [St][THIQ], $[THIQ][St]_2$, $[THIQ]_2[St]$, $[THIQ]_3[St]$

[a] [THIQ]: **15** or **21**, [St]: **56**.



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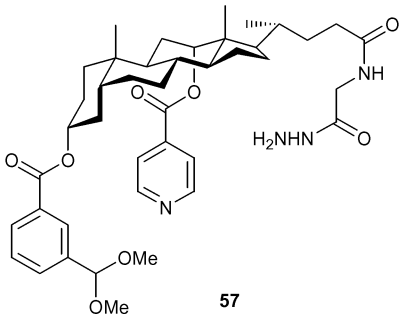

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Fig. 7 Structure of *para*-substituted building block (**56**) and extended steroid building blocks (**57**).

Mixing isomers of heterocyclic hydrazides

The preference for the heterocyclic building blocks (**15**, **16**, **21** and **22**) to form cyclic dimers was further studied by making libraries of all possible mixtures of regioisomers and stereoisomers. This allowed assignment of the different species observed in solution using LC-MS analysis. The LC-MS analysis revealed the presence of six distinct homo- and hetero-dimers upon mixing the four building blocks. In fact, ten different compounds are possible but four of them are enantiomers of other species and the actual number of expected peaks in the HPLC chromatogram is therefore six. To confirm the reversible nature of the systems, two cyclic dimers (**58** and **59**) were isolated (Fig. 8) and used as starting material in library formation with the other isomers. The libraries using these cyclic dimers gave library mixtures with identical composition to the libraries formed directly from the corresponding building blocks. This again confirms that the libraries are equilibrating under thermodynamic control.

Conclusions

We have shown that building blocks for hydrazone based dynamic combinatorial chemistry containing a hydrazide and a dimethylacetal protected aldehyde can conveniently be prepared from the corresponding amino acid methyl ester derivatives. A series of steroidal and heterocyclic compounds have been prepared showing the versatility of the synthetic protocol. Upon treatment of a building block or of a mixture of building blocks in organic solvents with TFA the dominant products were cyclic dimers at thermodynamic equilibrium. Larger macrocycles were present as kinetic intermediates in most experiments. The relative lack of diversity in DCLs derived from single or mixed building blocks

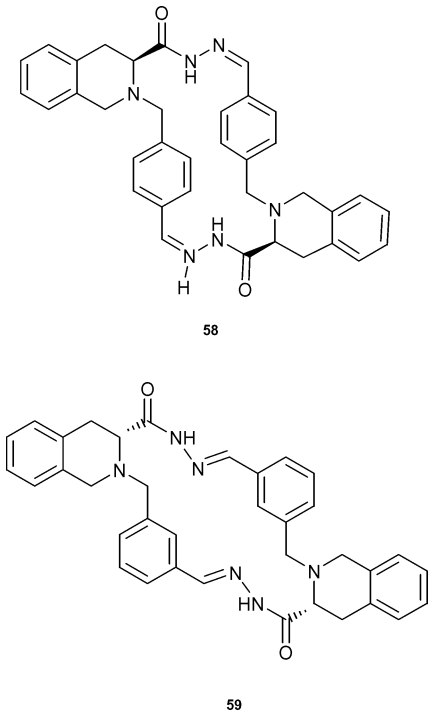

Fig. 8 Structure of homodimers of THIQs **58** and **59**.

is, however, disappointing. Hydrazones derived from flexible dipeptides turn out to generate more diversity and to be susceptible to templating effects as described elsewhere.[3]

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