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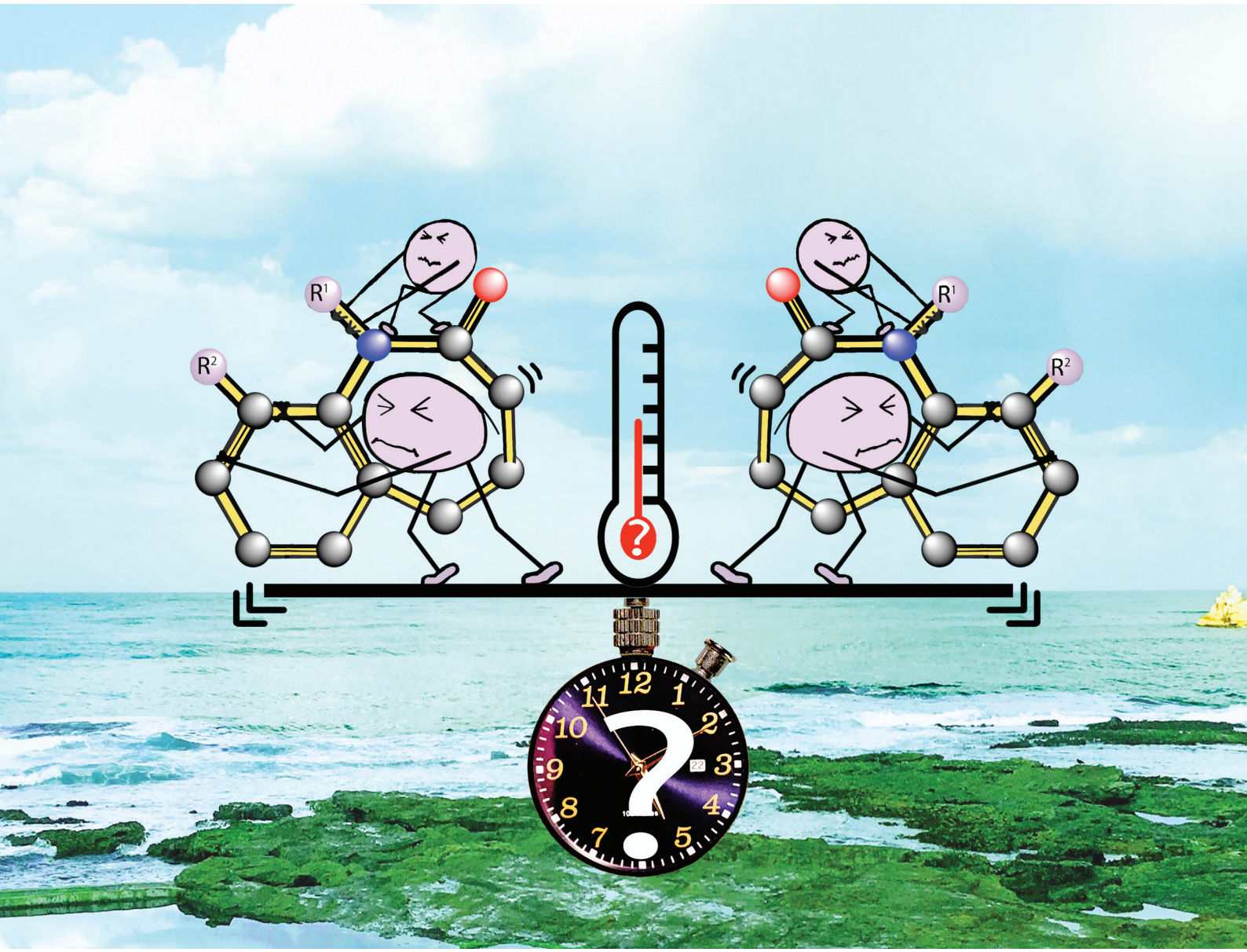

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REVIEW ARTICLE

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REVIEW

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Stereogenic and conformational properties of medium-ring benzo-fused N-heterocycle atropisomers

Lillian A. de Ceuninck van Capelle, *[a] James M. Macdonald[b] and Christopher J. T. Hyland *[a]

Medium-ring (7–9-membered) benzo-fused N-heterocycles – a core structure in several important pharmaceuticals – have a diverse range of interesting conformational and stereochemical properties which arise from restricted bond rotation in the non-aromatic ring. The atropisomers of these pharmaceutically relevant N-heterocycles typically exhibit different biological activities, warranting the need to deeply understand the factors controlling the conformation and stereochemistry of the systems. Beginning with a brief introduction to atropisomer classification, this review will detail a number of medium-ring benzo-fused N-heterocycle systems from the recent literature to provide an overview of structural factors which can affect the atropisomeric nature of the systems by altering the overall conformation and rate of stereo-inversion. As well as general factors such as ring-size and sterics, the impact of additional stereocentres in these systems will be addressed. This includes the differences between sulfur, nitrogen and carbon stereocentres, and the consequences of stereocentre placement around the N-heterocycle ring. Further, conformational stabilisation *via* non-covalent intramolecular bonds will be explored. As such, this review represents a significant resource for aiding in the design, synthesis and study of new and potentially bioactive medium-ring benzo-fused N-heterocycles.

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(a) Introduction

The pharmacodynamic and pharmacokinetic properties of drugs are in part regulated by how their three-dimensional molecular conformations engage with the chiral environment of the human body.[1,2] With bioactivity generally more potent

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Lillian A. de Ceuninck van Capelle

Lillian A. de Ceuninck van Capelle received her International Bachelor of Science (Honours) degree in chemistry from the University of Wollongong (Australia) in 2020. She is currently studying towards a PhD at the same institution in collaboration with the CSIRO under the supervision of Associate Professor Chris Hyland and Dr James Macdonald. Her research is focused on the synthesis of heterocycle atropisomers and the study of their chirality.

James M. Macdonald

James Macdonald is currently a principal research scientist and team leader for medicinal chemistry within the Biomedical Synthetic Chemistry group at CSIRO. Dr Macdonald carried out his PhD in the area of carbohydrate chemistry under the supervision of Professor Bob Stick (University of Western Australia), and his postdoctoral fellowship under the supervision of Professor Steve Withers (University of British Columbia). Since joining CSIRO, his research has spanned natural product synthesis, new materials for organic light emitting diodes and medicinal chemistry.

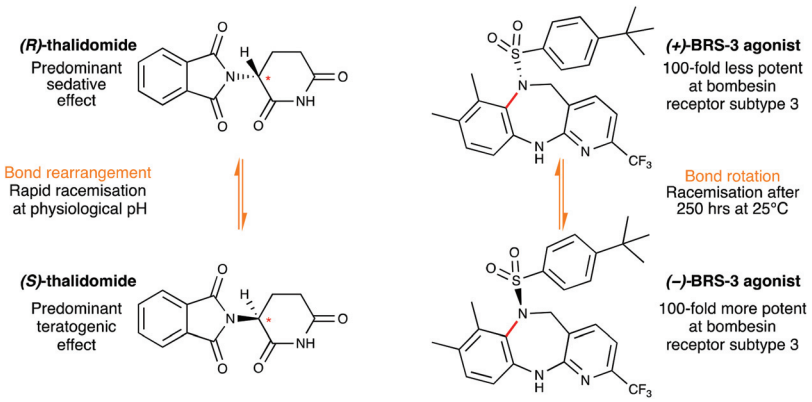


Fig. 1 While enantiomers of both point chiral (left) and atropisomeric (right) molecules can elicit drastically different effects on the body, the latter is much less explored. Stereocentres and axes of chirality indicated by red asterisks and red bonds respectively.

and controlled when drug conformation is well aligned with that of the drug target, the development of drugs in an enantio-defined fashion has become increasingly more common than the development of racemates.[1] Further, as demonstrated by the pharmaceutical disaster of thalidomide, which caused major birth defects due to the generally accepted teratogenic activity of the (*S*) enantiomer (Fig. 1),[3–7] investigation of the biological profiles of chiral molecules and their stability against stereo-inversion is an essential aspect of the drug discovery process.[8,9] Highlighted in a number of recent reviews, the issue of stereochemical stability is of particular concern for atropisomeric compounds, which are chiral due to restricted bond rotation and isomerise on a time/temperature-dependant basis.[1,8,10–12] While the first atropisomer resolution took place in the 1920s,[13] and despite the impact of atropisomerism on bioactivity, axial chirality in bioactive molecules was largely overlooked until the beginning of the 21st century.[1,8,14] Since then, research into various atropisomeric systems has blossomed but the scope of this review will be limited to the biologically important class of 'medium-ring (7–9 membered) benzo-fused N-heterocycles'. Featured in high profile drugs such as diazepam (valium, for anxiety)[15] and nevirapine (for HIV)[16] as well as drug leads such as BRS-3 agonists (for obesity, Fig. 1),[17] medium-ring benzo-fused N-heterocycles have broad pharmaceutical relevance as well as rich stereochemical and conformational properties. In many cases it is understood that one enantiomer has superior bioactivity than the other – which, with half-lives of racemisation ranging from seconds to years, warrants thorough investigation of atropisomeric stability.[1,10,11] Nevertheless, the exploration of medium-ring benzo-fused N-heterocycle atropisomerism is still underrepresented in the literature.[11,12,18] This review seeks to provide an overview of recent research illustrating how the structural features of atropisomeric medium-ring benzo-fused N-heterocycles can affect both the energy barriers for stereo-inversion and the overall conformational geometry of the systems. This review will focus on literature published from 2010 to present.[10]

Christopher J. T. Hyland

Chris Hyland is currently an Associate Professor of Chemistry at the Molecular Horizons Research Institute at the University of Wollongong, Australia. His primary research interests are in chemical synthesis, with a focus on developing homogenous catalytic reactions for the synthesis of heterocycles. He carried out his PhD with Professor Donald Craig at Imperial College London and worked as a postdoctoral fellow with Professor Louis Hegedus at Colorado State University.

(b) Introduction to chirality and atropisomer classification

Traditional 'point' chirality is typified by the static tetrahedral arrangement of inequivalent groups around an sp^3 hybridized atom, labelled a 'stereocentre' (Fig. 2). As bond breakage and formation is typically required for interconversion between two configurations, the stereochemistry of these configurational isomers is relatively stable, notwithstanding a chemical reaction such as acid-catalysed epimerisation. Derived from the

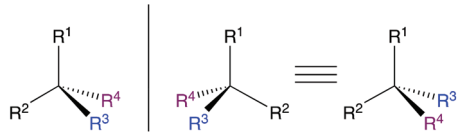


Fig. 2 Generalised example of 'point' chiral enantiomers.

Greek *a* and *trop*-meaning "not" and "turning",[19,20] 'atropisomerism' is a dynamic chirality arising from restricted bond rotation. Originally used to describe conformational isomers of substituted biaryls[21] (Fig. 3a), the definition has since been expanded to include structures with restricted bond rotation such as arylamides (Fig. 3b) and rings with hindered ring-flip inversion (Fig. 3c). Existing in equilibrium, the rate of atropisomer racemisation is determined by the interplay of temperature and the Gibbs free energy of activation ($\Delta G^{\ddagger}$) for rotation of the bond per s situated along the axis of chirality.[21]

To be considered atropisomeric at a given temperature, an isomer must, by convention, have a half-life of at least 1000 seconds – the minimum time required for facile analytical isolation.[21] In the context of pharmaceuticals however, this definition is insufficient to distinguish between atropisomers stable enough to be developed as enantiopure drugs and those which will racemise during production, storage and passage through the body.[1] To rectify this, LaPlante *et al.*[1] proposed grouping atropisomers into three classes based on their free energy of rotation (ΔE_{Rot}), equivalent to $\Delta G^{\ddagger}$. This can be calculated *via* techniques including dynamic NMR spectroscopy, chiral/non-chiral high performance liquid chromatography (HPLC) and vibrational circular dichroism (VCD).[10,12] In keeping with the earlier '1000 second' definition, 'class 1' atropisomers, which have a ΔE_{Rot} of <~20 kcal mol^{-1}, cannot be isolated in enantiopure form at room temperature and are considered achiral for pharmaceutical purposes. Meanwhile, 'class 2' structures, which have a ΔE_{Rot} between ~20 kcal mol^{-1} and ~30 kcal mol^{-1} exhibit half-lives on the scale of minutes to days, positioning them as chiral but not stable enough for drug development as pure isomers. Finally, 'class 3' systems, with ΔE_{Rot} > ~30 kcal mol^{-1}, remain optically pure for years and are thus sufficiently stable to be developed in the same fashion as traditional 'point' chiral drugs.[1]

(c) Overview of factors influencing axial chirality in medium-ring benzo-fused N-heterocycles

While the steric hindrance towards single bond rotation is readily conceptualised for biaryl and arylamide atropisomers, the bonds and substituents that regulate atropisomerism in ring-flip systems are often more complicated. Based on their pioneering studies in the field,[22,23] in 2008 and 2010, the Natsugari group investigated the dibenzoazepine **1a–j** – the structural nucleus of the γ-secretase inhibitor LY-411575 (Fig. 4).[24,25] While initially only the chiral axis a^1 was identified due to its familiar Ar–Ar structure, X-ray crystal structure analysis indicated a second 'latent' chirality at the Ar–N(C=O) axis a^2, revealing that the system actually existed as (a^1S, a^2R) and (a^1R, a^2S) enantiomers. Consistent with molecular modelling favouring the (a^1R, a^2S) isomer over the strained (a^1R, a^2R) form, a lack of diastereomers observed *via* NMR spectroscopy and HPLC analysis suggested that the chiral axes experienced 'geared rotation', with the two bonds rotating in a linked process – as opposed to independently – resulting in enantiomers but no diastereomers. This occurrence of 'geared rotation' is also supported by research on the dibenzazepines **1k–l** (Fig. 4). Despite not recognising the Ar–N bond as an axis of chirality, Newton *et al.* found that the minimal the steric bulk of the **1l** *N*-substituent eased rotation of the remote Ar–Ar bond, lowering the $\Delta G^{\ddagger}$ of racemisation relative to **1k**.[26] Clarifying the mechanistic nature of the 'geared' atropisomerism of cyclic biaryls like **1**, a detailed NMR and DFT study of similar structures proposed that the bond rotations which amount to the atropisomeric heterocycle ring-flip actually occur as the sequential inversion of endocyclic torsion

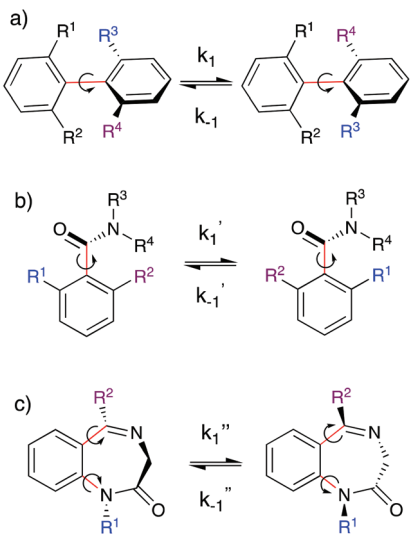


Fig. 3 Generalised examples of biphenyl atropisomers (a), arylamide atropisomers (b) and ring inversion atropisomers (c). Axes of chirality along red bonds.

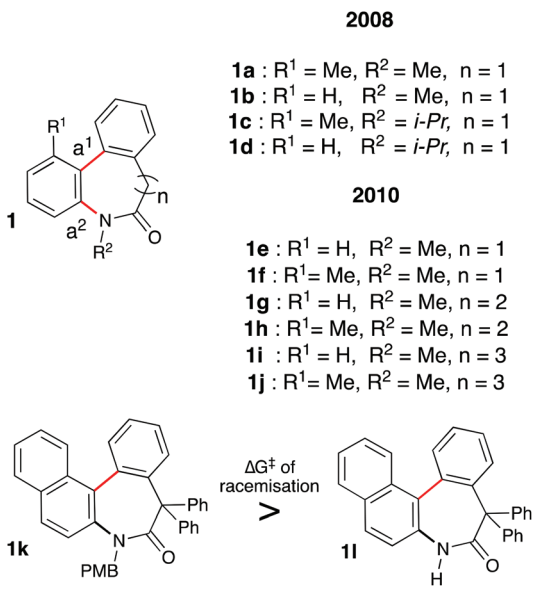


Fig. 4 Substrate scope of dibenzoazepines exhibiting two axes of chirality (along bonds in red).

angles.[27] Thus rather than occurring simultaneously or at random, the interdependent 'geared' nature of the bond rotations likely occurs in a step-wise fashion that nevertheless precludes the generation of visible diastereomers.

Regarding conformational stability, atropisomers of **1** were all relatively resistant to racemisation ($\Delta G^{\ddagger}$ > 23 kcal mol^{-1}). Consistent with geared rotation, an increase in steric hindrance around either axis by substituting the R^1 and R^2 positions (R^1 = Me or R^2 = Me, i-Pr) augmented the overall barrier to enantiomerisation ($\Delta G^{\ddagger}$).[24] To verify whether the latent Ar–N chirality was simply a consequence of the Ar–Ar chirality, an ensuing study removed the latter moiety and found that the independent Ar–N axis retained its chirality (Fig. 5).[28] The consequence of removing the second aryl group however, was that degree of steric hindrance required to isolate atropisomers of **2** became greater, rendering the atropisomers less stable to interconversion. Assuming a flat transition state, the steric barrier to inversion arises mainly from *peri*-like steric interactions between the N–R^2 and Ar–R^1 groups adjacent to the ring junction (Fig. 5). While dibenzoazepine **1** did not require substitution of the equivalent Ar–R^1 position to maintain the atropisomeric character of the system, in the case of benzazepine **2** – when either R^1 or R^2 of was unsubstituted, ^{1}H NMR analysis showed coalescence of the peaks attributed to the nearby methylene protons, indicating rotation at the Ar–N axis was too rapid to render the system atropisomeric on an NMR timescale at room temperature (Fig. 5).[28] To probe the impact of substitution at the other end of the ring junction, the X position of **2** was also varied, but appeared to have little effect on the atropisomeric properties of the system (Fig. 5). However, ensuing studies have found that in the right circumstances it is possible for variation of X and other positions around the heterocyclic ring to dramatically impact the atropisomerism and overall conformation of such molecules.[29–32] One example of this is the vasopressin receptor antagonist **3**, which features an exocyclic amide Ar–N5(CO) adjacent to the ring junction which is central to the atropisomeric nature of the system (Fig. 6).[32]

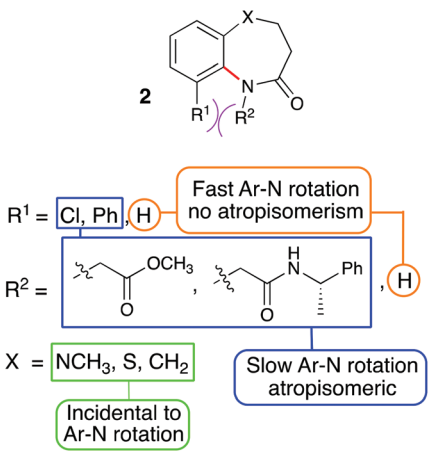


Fig. 5 Benzoazepine skeleton **2** with substituent variation adjacent to the ring junction. Axis of chirality along red bond, *peri*-like steric interactions in purple.

Contrary to expectation, the Ar–N1 bond of **3a–c** was not identified as lying along an axis of chirality.[32] Given that the ring-flip $\Delta G^{\ddagger}$ for a simple 8-membered benzazepine is calculated to be almost 24 kcal mol^{-1} with the axis of chirality along the lactam Ar–N bond,[33] it is also possible that the both Ar–N bonds in **3** have axes of chirality but do not result in diastereomers due to 'geared' rotation. In other words, Ar–N1(CO) and Ar–N5(CO) likely exist as two sp^2–sp^2 axes, which move in concerted manner, such that only one diastereoisomer is observed. It should also be acknowledged that diastereoisomers may also not be observed if Ar–N1 rotation is too fast to be classed as truly atropisomeric – meaning a single axis of chirality was present.[25,28,34]

Regardless of whether the Ar–N1 bond of **3** has restricted rotation or not, the lower $\Delta G^{\ddagger}$ of **3d** (Y = CH_2) than **3b** (Y = CO) demonstrates that the lactam structure serves an important function in regulating the atropisomerism of the system. Supported by research on related systems, there is an inverse relationship between ring flexibility and ring-flip $\Delta G^{\ddagger}$.[27,35] For the lactam **3b**, the double-bond character of the N1–CO bond increases the heterocycle rigidity relative to the benzodiazepine **3d**, in turn raising the energy barrier to ring-flip inversion and stabilising the overall stereo-conformation.[32]

In the structure of **3**, *E*/*Z* isomers are also expected at the exocyclic amide N5–C(=O) bond (green in Fig. 6). From analysis of the ^{1}H NMR spectra however, the *E* stereo-conformation is strongly favoured – a bias which is consistent across all exocyclic ArN–CO amides featured in this review and will be discussed in section h. Meanwhile, restricted rotation of the Ar–N5(CO) bond (red in Fig. 6) classes the system as atropisomeric when R^1 > H, despite the adjacent carbonyl constituting an exocyclic amide rather than the usual lactam. The lower $\Delta G^{\ddagger}$ for rotation of this bond when R^1 = Cl compared to when R^1 = CH_3 was attributed to the smaller size of Cl as well as a possible withdrawal of electron density from N5 by induction.[32] To explain this, it is important to clarify the role of the carbonyl in Ar–N(C=O) atropisomerism. The amide nitrogen lone pair of electrons exist in resonance with the carbonyl double bond, rendering the nitrogen sp^2 hybridised in most cases.[36] In a typical arylamide, this creates an amide plane which clashes sterically with the plane of the aryl, restricting Ar–N(C=O) bond rotation, generating an axis of chirality along

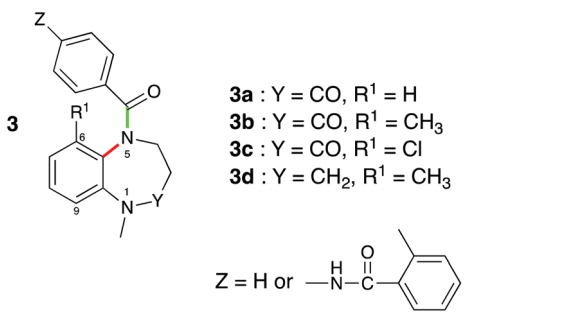


Fig. 6 Scope of benzodiazepine skeleton **3**. Axis of chirality along red bonds, *E*/*Z* axis in green – *E* pictured.

the bond and rendering the molecule atropisomeric. While amide carbonyls can contribute to ring-flip atropisomerism in this fashion, it should be noted that the sp^2 hybridisation necessary for Ar–N atropisomerism to exist can equally be fostered by other π-resonance systems which will be discussed later in this review. Regarding **3c**, while the details of how Cl might lower the Ar–N rotation barrier were not discussed in detail,[32] it is possible that inductive withdrawal of electron density from N5 would limit the nitrogen lone pair resonance delocalisation into the amide carbonyl, increasing the sp^3 character of the nitrogen and so increasing the flexibility of the heterocycle.[37] Alternatively, it is possible that the electronic effect of the Cl is a cross-conjugation of the amide nitrogen lone pair, lowering the $\Delta G^{\ddagger}$ of enantiomerisation by stabilising the more planar transition state.[34]

In addition being moderated by heterocycle substituents, the flexibility and thus ring-flip $\Delta G^{\ddagger}$ of a system can be moderated by ring-size. From analysis of the X-ray crystal structures of the methyl-substituted dibenzoazepines **1f**, **1h** and **1j**, the Natsugari group determined that the dibenzoazepine system **1** adopts a 'cage' conformation which deepens as the azepine ring becomes larger (Fig. 7).[25] As enantiomerisation in this instance would require inversion of the cage, the deepened conformation is reasoned to increase the rigidity of the 8-membered ring and the energetic strain of inversion – augmenting the value of $\Delta G^{\ddagger}$ relative to the 7-membered ring structures. While the $\Delta G^{\ddagger}$ values of the methylated **1h** and **1j** were too high to be calculated exactly *via* chiral HPLC – likely due to steric hindrance from the methyl group restricting bond rotation – the unsubstituted 9-membered dibenzoazepine **1i** exhibited a $\Delta G^{\ddagger}$ value comparable with the 7-membered ring **1e**. Although the reason for this trend reversal is not certain, the authors proposed that the heterocycle flexibility gained by the extra methylene group improved access to the transition state, undermining any stabilising effect of the deeper cage.[25] This theory is supported by the work of De Benassuti *et al.* on 9- and 10-membered benzo-fused N-heterocycles, which also assume cage conformations.[38] Here, the 10-membered ring was reported as having a much lower $\Delta G^{\ddagger}$ than the 9-membered ring, which had a similar $\Delta G^{\ddagger}$ to **1i**.[25,28] Thus, although increasing ring size can elevate $\Delta G^{\ddagger}$ though conformational rigidity restricting access to the transition state, the relationship appears to be parabolic rather than linear due to the counter effects of flexibility that also come with increased size.

(d) Heteroatom point chirality in atropisomeric benzo-fused heterocyclic ring systems

So far, it has been established that factors such as steric hindrance, electronic effects, and system flexibility impact the $\Delta G^{\ddagger}$ of bond rotation and thus the atropisomeric stability of medium-ring benzo-fused N-heterocyclic systems. In each case, the axes of chirality were found along bonds between an amide nitrogen and a ring junction. However, when examining the chirality of these systems, it is important to recognise that nitrogen and other heteroatoms can alternatively function as stereocentres. This is demonstrated by studies expanding on the research by the Natsugari group[28] into the chirality of the benzo-fused lactam **2** (Fig. 5 and 8).[28–31]

When previously discussed, variations of the atom X in **2** had little impact on the conformation or chirality of the molecule (refer to Fig. 5). However, if when X = S the sulfur is oxidised, or when X = N the nitrogen substituent is sterically encumbered by proximity to other parts of the molecule, then the sulfur and nitrogen atoms can be rendered stereogenic centres respectively (Fig. 8). Earlier, traditional point chirality was defined as four different groups arranged tetrahedrally around an sp^3 hybridised atom. If one of these groups is an electron lone pair, chirality is retained but the molecular geometry becomes pyramidal. While point chiral enantiomerisation typically requires bond breakage, the enantiomerisation of a stereocentre with a lone pair can occur *via* pyramidal inversion. Here, the three bonds flatten out into the same plane as the centre atom then continue through this plane to resume a pyramidal arrangement on the other side (an analogy might be drawn to the geometrical change that occurs in an S_N2 inversion). Like atropisomerism, the rate of this inversion is relative to temperature and the free energy of activation for the conformational inversion.[39] For chiral sulfoxides, this energetic barrier is generally high enough ($\Delta G^{\ddagger}$ >

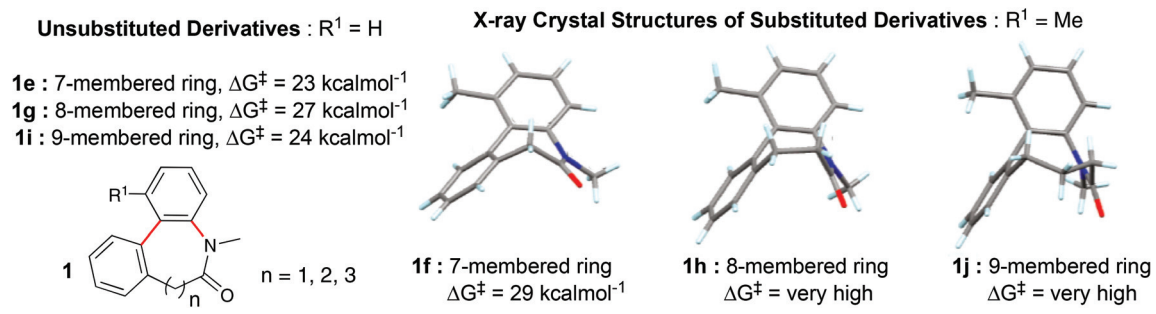


Fig. 7 Comparison of the X-ray crystal structure of 7-, 8-, and 9-membered dibenzoazepines illustrating deepening 'cage' conformation with greater ring size. Axes of chirality along red bonds. X-ray crystal structures adapted with permission from Tabata *et al.* (2010), copyright 2010 American Chemical Society.[25]

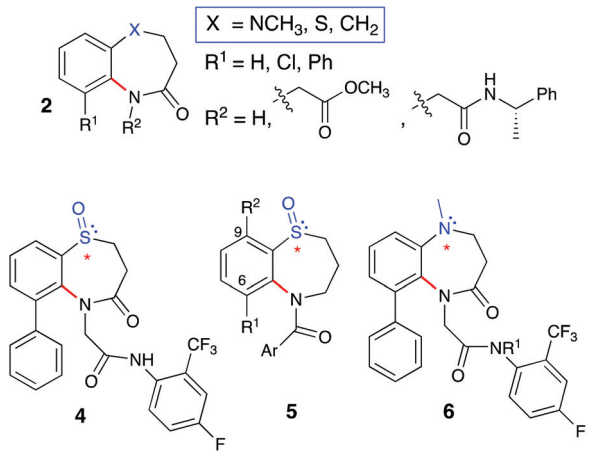
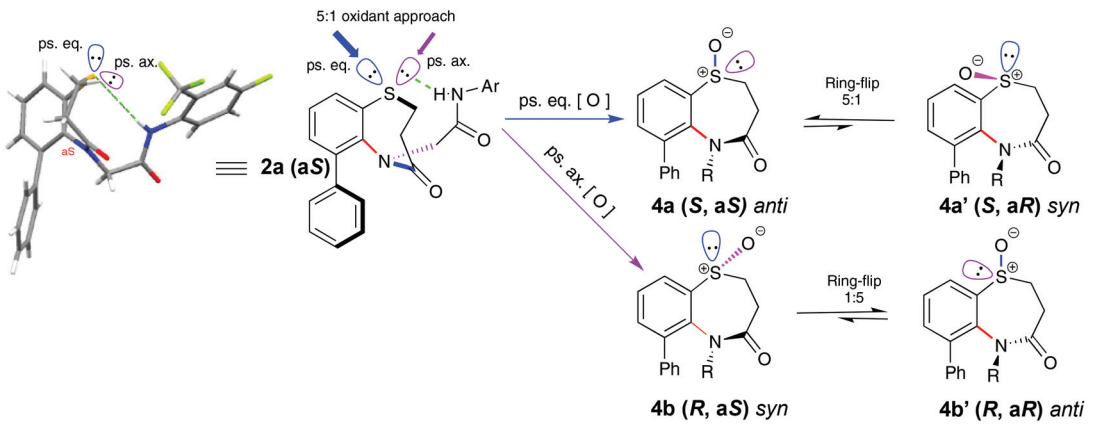


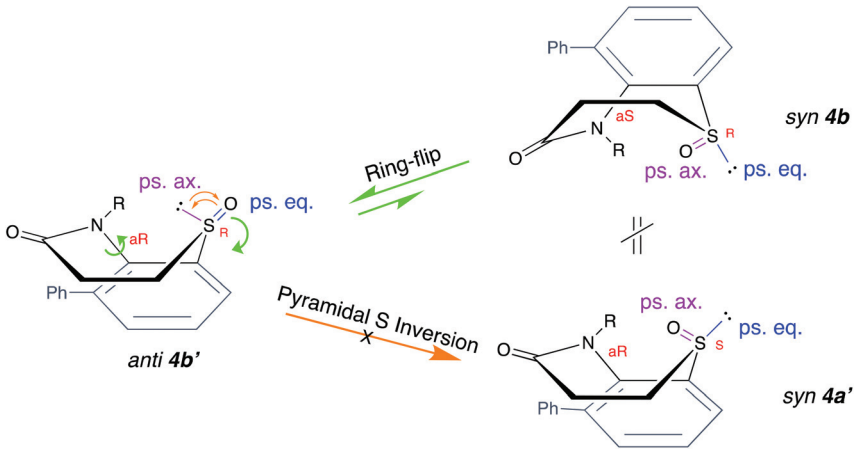
Fig. 8 Comparison of **2** with the derivative structures **4**, **5** and **6**, which all possess both point and axial chirality. Stereocentres axes of chirality indicated by red asterisks and red bonds respectively.

30 kcal mol^{-1}) that sulfoxide chirality can be considered equal in stability to classic sp^3 carbon stereocentres.[39] While chiral sulfoxides are not prone to inverting, sulfoxide derivatives of the benzazepine **2** have shown that the stereocentre can behave interdependently with a chiral axis to influence the overall stereogenic conformation of the system. Moreover, when the benzothiazepine **2** (X = S) is oxidised to the sulfoxide **4**, the process is stereoselective courtesy of the remote Ar–N axis.[29] Detailed in Scheme 1 for example, when the a*S* precursor **2a** is oxidised to the sulfoxide **4a** and **4b**, hydrogen bonding between the pendant amide and the pseudoaxial sulfur lone pair preferences oxidation at the unobstructed pseudoequatorial position (**4a**) in a 5 : 1 ratio over the pseudoaxial position (**4b**). Consistent with the high pyramidal inversion barrier of other chiral sulfoxides,[39] when the isomeric products of oxidation **4a** and **4b** were heated individually in solution, chiral HPLC analysis found that only the chiral axis was labile, producing ring-flip diastereomers in equilibrium but no enantiomerisation (Scheme 1).[29] Similar to the stereoselectivity of sulfur oxidation, this atropisomer equilibrium of the oxidised products was biased 5 : 1 towards the pseudoequatorial orientation of S=O, favouring **4a** and **4b′**. Again, this is attributed to the pseudoequatorial S=O minimising the steric relationship between the pendent ArN–R group and the oxidised sulfur by orientating the oxygen away from the encumbered side of the ring in an *anti*-fashion (Scheme 1 and 2). To fully understand the relationship between S=O orientation and ring-flip, note that a shift in the stereochemistry of the Ar–N axis affects the conformation of the molecule as a whole. When the Ar–N bond rotates, the ring-flip converts all pseudoequatorial substituents into pseudoaxial substituents and *vice versa*, with no stereogenic change at the sulphur stereocentre. For example, when the chiral axis of **4b′** rotates from a*R* to a*S*, the 1*R* chirality of the sulfur stereocentre remains constant but the pseudoequatorial S=O is rotated into the more sterically hindered pseudoaxial position as the ring inverts (Scheme 2). This converts the *anti* system **4b′** (defined by the relative position of the R group and the sulfoxide oxygen) to the more sterically strained *syn* system **4b**. The thermodynamic disadvantage of this is reflected in the dynamic equilibrium of the **4b′** and **4b** diastereomers, which favours the less crowded *anti* conformation of the a*R* isomer.

Benzothiazepine **5a–b** (Fig. 8 and 9), which is a more flexible – non-lactam, exocyclic amide – analogue of the benzothiazepine **4**, is also strongly biased towards the *anti* (pseudoequatorial S=O) isomers.[31] Contrary to systems that feature only axial chirality, the Ar–N axis of **5a** remains atropisomeric even when steric hindrance at the Ar–N axis is absent (R^1 = H), suggesting that the sulfur stereocentre has a stabilising effect. For clarity, when comparing benzothiazepines **4** and **5**, it should be noted while they both exhibit *anti* conformational bias, the amide carbonyl of **5** is not part of the heterocycle ring and so inverts the relative stereogenic label of the Ar–N axis. For example, when sulfur has '*S*' stereochemistry, the favoured *anti* conformation is (1*S*, a*S*) for **4** and (1*S*, a*R*) for **5** respect-



Scheme 1 Stereoselective oxidation of a*S* benzothiazepine **2a** (isomer chosen arbitrarily) to form major (a*S*,1*S*) and minor (a*S*,1*R*) sulfoxide diastereomers. Axes of chirality along red bonds, hydrogen bond in green, "ps. eq." = pseudoequatorial (blue), "ps. ax." = pseudoaxial (purple). **2a** and associated X-ray crystal structure adapted with permission from Tabata *et al.* (2013), copyright 2013 American Chemical Society.[29]



Scheme 2 Illustration of **4b**′ Ar–N rotation, resulting in a ring-flip and rotation of the S atom, which renders the previously ps. eq. (pseudoequatorial) oxygen as ps. ax. (pseudoaxial) in **4b** without affecting the sulfur stereochemistry (green arrows). Pyramidal S inversion (orange arrows) does not occur.

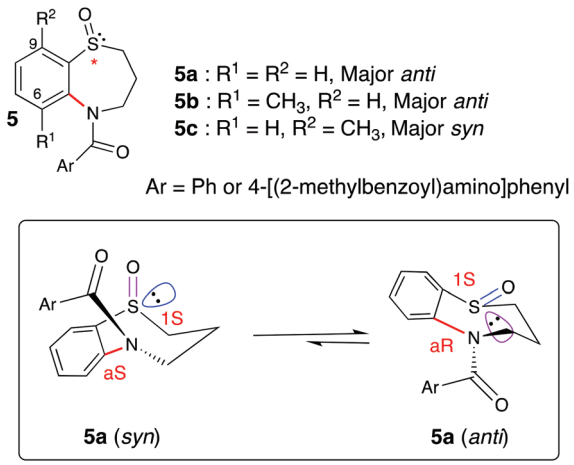
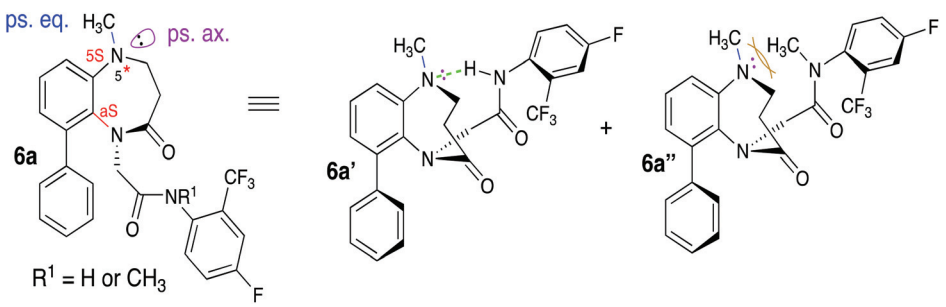


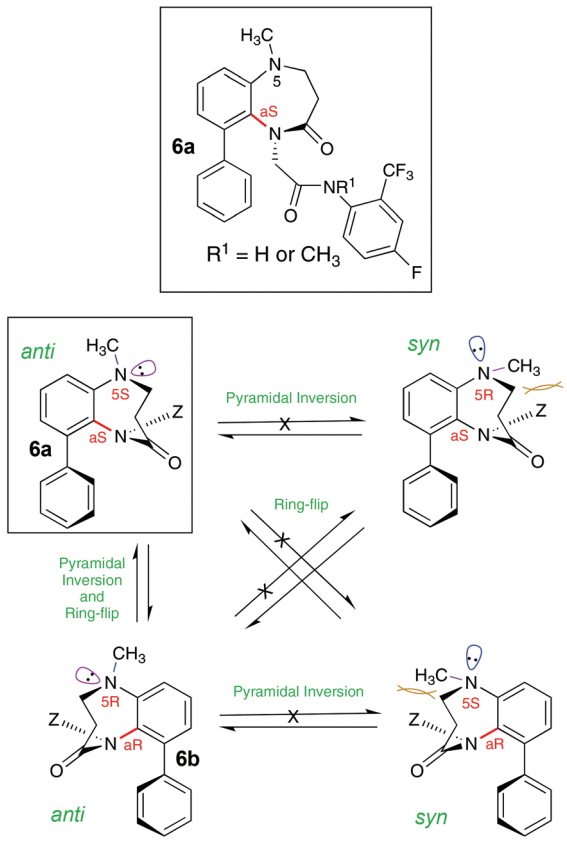
Fig. 9 Substrate scope of sulfoxide **5** and equilibrium of *syn* and *anti* 1*S* diastereomers favouring the less sterically encumbered *anti* conformation. Axes of chirality along red bonds. Blue = pseudoequatorial, purple = pseudoaxial.

ively. From a series of binding assays conducted for **5** by the Natsugari group, '*S*' chirality was determined to have greater bioactivity at the vasopressin receptor V_{1a} (implicated in water homeostasis) than '*R*' chirality for both the stereogenic sulfur and the chiral Ar–N axis.[31] As such, the (1*S*,a*S*) *syn* conformers of **5a–b** are the most pharmaceutically promising despite being the minor products. With C9 methyl substitution in **5c** however, the steric hindrance of the pseudoequatorial S=O position became superior to that of the pendent amide at the pseudoaxial position, resulting in 100% enantiomeric excess of the bioactive pseudoaxial S=O *syn* isomer (1*S*,a*S*).[31] Thus although these systems lack geared enantiomerisation due to the stability of the sulfoxide against pyramidal inversion, the point and axial chiral components are still interdependently responsible for the conformation of the system.

Unlike sulfoxides, amines typically have a low pyramidal inversion barrier and are considered achiral.[40] As demonstrated by the ACAT inhibitor **6a** however, intramolecular steric hindrance in 7-membered ring systems can raise this energy barrier high enough to render amines configurationally stable.[30] This is achieved by the pendent ArN–R group biasing the orientation of the N5 methyl substituent towards the pseudoequatorial *anti* position rather than the sterically hindered pseudoaxial *syn* position (Scheme 3).[30] Here, although a hydrogen-bond was found to form between N5 and the pendent amide when R^1 = H (**6a**′), replacement of R^1 with –CH_3 (**6a**″) changed the conformation of



Scheme 3 The amine methyl of benzodiazepine **6a** occupies the pseudoequatorial position *anti* to the pendent amide group of regardless of whether R^1 is capable of hydrogen bonding with N5 or not. H-bond in green ps. eq. = pseudoequatorial (blue), ps. ax. = pseudoaxial (purple).



Scheme 4 Proposed geared enantiomerisation of atropisomer **6a** to **6b**, maintaining *anti* conformation with N–CH_3 in the stable pseudo-equatorial position. Axes of chirality along red bonds. Blue = pseudo-equatorial, purple = pseudoaxial.

the system very little. Thus the preference for the pseudoequatorial *N*5–CH_3 *anti* conformation of **6a** is best attributed to steric hindrance destabilising the *syn* conformation rather than H-bonding stabilisation of the *anti* conformation.[30]

In contrast to the sulfoxide systems **4** and **5**, this preference for a pseudoequatorial *N*-methyl is not expected to augment the ring-flip barrier. Rather, although not confirmed experimentally, the *N*5–amine is thought to undergo pyramidal inversion upon rotation at the chiral axis to compensate for the pseudoaxial/equatorial exchange that occurs with a ring-flip (Scheme 4).[30] Thus, reminiscent of the dibenzoazepine systems discussed earlier, **6** is thought to feature geared enantiomerisation, avoiding the (5*R*,a*S*) and (5*S*,a*R*) *syn* diastereomers which would come from isolated pyramidal inversion or chiral bond rotation leading to a ring-flip (Scheme 4).

(e) Identification of nitrogen as a stereocentre or along an axis of chirality

Having established that nitrogens adjacent to the ring junction of benzo-fused heterocycles can be stereocentres or cultivate an axis of chirality, it is prudent to examine which scenarios cause nitrogens to behave each way. Hinted at in section b when discussing the role of the amide carbonyl in benzodiazepine **3**, the answer to this stems largely from the hybridisation of the N atom. Similar to how the $\Delta G^{\ddagger}$ of dibenzoazepine **1** is elevated upon deepening cage conformation, a study by the Ramig group found that the $\Delta G^{\ddagger}$ of ring-flip atropisomerism can be related to puckered boat character of a ring-system.[41] Where cage deepening eventuates with larger ring size, ring puckering is promoted by steric bulk and small bond angles which adds to strain in the ring-flip transition state. Investigating systems **7a–c** (Fig. 10), the Ramig group found that when N1 was sterically hindered *via* alkylation, the geometry of the amine became considerably flattened, shifting the hybridisation of the nitrogen from sp^3 towards sp^2.[42] As well as accentuating the puckered conformation of the boat, this change in hybridisation rendered pseudoequatorial and pseudoaxial *N*1-alkyl orientation almost indistinguishable from each other. Intrigued by this and other amine-based 7-membered ring-flip systems, the Ramig group undertook an NMR and computational study of **7** examining how nitrogen alkylation affects the relationship between ring-flip and nitrogen inversion.[43]

Consistent with their previous findings,[42] the computational work examining the ground states of **7** concluded that the substituted nitrogens are practically planar and sp^2 hybridised.[43] Due to the subsequent increase in ring strain, plus *peri*-like steric interaction between the alkyl and the C9 hydrogen, the boat conformations of *N*-substituted systems

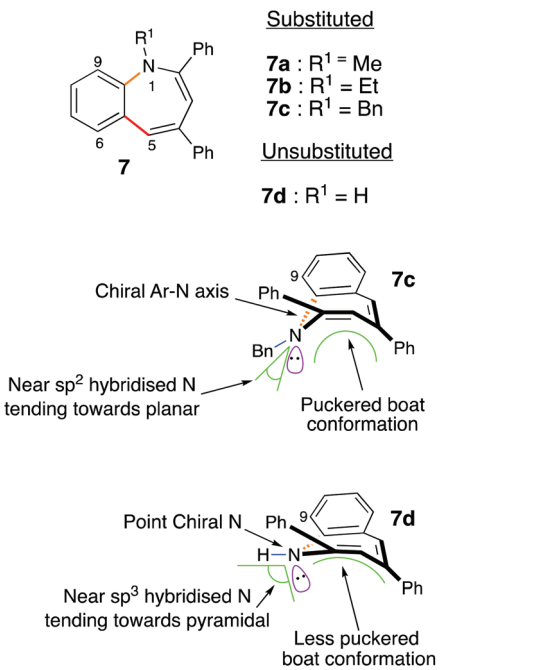


Fig. 10 Substrate scope of benzoazepine **7** which displays axial chirality for substituted nitrogens and point chirality for unsubstituted nitrogens. Conditional axis of chirality along orange bond, proposed permanent axis of chirality along red bond.

are notably puckered. In contrast, the unsubstituted nitrogen of **7d** is more pyramidal, with N-hybridisation roughly halfway between sp^2 and sp^3 hybridised (Fig. 10 and 11b). In turn, as ring strain and *peri*-like steric interaction are lower than for the *N*-substituted derivatives, the boat conformation of the *N*–H system is less puckered. Moreover, while the unsubstituted nitrogen atom is not definitively sp^3 hybridised, the pseudo-equatorial *N*–H ground state is favoured almost exclusively over the pseudoaxial ground state, indicating that the group is stabilised against pyramidal inversion, rendering the nitrogen atom a stereocentre. The consequence of this differing hybridisation and ring puckering is that for the *N*-substituted systems **7b–c**, the $\Delta G^{\ddagger}$ barrier for ring-flip is larger than for N-inversion whereas for **7a** (N–Me) and the N-unsubstituted systems **7d**, the two become conflated. For example, in *N*-substituted **7c** (Fig. 11a) the similarity between the geometry of the flattened amine and the N-inversion transition state results in a low $\Delta G^{\ddagger}$ for N-inversion. Meanwhile, because the puckered boat conformation of **7c** deviates greatly from the ring-flip transition state, the ring-flip $\Delta G^{\ddagger}$ barrier is much larger. Consequently, independent from the ring-flip, the N atom inverts rapidly, excluding it from being a stereocentre. It should also be noted that although the $\Delta G^{\ddagger}$ of **7c** ring-flip is technically low enough for the system to be non-atropisomeric ($\Delta G^{\ddagger}$ < 20 kcal mol^{-1}), the barrier's dependence on the steric bulk of the benzyl substituent (which increases puckering) clearly identifies the Ar–N bond as a potential axis of chirality. If greater steric hindrance was added at the ring junction, it is likely that the energetic barrier to Ar–N rotation would be raised and the system would become truly atropisomeric. For the benzazepine lacking an N substituent (**7d** Fig. 11b), the energetic accessibility of isolated N-inversion is undermined by the lower barrier for simultaneous N-inversion and ring-flip (5.1 kcal mol^{-1} for N-inversion *vs.* 3.5 kcal mol^{-1} for both). Consequently, even though the $\Delta G^{\ddagger}$ for N-inversion of **7d** is close to that of the benzylated **7c** (5.1 kcal mol^{-1} *vs.* 4.6 kcal mol^{-1} respectively), **7d** behaves differently, with pyramidal N-inversion invariably occurring with ring-flip. This renders the amine nitrogen atom a stereocentre with stereogenic stability that is interdependent with that of the chiral axis. Thus, alike the benzodiazepine system **6**, benzazepine **7d** is capable of enantiomerisation but not diastereomerisation, ensuring N–H is orientated exclusively in the pseudoequatorial position. Curiously, when the researchers examined the substituted N–CH_3 system **7a**, it behaved as an outlier, exhibiting simultaneous ring-flip and N-inversion like **7d** despite its supposed near-sp^2 N hybridisation like **7b–c**. Also inconsistent with **7b–c**, the analogous N–CH_3 moiety of the earlier discussed benzodiazepine **6** showed clear distinction between pseudoaxial and pseudoequatorial methyl orientation – if like **7a**, the N atom was near-sp^2 hybridised due to the bulk of the methyl, these orientations should have been indistinguishable. Considering this conflicting data, it appears that –CH_3 approaches the limit of steric bulk that can be bonded to the N atom before it shifts from point chiral to axially chiral, with the nitrogen atom of **6** and **7a** landing on the side of point chiral behaviour. It should also be noted that like **7c**, the low $\Delta G^{\ddagger}$ of enantiomerisation for **7a** and **7d** technically class the systems as non-atropisomeric. In a follow-up computational experiment, Ramig *et al.* determined that C9-methylation of **7a** (Fig. 11) would raise the ring-flip barrier to 25.8 kcal mol^{-1}, rendering the system a class 2 atropisomer.[1,43] However, it is not clear if this slower ring-flip would still occur simultaneously with N-inversion, or whether the additional steric hindrance across the ring junc-

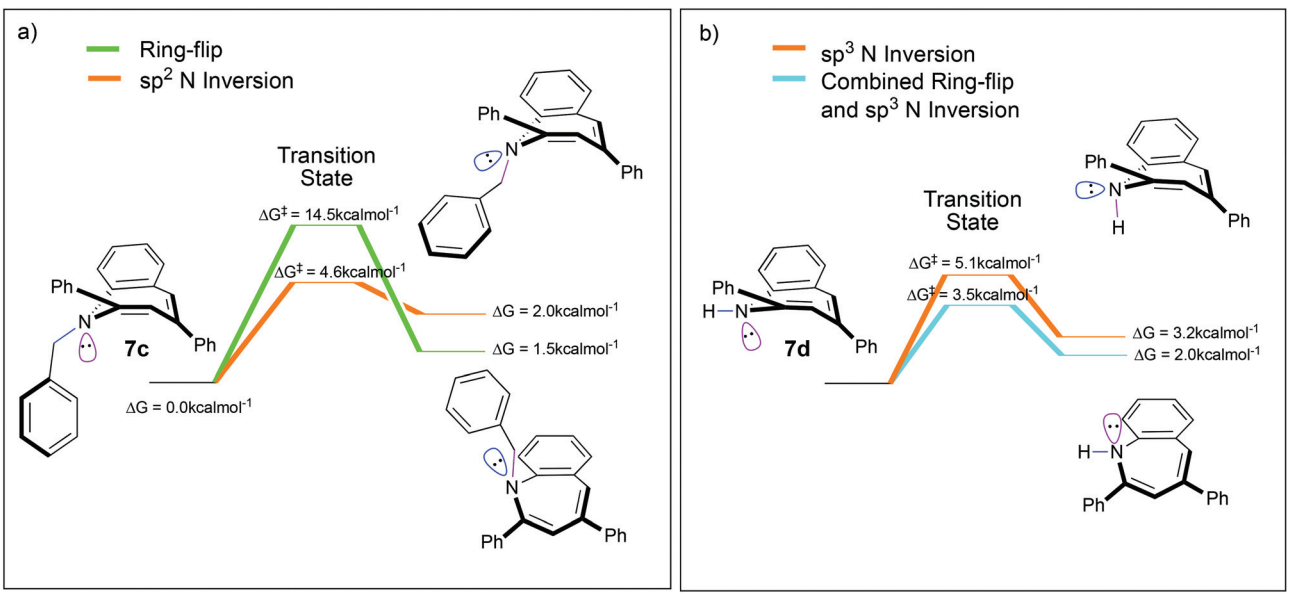


Fig. 11 (a) Energy diagram of separate ring-flip and N-inversion for **7c**. (b) Energy diagram of isolated N-inversion and combined ring-flip and N-inversion for **7d**. Blue = pseudoequatorial, purple = pseudoaxial. Adapted with permission from Ramig *et al.* (2016), copyright 2016 American Chemical Society.[43]

tion would impact the hybridisation and thus point/axial chirality of the nitrogen. While not discussed by the authors of the study, it is worth noting that the C9 substituted system would remain atropisomeric regardless of whether N was a stereocentre or Ar–N was a chiral axis. Likewise, **7a** and **7d** would still be atropisomeric if the ring-flip occurred slow enough, despite lacking a chiral Ar–N axis. Rather, the atropisomerism of the N stereocentre systems presumably stems from a separate chiral axis which orchestrates the ring-flip. Given that the C5 is sp^2 hybridised (Fig. 11), it is possible that this chiral axis is along the Ar–C5 bond. For **7b–c**, it is unlikely that the Ar–C5 chirality would be lost when the Ar–N axis is also chiral. More likely, the lack of visible diastereomers by ^{1}H NMR spectroscopy can be explained by the two bonds rotating simultaneously in a gear-like fashion, producing only enantiomeric atropisomers.[43]

(f) Point chiral carbons *ortho* to the ring junction of atropisomeric benzo-fused heterocyclic ring systems

The interdependent relationship between point and axial chirality is also present for 7-membered N-heterocycles with a carbon stereocentre. The Natsugari group found that when the chiral sulfoxide (**5**) was replaced by a chiral carbon (**8**), benzene substitution *ortho* to the ring junction afforded similar trends in preferred overall system conformation (Fig. 12).[31,44,45]

When there was no added steric hindrance *ortho* to the ring junction (**8a** Fig. 12), the *anti* conformation **8a″** (pseudoequatorial –OH orientated away from the amide group) was dominant with an *anti*/*syn* ratio of 1 : 0.31, although isomerisation between the two conformations occurred readily in solution at ambient temperature (Scheme 5). When Ar–N rotation was more restricted by steric bulk at C9 (**8b**), the *anti* diastereomer was even more dominant with an *anti*/*syn* ratio of 1 : 0.17. In this case, isomerisation of the *anti* conformation to diastereomeric equilibrium was slower but still occurred fast enough to disrupt *in vitro* affinity testing as discussed below.[45] In contrast, when steric bulk was added at C6 (**8c**), the steric hindrance between –R^2 and –OH forced a pseudoaxial *syn* orientation and rendered the *anti* conformation so unfavourable that there was no ring-flip equilibrium, only *syn* enantiomers.[44,45] To clarify this, recall that as **8** is a ring-flip system with point *and* axial chirality. Each '*R*' and '*S*' alcohol has fixed configuration but shifts between a pseudoaxial (*syn*) and a pseudoequatorial (*anti*) –OH orientation during the ring-flip that occurs when the Ar–N axis rotates between 'a*S*' (**8a′**) and 'a*R*' (**8a″**) conformations (Scheme 5).

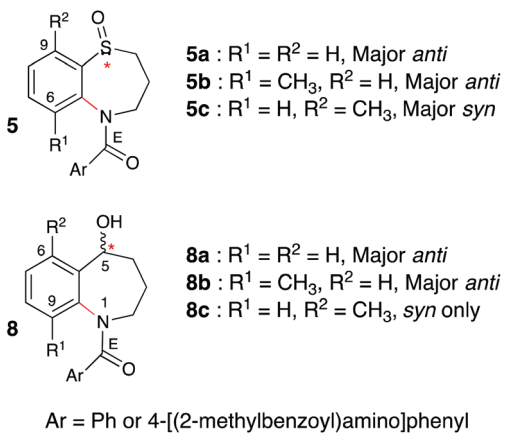
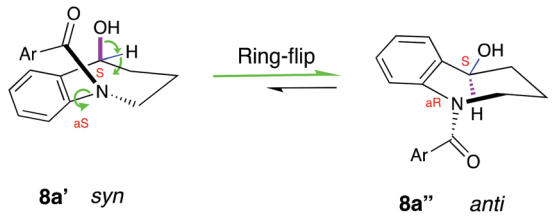
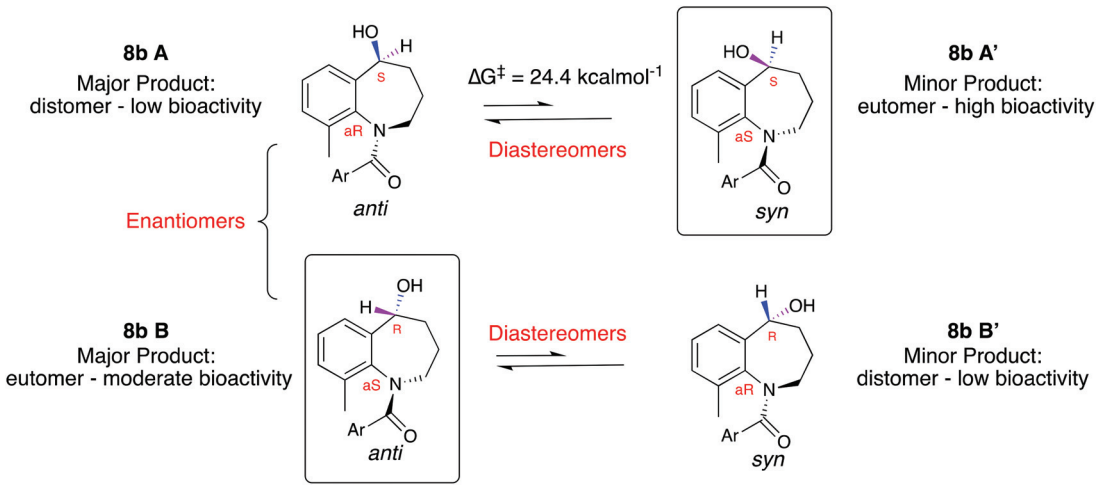


Fig. 12 Comparative substrate scope of **5** and **8**, which are similar systems but have heteroatom and carbon stereocentres respectively. Stereocentres and axes of chirality indicated by red asterisks and red bonds respectively.



Scheme 5 Illustration of the ring-flip process of **8a** which prompts simultaneous rotation of the carbon stereocentre.

In addition to being consistent with heterocycles with heteroatom stereocentres, the Natsugari group's study of **8** also gives valuable insight into the bioactivity of these benzoazepine systems.[45] Generally, benzoazepine N1–benzoyl structures are classed as 'vaptan' ligands and function as antagonists to the nonpeptide arginine vasopressin receptors V_{1a}, V_{1b} and V_2, which are implicated in human water homeostasis.[32,45] In binding assays, **8** exhibited a strong affinity for the V_{1a} receptor.[45] As discussed earlier, the three-dimensional nature of receptor binding emphasises the importance of atropisomer stability in ensuring that throughout the lifetime of a drug, the isomer with the greatest biological effect (the eutomer), as opposed to the less bioactive isomer (the distomer), is the most abundant. Consistent with assessment of **5**[31] and **3**,[32] which are also vaptan class receptor ligands, the 'a*S*' atropisomers of **8** are the eutomers.[45] For **8a** and **8b** however this was not immediately apparent as the major *anti* (a*R*,5*S*) and (a*S*,5*R*) enantiomers appeared to show similar activity. For **8a** (R^1 = R^2 = H) this could be explained by rapid axial rotation allowing for the active a*S* isomer to be present in equilibrium with the (a*R*,5*S*) diastereomer at all times. Because the diastereomers of **8b** (R^1 = CH_3) could be resolved however, the lack of a*S* chirality in **8b A** (a*R*,5*S*) should have resulted in negligible bioactivity. Illustrated in Scheme 6, further investigation revealed that although **8b A** was stable enough to be resolved, the system has a sufficiently low $\Delta G^{\ddagger}$ that it began isomerising *via* axial rotation during the receptor binding experiment. Thus, the binding activity seen for **8b A** (a*R*,5*S*) is actually best attributed to the minor *syn* diastereomer **8b A′** (a*S*,5*S*). Moreover, considering the similarity between the binding affinity of the small amount of *syn* **8b A′** (a*S*,5*S*) and the abun-



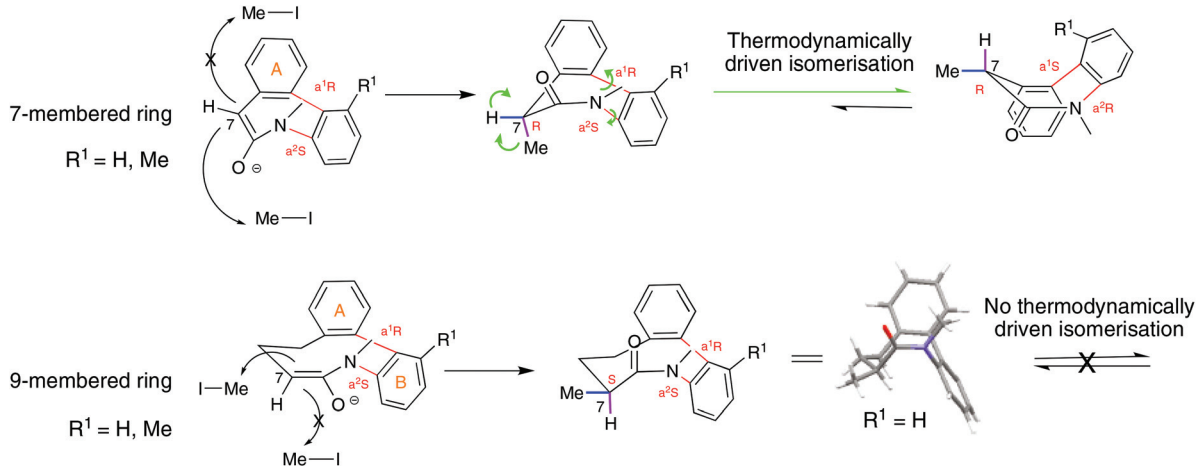
Scheme 6 Dynamic equilibrium between the atropisomers of the 5*S* system (top) and the 5*R* system (bottom) of **8b**. In each case, the a*S* isomer is identified as the eutomer responsible for the bioactivity seen in the V_{1a} receptor binding experiment. Blue = pseudoequatorial, purple = pseudoaxial.

dant *anti* **8b B** (a*S*,5*R*), the researchers reasoned that the **8b A′** (a*S*,5*S*) isomer was the most potent of the four diastereomers.[45] Although 5*S* stereochemistry increased the potency of a*S* isomers, it did not appear to greatly impact the bioactivity of the a*R* isomers. Thus it was also concluded that while point chirality could impact the potency of bioactivity, axial chirality held superior importance for receptor recognition in this instance.[45] In addition to asserting that atropisomerism can have great significance for bioactivity, this study also supports the notion that the short-term stability against ring-flip of class 2 atropisomers like **8b** can be problematic for both identifying and isolating the eutomer of a system. As such, investigation of atropisomer stability is extremely important for gauging the compatibility of a atropisomeric system with further drug development.[1,8]

(g) Carbon stereocentres remote from the ring junction of atropisomeric medium-ring benzo-fused N-heterocyclic ring systems

While benzothiazepine **4** (refer to Scheme 1) demonstrated that the chiral axis of a benzo-fused N-heterocycle can bias the stereoselectivity of oxidation of an atom *ortho* to the ring junction, the influence of atropisomerism can also extend to the rest of the heterocycle. For the dibenzoazepine system **1**, noted previously for its geared enantiomerisation and the deepening of its cage conformation with ring-size, methylation of C7 occurs pseudoaxially for 7- and 8-membered rings and pseudoequatorially for 9-membered rings (Scheme 7).[25] For the (a^1R, a^2S) enantiomers of **1**, this stereoselective methylation results in (7*R*, a^1R, a^2S) isomers for the smaller rings and (7*S*, a^1R, a^2S) isomers for the 9-membered rings. The reason for this difference is a kinetically controlled reaction which occurs *via* different mechanisms depending on ring size.[25] For the smaller rings, methylation *via* an enol resonance structure is proposed to occur at the lower concave face of the structure because the top face is crowded by aryl-ring 'A' (Scheme 7, top). For the larger 9-membered system however, the location of the aryl-ring 'B' further over the concave face due to the deeper cage conformation is proposed to be more obstructive than aryl-ring 'A', preferencing pseudoequatorial methylation from the top convex face of the ring (Scheme 7, bottom). Although the C7 stereocentre in the 7-membered system is still technically *ortho* to a ring junction, this result combined with the stereoselective methylation of the 8- and 9-membered systems altogether emphasises that by controlling the overall conformation of the whole system, remote chiral axes can influence the stereoselectivity of new stereocentres anywhere in the heterocycle of benzo-fused systems.

While the conformational influence of the chiral axes results in kinetic products, it should be noted that this does not always produce the most thermodynamically stable diastereomer directly. Aside from the highly rigid 8-membered R^1 = CH_3 system, which is very stable against ring-flip inversion, all of the 7- and 8-membered systems isomerised from the pseudoaxial C7–Me conformer to form an equilibrium favouring the pseudoequatorial C7–Me conformer (Scheme 7, top).[25] Meanwhile, even the most flexible of the 9-membered systems (R^1 = H) exhibited no ring-flip isomerisation to the pseudoaxial C7–Me product (Scheme 7, bottom). Consequently, like in the *ortho* stereocentre equilibriums of **5–8** discussed earlier, the researchers concluded that pseudoequatorial orientation of C7–Me was the most thermodynamically stable atropisomer in this system.[25] Also, the $\Delta G^{\ddagger}$ of the ring-flip converting the C7–Me orientation from pseudoaxial to pseudoequatorial was found to be lower than the ring-flip $\Delta G^{\ddagger}$ of the unmethylated precursor **1** (refer to Fig. 4). This suggests that methylation can alter the thermodynamic stability of atropisomer ground states.[25] This illustrates that the stereochemistry of axial and

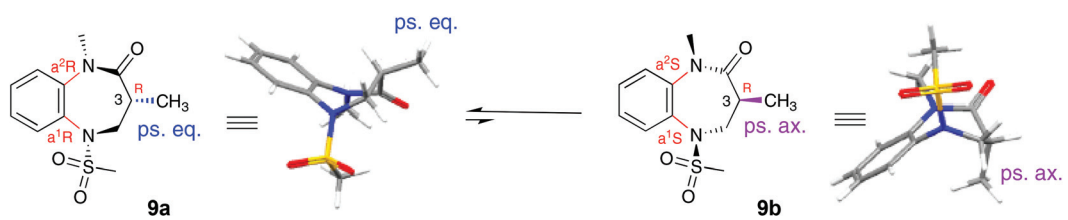


Scheme 7 Proposed mechanism for kinetically stereoselective pseudoaxial methylation and thermodynamically selective isomerisation for 7- (pictured), 8-membered (not pictured), and 9-membered (pictured) systems. Axes of chirality along red bonds. Blue = pseudoequatorial, purple = pseudoaxial. X-ray crystal structure reprinted with permission from Tabata *et al.* (2010), copyright 2010 American Chemical Society.[25]

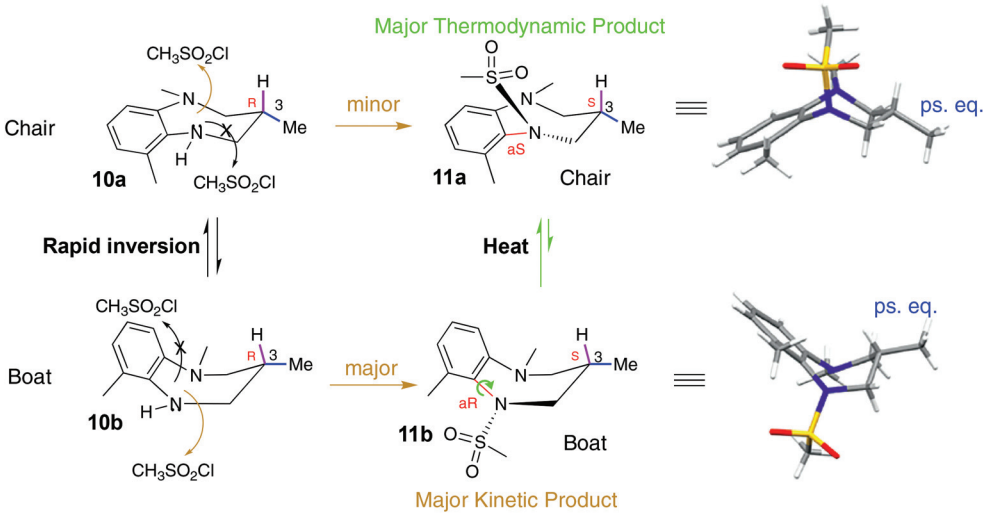
point chiral components of medium-ring benzo-fused N-heterocycle systems can be interdependent regardless of where they are located on the heterocyclic ring.

This stereogenic interdependence between chiral components is also exhibited by other methyl-substituted, dual chiral axis systems.[46,47] For the *N*-mesyl benzodiazepinone **9** (Scheme 8), a methyl group at C3 results in such a difference in biased thermodynamic stability that only one diastereomer is detectable *via* ^{1}H NMR analysis.[47]

As confirmed *via* X-ray crystallographic analysis, the dominant diastereomer is the pseudoequatorial C3–Me conformation – illustrating that like the 9-membered system in scheme, the Ar–N axes of **9a** are essentially 'frozen' to maintain pseudoequatorial orientation of the C3–Me.[47] This conclusion is further supported by DFT calculations which estimated a 3.4 kcal mol^{-1} difference between the two conformers. This said, while the methyl stereocentres of **9** and the methylated derivatives of **1** are remote from the ring junction, their location next to rigid lactam functionalities may moderate the conformational influence of the stereocentres over the system. To gain a full understanding of the potential influence of stereocentres on the atropisomerism of medium-ring benzo-fused N-heterocyclic systems, it is prudent to consider more flexible analogues of **9** that lack the rigidifying lactam component. In a study of benzodiazepines **10** and **11**, the Natsugari group illustrate the consequences of replacing the lactam carbonyl of benzodiazepine **9** with a methylene group (Scheme 9).[48] While the Ar–N axes of **9** and **11** are both formed *via* the mesylation of diazepine systems with C3 stereocentres, the conformations of the products and precursors differ.[47,48] The benzodiazepine precursor **10** interconverts between boat (**10b**) and chair (**10a**) conformers, maintaining pseudoequatorial orientation of C3–Me in both (Scheme 9, left).[48] Meanwhile, the precursor to the mesylated lactam **9** is understood to exist as two boat conformers with pseudoaxial and pseudoequatorial C3–Me orientation respectively.[28,44,47,49] Initially this conformational variance between the lactam and non-lactam precursor systems appears fairly innocuous because in both cases, the kinetically favoured products of mesylation are boat conformers with pseudoequatorial C3–Me orientation (**9a** in Scheme 8 and **11b** in Scheme 9). However, examination of the thermodynamic equilibria of the diastereomers **11b** and **11a** highlights that the lack of a rigid lactam enables the C3 stereocentre to not just influence atropisomer stability, but to also control the overall conformation of the system. Notwithstanding the high energy of activation favouring the lactam **9a**, rotation of the Ar–N(SO$_2$) axis (red in Scheme 8) is predicted to result in a ring-flip between pseudoe-



Scheme 8 Skewed equilibrium between the ps. eq. (pseudoequatorial) orientation of C3–Me in **9a** and the thermodynamically unstable ps. ax. (pseudoaxial) orientation of C3–Me in **9b**. Structures determined *via* DFT calculations. Axes of chirality along red bonds. Adapted with permission from Tabata *et al.* (2019), copyright 2019 American Chemical Society.[47]



Scheme 9 Stereoselective mesylation of the flexible benzodiazepine **10** and subsequent thermal equilibrium of boat and chair conformers of **11**, maintaining favourable pseudoequatorial (blue) orientation of the chiral C3–Me at all stages. Note, the shift from '*R*' to '*S*' C3 stereochemistry is a consequence of changed priority due to mesylation. Axes of chirality along red bonds. X-ray crystal structures reproduced from ref. 48 with permission from Georg Thieme Verlag KG, copyright 2018.

quatorial and pseudoaxial C3–Me boat conformers (Scheme 8).[47] In contrast, atropisomerism of amine **11** does not involve ring-flip of the entire heterocycle from one boat conformer to another. Rather, **11** undergoes inversion between boat (**11b**) and chair (**11a**) conformations, which serves to preserve the stable pseudoequatorial orientation of C3–Me (Scheme 9, middle/right).[48] Although not commented on by the authors, this boat/chair equilibrium of **10** and **11** is most likely rationalised by the flexibility of the system. This is supported by an extensive study of the benzoazepine system **12** (Fig. 13) by the Natsugari group which determined that the presence of two axes of chirality and a lactam carbonyl in **12a** (X = CO) constrained the system, prompting it to assume the highly rigid boat conformation to relieve strain.[49] In contrast, the much more flexible system **12c** (X = CH_2, Y = H) assumed a less strained chair conformation. Although **12b** (X = CH_2, Y = CH_3) also had a flexible heterocycle, the C9 methyl appeared to repel the R group across the diazepine ring, pushing C3 to favour the rigid boat conformation. On closer examination, a discrepancy between of the observed ^{1}H NMR coupling values and those estimated from the X-ray crystal structures indicated that the **12b** boat conformation actually exists in equilibrium with the chair conformer.[49] Although similar in structure and flexibility to the C3-methylated benzodiazepine **11**, this study does not comment on whether the boat/chair inversion of **12b** likewise involves rotation of the chiral axis.

As an aside for continuity, it is important to clarify the chirality of N1 in **12**. When the N is part of a lactam (X = CO), the identification of Ar–N1 as a chiral axis is rationalised by the resonance delocalisation of the amide N lone pair, rendering N sp^2 hybridised. Considering earlier discussion, when X = CH_2, N1 is likely sp^3 hybridised and either inverts rapidly enough to be considered achiral or otherwise inverts simultaneously with the Ar–N5 axis, which is rendered chiral by N

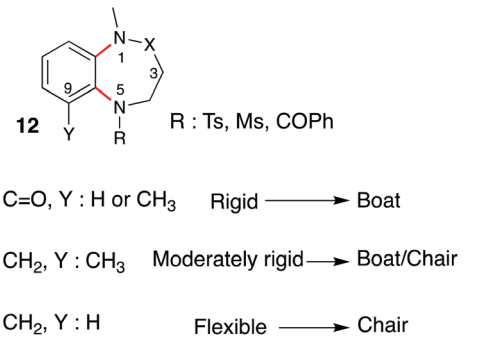
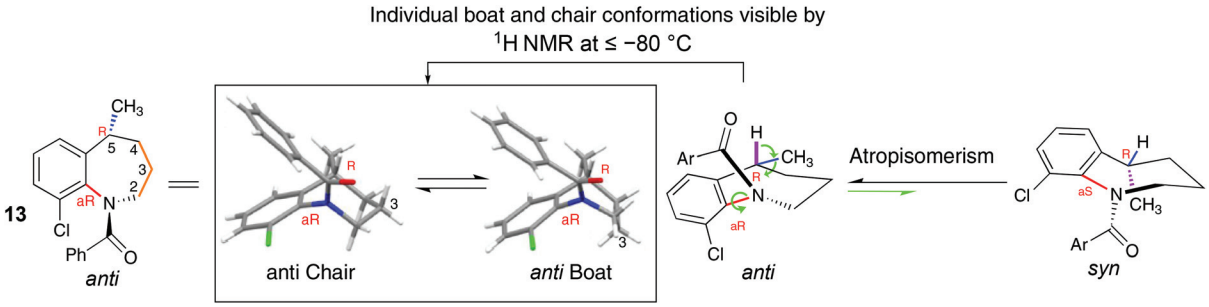


Fig. 13 Substrate scope of the benzodiazepine system **12** which, depending on level of rigidity, assumes a boat or chair conformation. Axes of chirality along red bonds.

lone pair delocalisation into the benzoyl and sulfonyl substituents, respectively.[36,50]

To predict whether the boat/chair conformers of **12b** are atropisomeric, it is reasonable to compare the benzoazepine analogue **13**. From the X-ray crystal structures (Scheme 10), the boat/chair conformers of the C3-unsubstituted system **13** invert *via* a non-atropisomeric 'ring-flip' of only one side of the heterocycle.[44] Pictured below, this involves a 'ring-flip' of C2–C3–C4 (in orange), inverting the pseudoaxial and pseudoequatorial substituents of each, but excluding rotation at the Ar–N axis and thus avoiding atropisomerism (Scheme 10).[44] As the benzodiazepine **12** is similarly reduced and not methylated at C3, it is probable that the boat/chair inversions are similarly non-atropisomeric. The significance of this is that while access to boat/chair conformers is a consistent symptom of flexibility for the reduced benzo-fused N-heterocycles **11**, **12** and **13**, it is apparent that stereocentre location around the heterocycle can drastically impact the atropisomeric nature of such confor-



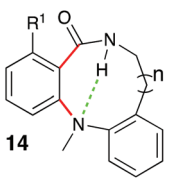
Scheme 10 Comparison of boat/chair conformational equilibrium and *anti*/*syn* atropisomeric equilibrium of **13**. Shown arbitrarily for 5*R* isomer. Bonds which undergo boat/chair ring-flip in orange, axes of chirality along red bonds. X-ray crystal structures reprinted with permission from Tabata *et al.* (2016), copyright 2016 American Chemical Society.[44]

mations. For **13**, which has a C5 stereocentre *ortho* to the ring junction, and likely **12b** which has no stereocentre at all, ring-flip is limited to the portion of the heterocycle opposite the ring junction, leaving both the pseudoequatorial C5–Me and chiral axis unaffected (Scheme 10). For **11** however, the C3 location of the stereocentre and the thermodynamic stability of the pseudoequatorial C3–Me appears to limit the ring-flip to the ring-junction-side of the heterocycle, rotating the Ar–N axes and inverting the atropisomer chirality without affecting the C2–C3–C4 carbons (Scheme 9). It should also be noted that the boat/chair forms of **11** are separable at moderate to high temperatures and the system displays no other conformational equilibrium. In contrast, the boat/chair equilibrium of **13** is rapid with individual conformers only visible at temperatures −80 °C or less. Overlaying this is a second equilibrium between *syn*/*anti* conformers which, like those observed in other chiral benzoazepine systems, occur though rotation at the chiral Ar–N axis (Scheme 10).[44] Overall, stereocentres and chiral axes in medium-ring benzo-fused N-heterocyclic ring systems have an interdependent relationship towards controlling system conformation no matter where on the heterocycle the stereocentre is located. From comparing the C3-methylated lactam **9**, the reduced C3-methylated system **11**, the variably reduced but non-methylated **12**, and the reduced C5-methylated **13**, it appears that when the stereocentre is located away from the ring junction, the influence it has over atropisomerism and overall system conformation increases with heterocycle flexibility. This said, more research into the interplay between stereocentre placement and atropisomer flexibility is needed to gain a confident understanding of how the conformations of such systems are regulated.

(h) Transannular non-covalent interactions – hydrogen bonding

In addition to substitution and intramolecular steric interactions, the conformational arrangement and thermodynamic stability of medium-ring benzo-fused N-heterocycle systems can be regulated by non-covalent intramolecular bonding interactions. For hydrogen bonds, as demonstrated by dibenzodiazepine **14** (Fig. 14), this regulatory capacity is itself dependent on system flexibility. Flexibility affects the distance between groups, as well as solvent polarity, both of which can profoundly affect hydrogen bonding.[51,52] In **14** the chiral axes are identified as the Ar–CO (amide) and the Ar–N (amine). In contrast to other *N*-methylated medium-ring benzo-fused N-heterocycles featured in this review, Costil *et al.* draw no attention to the pseudoaxial/equatorial orientation of *N*–Me, which suggests that the amine N of **14** does not function as a stereocentre.[51]

Consistent with dibenzoazepine **1**, the ring-size increase across **14b–d** (10–12-membered rings) is associated with an increase in system flexibility, lowering the barrier to atropisomer inversion. On the other hand, as ring-size increases, the flexibility of the systems also enables the amide to tend towards co-planar alignment with the adjacent benzo group. This shortens the distance between the amide N–H and the N atom across the ring, thus strengthening the hydrogen bond between them and increasing the stability of ground state conformers. As the strength of the stabilising hydrogen bond increases however, so too does the importance of solvent polarity to conformer stability. Polar solvents can form hydrogen bonds with the solute which compete with and destabilise the intramolecular hydrogen bonds, causing the larger **14c–d** systems, which rely on hydrogen bonding for stability, to experience a pronounced drop in ring-flip $\Delta G^{\ddagger}$ in polar solvents. In contrast **14b**, which only has weak intramolecular hydrogen bonding, exhibits consistent atropisomer stability regardless of solvent polarity.[51]



14a n = 1 (9-membered), R^1 = H
14b n = 2 (10-membered), R^1 = H
14c n = 3 (11-membered), R^1 = H
14d n = 4 (12-membered), R^1 = H

14e n = 3 (11-membered), R^1 = CH_3

Fig. 14 Dibenzodiazepine **14** substrate scope with variable ring-size and benzene substitution. Green = H-bond. Axes of chirality along red bonds.

In addition to ring-size and solvent effects, accessibility to hydrogen bond stabilisation can also be affected by sterics. This is illustrated by **14e** wherein methyl substitution at R^1 pushes the amide into a roughly perpendicular alignment with the benzene plane, resulting in weaker transannular hydrogen bonding than the non-methylated equivalent **14c**. Further, amide distortion can also result in diastereomers whose stability is biased by accessibility to hydrogen bonding in either ground or transition states. For **14e**, hydrogen bonding is stronger in the minor diastereomer, with access to diastereomer inversion also increased by a transient hydrogen bond as the amide passes through co-planar alignment with the benzene. For **14a** however, which also has a distorted amide (likely due to torsional strain from the smaller ring-size), hydrogen bonding stabilises the major not the minor diastereomer. Thus, while it is apparent that intramolecular hydrogen bonding can greatly affect conformational stability of a system and its subsequent sensitivity to solvent polarity, it must be noted that, particularly in the case of diastereomers, access to hydrogen bonding can vary greatly with small changes to the system.

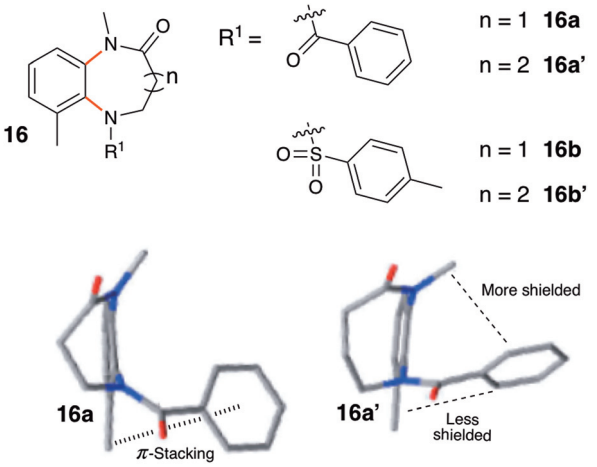
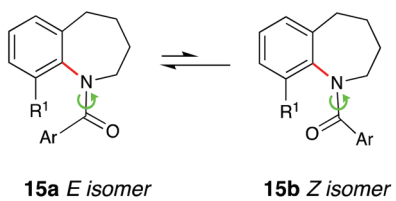


Fig. 15 Substrate scope of benzodiazepine **16** with X-ray crystal structures of the benzoyl derivatives illustrating the impact that ring-size has on benzoyl orientation. Axes of chirality along red bonds. X-ray crystal structures originally posted on H. Tabata, K. Muari, K. Funaki, C. Takemae, T. Tasaka, T. Oshitari, H. Takahashi and H. Natsugari, *Heterocycles*, 2019, **99**, 566–581.[53]

(i) Intramolecular non-covalent interactions – π-stacking

In addition to modulating heterocycle conformational stability, non-covalent interactions can also influence how the N-substituent of a benzo-fused N-heterocycle atropisomer relates spatially to the core bicyclic structure. Acknowledged earlier in section b, all systems featured in this review with an exocyclic amide *ortho* to R^1 are observed to favour the *E* rotamer of the ArN–CO bond (exemplified by **15**, Scheme 11).[31,32,44,45,49] Although in most cases this bias was recognised without comment, it has been proposed by the Natsugari group regarding **16** (Fig. 15) that this preference for an *E*-conformation is a consequence of π-stacking interactions between the benzene core structure and the aryl of the pendent amide.[53] This π-stacking (or π–π-interaction) is electrostatic interaction between aromatic rings or more broadly, can refer to electrostatic CH–π interactions which function in much the same way.[54] Described as a quadrupole moment, the π-electron density of aromatic rings is polarised with negative electrostatic potential centred on the ring faces, and positive electrostatic potential concentrated around the perimeter (Fig. 16a).[55] Consequently of this polarisation, aromatic rings typically interact in four main geometries (Fig. 16b).[54,55] While the specific π-stacking geometry of **16a** is not identified by the Natsugari group, their suggestion that π-stacking stabilises the *E*-amide conformation is supported by the group's analysis of a similar, *ortho*-methylated structure which lacks an aryl on the pendent amide. Here, despite a comparable steric and electronic environment, the lost capacity for π-stacking between the pendent group and the core aryl lowered the selectivity of the *E*/*Z* amide by 8-fold relative to **16a**.[53,56] Moreover, the Natsugari group also found that when an extra methylene was added to the diazepine heterocycle of **16a** to form **16a′** (rendering it an 8-membered diazocine) the presence of the *Z* conformer increased, suggesting that the π-stacking effect was weakened.[53] From comparison of the X-ray crystal structures and ^{1}H NMR spectra, this was attributed to conformational



Scheme 11 General representation of the *E*/*Z* equilibrium of benzazepine exocyclic amides favouring the *E* conformer. Axes of chirality along red bonds.

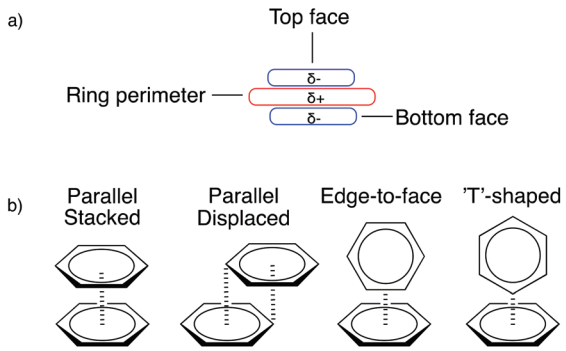


Fig. 16 (a) Model of benzene quadrupole moment and (b) the four main geometries of π-stacking. Panel (b) adapted with permission from Macmillan Publishers Ltd: Nature, ref. 54, copyright 2017.

changes disturbing the alignment of the two aryl rings (Fig. 15).[53] Like for dibenzoazepine **1** discussed earlier (Fig. 7), the X-ray crystal structures of **16** show a positive correlation between heterocycle ring-size and the depth of the boat-like cage conformation of the system. As cage-depth increases, the pendent *N*-benzoyl substituent also appears to change orientation. From ^{1}H NMR analysis, it appears that this change in *N*-benzoyl orientation moves the pendent phenyl so that in the 8-membered system **16a′** it shields the *N*-methyl instead of the Ar–methyl, disturbing the π-stacking between the two aromatic rings. Thus, similarly to hydrogen bonding in dibenzodiazepine **14**, π-stacking can stabilise specific conformational preferences in benzo-fused heterocyclic systems but the strength of this stabilisation is vulnerable to changes in the overall flexibility and conformation of the system.

Despite also possessing a pendent aryl which is capable of π-stacking, the sulfonamide derivatives of **16** behave very differently to the benzoyl analogues, locating vertically over the heterocycle ring in a folded (**16b**) or extended (**16b′**) position rather than a horizontal *E*/*Z* alignment (Fig. 17). While the authors did not comment on the reason for this horizontal/vertical difference, the preference for extended or folded sulfonyl conformations was rationalised by sterics.[53] Consistent with the benzoyl analogues, the cage conformations of the sulfonyls **16b–b′** deepened with increased ring-size, shortening the distance between the amide *N*–Me and the sulfur of the pendent *N*-tosyl (Fig. 17). Because in the diazepine **16b** the *N*-tosyl folds across the heterocycle, the shortening of the NMe–SO_2 distance with increase in ring-size/cage depth would augment transannular steric interaction between the tosyl and methyl groups, thereby rationalising why the 8-membered **16b′** shows a thermodynamic bias towards the extended conformation.[53]

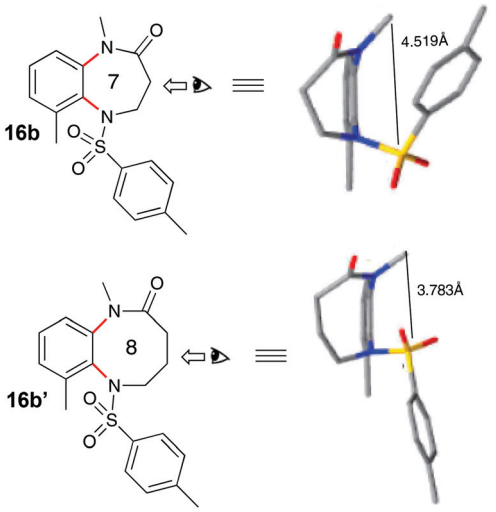


Fig. 17 Alternatively folded or extended orientation of the sulfonamide structure relative to heterocycle ring-size. Axes of chirality along red bonds. X-ray crystal structures originally posted on H. Tabata, K. Muari, K. Funaki, C. Takemae, T. Tasaka, T. Oshitari, H. Takahashi and H. Natsugari, *Heterocycles*, 2019, **99**, 566–581.[53]

Sulfonyl folding over benzodiazepine rings has been observed in a range of systems in the last decade, suggesting that there is generally some thermodynamic advantage to the folded conformation.[17,47,49,57] Presently however, this remains an area of research that is little discussed. Given the role of π-stacking in benzoyl stabilisation, it is tempting to consider that π-stacking, either in the form of aryl–aryl or CH–π interactions, might be the hidden stabilisation mechanism behind sulfonyl folding. On the other hand, the persistence of sulfonyl folding in systems such as **12** when the tosyl is replaced by a non-aromatic methylsulfonyl[49] suggests that the bias towards folding or extending away from the core benzoazepine structure is related to the *N*-SO_2 moiety more than any attached structures – although the reason for this is yet to be uncovered.

(j) Conclusion

Medium-ring benzo-fused N-heterocycles are rich and complex atropisomeric systems for which even small isolated changes in ring-size or substitution can drastically alter the stability and conformational properties of the entire system. While the combination of these changes affords a myriad of uniquely characterised systems, this review has explored a range of trends which can serve as a framework to understand the likely impact of certain features. Regarding the chiral nature of these systems, there is generally at least one chiral axis by the ring junction (usually Ar–N) which causes a ring flip when it rotates. The free-energy barrier of this rotation, which determines whether a system is atropisomeric, and the overall conformation of the system are moderated by a number of factors. These include steric hindrance *ortho* to the ring junction, substituent electronegativity, system flexibility, H-bonding and the presence of stereocentres on the heterocyclic ring. Regarding amines in the heterocycle, careful attention must also be paid to nitrogen hybridisation and steric environment as these factors can influence whether the N is point chiral, axially chiral, or achiral. These systems may also feature exocyclic rotamers which are stabilised *via* non-covalent intramolecular interactions. While the capacity for these non-covalent bonds to influence atropisomer stabilisation is yet underexplored, the investigation of the relationship between forces like π-stacking and atropisomer conformational stability stands as a valuable pursuit for future research. With increased knowledge of the factors contributing to atropisomeric systems, design and synthesis of systems with desired conformational properties become more feasible.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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