Conglomerate Crystallization in the CSD (2020–2021)

Mark P. Walsh,*,† James A. Barclay,‡ Callum S. Begg,‡ Jinyi Xuan,‡ and Matthew O. Kitching*,‡

†*Process Research and Development, Carbogen Amcis Ltd., 303 Clayton Lane, Manchester, M11 4SX, UK*

‡*Department of Chemistry, Durham University, Lower Mount Joy, South Rd., Durham, DH1 3LE, UK.*

E-mail: markpwalsh1@gmail.com; matthew.o.kitching@durham.ac.uk

---

Abstract

Conglomerate crystals are materials capable of undergoing spontaneous resolution and were responsible for the discovery of molecular chirality. Their relevance to modern chemical and crystallographic sciences has been hindered by the difficulty in identifying and searching materials with this characteristic ability to bias their own enantioenrichment. With the release of the November 2021 distribution of the CSD (version 5.43), a fresh quantity of chiral conglomerate crystals is expected to have been published in the CSD without identification. Indeed, no crystals in the CSD have been identified as a spontaneously resolving conglomerate crystal in their CIF since the 2019 release, despite the deposition of over 108,000 new crystal structures into the database over the same time period. A manual inspection of crystals deposited between 2020–2021 was conducted to identify 343 new chiral materials which exhibit conglomerate crystallization behavior. It is hoped that the continued manual curation of this list will

aid those in the crystallographic and synthetic communities to study and exploit this spontaneous enantioenrichment behavior.

Keywords: chirality; conglomerate crystallization; CSD; spontaneous resolution; spontaneous deracemization

Introduction

The Cambridge Structural Database (CSD) is undergoing continued growth and has proven to be an invaluable resource for the study of crystallographic phenomena. Landmark papers which underpin our understanding of broad crystallographic trends often rely on the ability to survey the millions of crystal entries contained within the CSD with the aid of automatic searching tools. Research into topics such as: C–H$\cdots$O, C–H$\cdots$N, and C–H$\cdots$Cl hydrogen bonding,[1] N–H$\cdots$F, O–H$\cdots$F hydrogen bonding,[2] false conglomerates,[3] kryptoracemates,[4,5] molecular symmetry assignment,[6] achiral molecules in non-centrosymmetric space groups,[7] crystallization of chiral compounds,[8] hydrogen bond prediction,[9,10] and high Z′ crystallization[11,12] have all benefited from such an approach. These efforts have been fruitful because of the high quality crystallographic data and metadata recorded within each individual CIF entry, which have been collected by the crystallographic community and made available by the deposition to a crystallographic database.

However crystallographic databases such as the CSD cannot currently be used to automatically analyze a fundamental crystallographic phenomenon: spontaneous resolution. A racemic material may spontaneously resolve by crystallizing as conglomerate crystals, that is, the spontaneous formation of individually enantioenriched crystals. The implications of this behavior and how to implement a conglomerate crystallization as a strategy for resolution and asymmetric synthesis have been discussed previously.[13] This conglomerate crystallization behavior is not being actively tracked within crystallographic databases because it is not

standard practice to include the necessary metadata within a CIF. Without the inclusion of the relevant information which would identify a crystal as a conglomerate upon deposition of the CIF to a crystallographic database, chiral conglomerate crystals will be indistinguishable from other enantioenriched crystals which have originated from non-spontaneous asymmetric synthesis or have been isolated from natural sources when searched by automated means.

The identification of conglomerate crystals prior to deposition to a crystallographic database is hindered by the fact that most chiral conglomerate crystals are synthesized and crystallized by synthetic chemists. Whilst synthetic chemists are familiar with Pasteur's spontaneous resolution of tartrate salts,[14] they may not be fully aware of the synthetic potential that this behavior presents. For most synthetic chemists, identifying and reporting on crystallographic phenomena is not the focus in their publications. It is not unreasonable for the synthetic chemist to assume that a racemic material would also produce racemic crystals. However, in roughly 10% of cases the crystals will exhibit conglomerate behavior and therefore each individual crystal will no longer be racemic. While it is not the responsibility of the synthetic community to record and discuss crystallographic behaviors, the identification of conglomerate crystallization requires the co-operation between the synthetic and crystallographic communities. More effective communication between these traditionally separate fields would be to their mutual benefit.

Previous work on cataloging the phenomenon of conglomerate crystallization was initially conducted by Jacques, Colet, and Wilen in their definitive book.[15] Our group recently conducted a manual search of the CSD to unearth previously unreported instances of chiral molecules undergoing conglomerate crystallization, encompassing crystals deposited to the CSD from 1963–2019 as well as literature sources.[13] Since the completion of that search, updated distributions of the CSD have been released containing approximately 108,000 new crystal entries by the end of 2021 (as per version 5.43; November 2021). Since no means to automatically record and search conglomerate crystallizations are currently available, we sought to continue to manually catalogue this important crystallographic behavior. By con-

tinuing this identification of chiral conglomerate crystals we hope to aid the crystallographic community in understanding this special crystallographic behavior and allow the synthetic community to exploit these substrates in their pursuits to obtain enantioenriched materials *via* preferential crystallization and spontaneous deracemization.

Application in asymmetric synthesis. Despite the lack of means to search for conglomerate behaviors in crystallographic databases, there is a continued interest in developing spontaneous deracemization protocols for asymmetric synthesis,[16] which is evident by the number of high quality publications being published on this topic between 2020–2021.[17–27] Often the method for finding a new a substrate capable of conglomerate crystallization is by brute force – the chemist(s) will synthesize a small library of a core scaffold in a racemic fashion and subsequently grow and analyze the crystals of each substrate. In some cases, multiple substrates with similar substitutions can exhibit conglomerate behavior.[24]

Exploiting crystallization as a means to achieve asymmetric synthesis is not typically considered by synthetic chemists. Recent reports of crystallization-driven enantioselective syntheses have demonstrated impressive stereocontrol in their products.[28,29] Protocols which combine a co-crystallization event with solution phase racemization also demonstrate the viability of combining synthetic transformations with crystallization in producing enantioenriched materials.[30–32] Whilst these protocols are not classed as spontaneous deracemizations, since they employ an enantioenriched agent to bias the diastereomeric relationship in the crystal, they highlight the possibility of engineering a conglomerate *via* co-crystallization and racemizing the desired stereocenter(s) in order to achieve a spontaneous deracemization. Excitingly, a recent report of co-crystallization of two racemic compounds to form a stable conglomerate system allowed for the preferential crystallization and resolution of both compounds.[33] The possibility of combining an engineered co-crystallization conglomerate system with simultaneous racemization to access spontaneously enantioenriched materials should be an exciting prospect for those in the field of asymmetric synthesis.

Although achieving spontaneous chiral symmetry breaking and amplification of chiral

information is an enticing proposal, the major bottleneck for the widespread uptake of this strategy by synthetic chemists has been the inability for the synthetic chemist to know what substrates will be suitable for this process. Identifying a material which is capable of conglomerate crystallization behavior is the step which is the least predictable and most difficult to control. With the continued manual curation of a list of chiral materials capable of crystallizing in this manner, synthetic chemists will be able to survey the potential substrates and then focus on developing racemization conditions in order to enable spontaneous deracemization of the substrate(s).

Results and discussion

Searching the CSD. The CSD version 5.43 (November 2021) distribution was used to conduct the search for chiral conglomerates published between 2020–2021. Search queries were generated using the CCDC software *Conquest*, with parameters chosen to try and minimise the total number of crystals to be manually checked while also maximising the potential number of chiral conglomerate candidates. Crystals $MUST$ exist in Sohncke space group AND $Z' = 1$ AND were published between 2020–2021. The crystals $MUST$ be organic, no polymers, single crystal only, $R_1 < 0.075$, with no errors, and allowing for disorder and salts. Crystals which were published solely as a *CSD Communication* had to be excluded as the synthetic routes for the crystallized materials could not be interrogated. The crystal entries must NOT be in carbohydrate, steroid, peptide or nucleoside/nucleotide classes as these could be enantioenriched by natural sources. In order to minimise the retrieval of achiral molecules from the CSD, all crystal entries $MUST$ also contain a carbon center with C(Non-metal)$_4$ OR H-C(Non-metal)$_3$. Even with this constraint the search would still contain achiral molecules which crystallised as conglomerates, however we were only concerned with conglomerates which contained a stereogenic element which would be

recognised by a synthetic chemist (i.e. a stereogenic element which may exist in the solution phase). From our search, 898 achiral conglomerate crystals were identified in this search list (available in the *Supporting Information*).

It was also found that specific strings of text could be used to exclude certain natural products, including: "isolated", "sourced from", "extracted", "bark", "marine", "sponge", "penicillium". These combined queries created within *Conquest* generated a list of 5,968 crystals as potential conglomerates. Natural products could be further filtered when sorting the resulting CSD hits by their structure names; generic naming such as "D-(+)-xylose", "crokonoid B", "wortmannolol" could be excluded due to their natural sources or as targets for asymmetric total syntheses. Compounds listed with known stereochemical assignments could also be excluded from the search. Compound names containing the following stereochemical notation: (+)–, (−)–, D–, L–, (*R*)– and (*S*)–, were removed from the search as these were either sourced from the natural chiral pool or were produced from enantioselective synthetic methodologies and XRD was used for absolute configurational assignment. *This produced a list of 5,465 crystal entries in the CSD which were interrogated manually.* From the manual interpretation of the synthetic routes described to produce each reported crystal, a total of 343 chiral conglomerate crystals were identified to have been published in the CSD between 2020–2021. The full list of chiral conglomerate structures with their associated Refcodes, molecular structures, and references are available in the *Supporting Information.*

Publishing trends. The trend noted in our previous study[13] – that synthetic chemists are the primary generators of chiral conglomerate crystals within the CSD – has only strengthened between 2020–2021. Only 7.5% of chiral conglomerate crystals discovered in the CSD between 2020–2021 were published in crystallographic focused journals, as displayed in Figure 1. Chiral conglomerate crystallization is prevalent in non-crystallographic journals and it remains mostly hidden. Only 38 of the identified conglomerate crystals mentioned the conglomerate behavior in the main text of the paper – most of these instances

are groups which pursue the use of conglomerate crystallization for spontaneous deracemization protocols. Of these 38 crystals which have their conglomerate behavior identified within their associated manuscript, none have their conglomerate behavior identified within their CIF using text comments or *CIF Dictionary* approved fields. For example, values of "_chemical_enantioexcess_bulk = 0", and "_chemical_enantioexcess_crystal = 1" would denote an enantiopure crystal arising from racemic bulk material, designating the crystal to be a conglomerate. A potential reason for this omission is the necessary experimental burden to accurately provide these values. The "_chemical_enantioexcess_*" values should be entered only when a suitable technique is described for measuring enantiopurity of a sample in the "_chemical_enantioexcess_*_technique" fields. The experimentalist should employ a valid technique to quantify the enantiopurity of the bulk material and the crystal used during the diffraction study before such values are described in a CIF. In fact, despite the increasing numbers of crystals deposited every year, no single crystal published in the CSD between 2020–2021 was identified as a conglomerate crystal within the deposited CIF. Searching text strings such as "conglomerate" and "spontaneous resolution" within *Conquest* yielded no hits during this timespan, highlighting that this crystallographic behavior requires the intervention of the crystallographic community in order for it to be recorded routinely during deposition to a database.

Spacegroup frequency. The frequency of the Sohncke space groups of the conglomerate crystallizations reported in 2020–2021 could be compared to both the previously unearthed conglomerate crystallizations[13] and the overall frequency of Sohncke space groups for enantioenriched species in the CSD.[8] Unsurprisingly, the overall distribution of the space groups of the current cohort of chiral conglomerate crystals reported in this work matches those of our previous conglomerate search and the distribution of Sohncke space groups in the CSD. However, there is a over-representation of the $P2_12_12_1$ space group in both conglomerate crystallization datasets (1963–2019: 65%; 2020–2021: 63%) versus that present for all

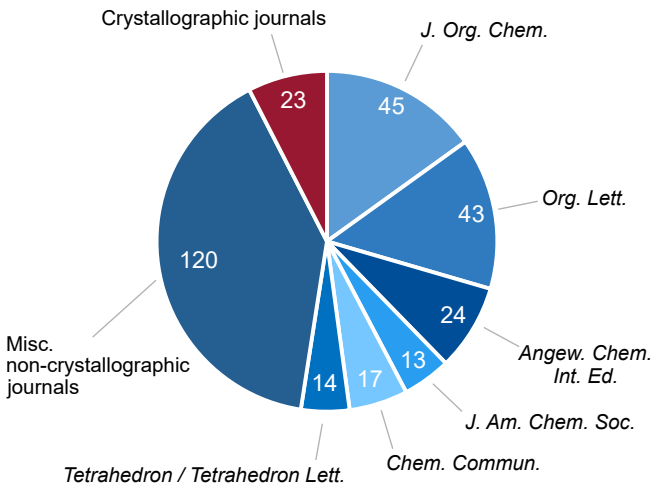

Figure 1: Publication trends of chiral conglomerate crystals (2020–2021).

enantioenriched chiral species in the CSD (52%). It is also noted that there is an under-representation of the $P2_1$ space group for the conglomerate crystal datasets (1963–2019: 27%; 2020–2021: 28%) versus the CSD dataset (34%). The reason for this discrepancy is unclear, but may hold a fundamental insight to the nature of conglomerate crystallizations. However, due to the high abundance of crystals appearing within these two space groups, this observation will not aid in predicting or searching conglomerate crystallization behaviors.

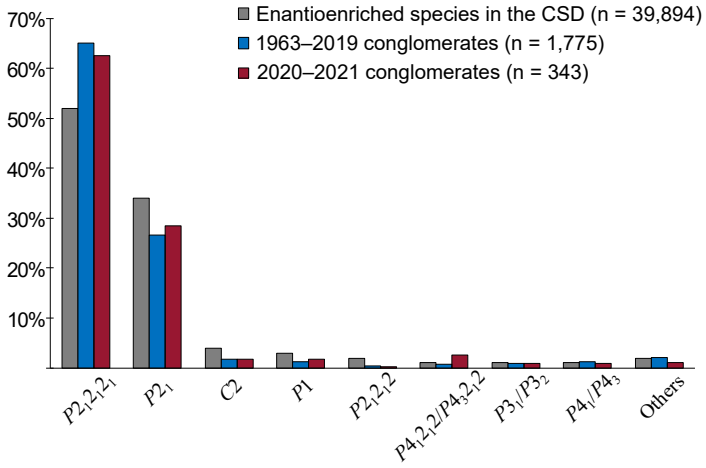

Figure 2: A comparison of the distribution of Sohncke space groups for enantioenriched chiral molecules held within the CSD (grey), our previous chiral conglomerate search (blue), and the chiral conglomerates found in this work (red).

Conglomerates of interest. The structural diversity of materials that undergo conglomerate crystallization is upheld in the set of chiral conglomerates presented in this search. The full list of chiral conglomerate crystals with their chemical structures, associated Refcodes, and literature references are available in the *Supporting Information*. Figure 3 highlights a small subset of the total list to display the diversity of the materials capable of conglomerate crystallization. Carbon, nitrogen, phosphorous, boron, sulfur, silicon, and arsenic based stereocenters are among the point stereogenic elements which have been resolved through this behavior. However, most stereocenters are unsurprisingly carbon-based, due to their prevalence in organic synthesis.

Stereocenters are not the only stereogenic elements observed within conglomerate crystallization. Helical based chirality is also possible to enantioenrich through crystallization. Whilst helical based conglomerate crystals grown from achiral monomers through impressive enantioselective supramolecular assembly in their crystal structures have been reported,[47,48] we wish to only highlight structures which may preserve their enantioenrichment upon dissolution of the crystal. Axial based chirality has also been present within chiral conglomerate crystallization, with atropisomeric scaffolds (UHECUI[44] & OMEXAI[45]) and even unsymmetrical allene systems (YUKNIE[46]).

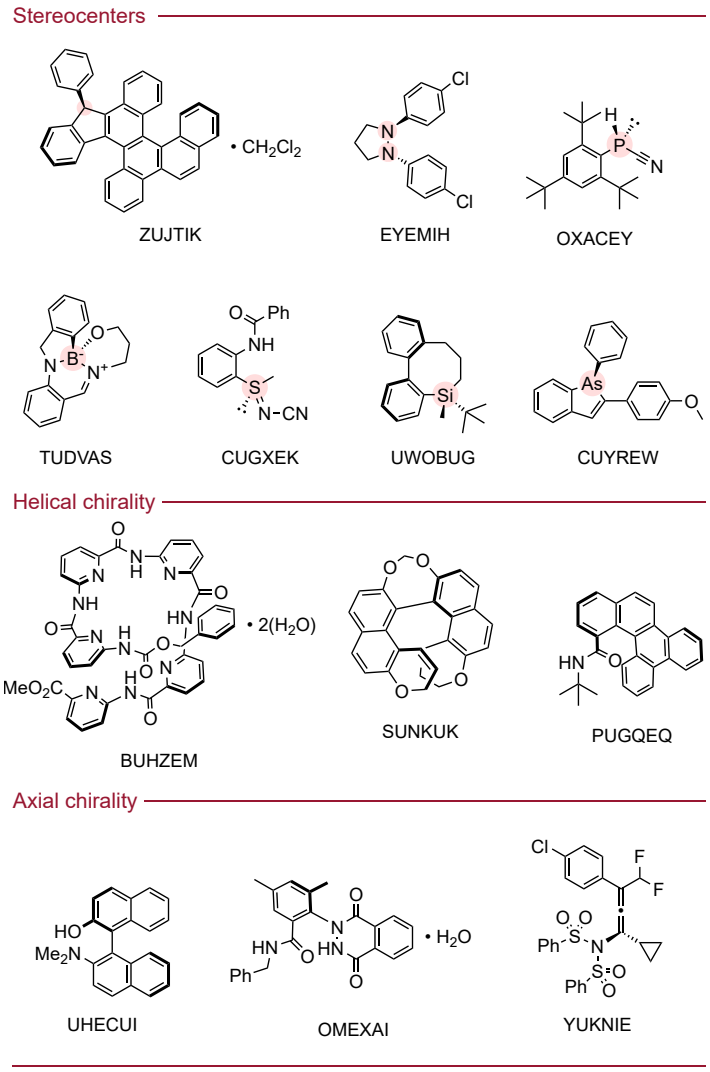

Figure 3: Examples of the stereogenic elements resolved by conglomerate crystallization. The identified conglomerate structures are labelled with their associated CSD Refcodes: ZUJTIK,[34] EYEMIH,[35] OXACEY,[36] TUDVAS,[37] CUGXEK,[38] UWOBUG,[39] CUYREW,[40] BUHZEM,[41] SUNKUK,[42] PUGQEQ,[43] UHECUI,[44] OMEXAI,[45] YUKNIE.[46]

Further examples of conglomerate crystallization were observed to have occurred within the synthesis of natural products in this updated distribution of the CSD, as shown in Figure 4 (OWUREG,[49] XOLNIY,[50] and OCUGOM[51]). Another example of a natural product structure, Sanctis B (SULHOZ[52]), was noted to have crystallized as a conglomerate crystal. Admittedly, these structures identified as conglomerate crystals would be too complex to undergo spontaneous deracemization under the current state-of-the-art racemization protocols. However, the use of preferential crystallization could allow for bulk resolution of these substrates. Furthermore, the possibility that synthetic chemists could design new racemization protocols for simpler conglomerate substrates would, through spontaneous deracemization, allow enantioselective synthesis of natural products without input from the natural chiral pool.

Engineered conglomerate crystals. More examples of the use of crystal engineering in order to produce conglomerate crystallizations have been noted and are presented in Figure 5. In two cases (QAKTAB[53] & DAJYUM[54]), a co-crystallization strategy was employed. In the remaining three examples (EMUZEU,[55] GUPBOL[56] & IGIXII[57]) the substrates were transformed into an organic salt. Notably, all examples presented in Figure 5 use an achiral agent to form the required co-crystal or salt in the engineered crystal. Further study into the engineering of conglomerate crystallizations would enable more control of which target substrates can undergo this type of crystallization behavior, without being at the mercy of the current probabilistic nature of this phenomenon.

The second instance of conglomerate polymorphism (OSUNEY/$P6_1$ & OSUNEY01/$P2_1$) was painstakingly observed and isolated from precise melting experiments.[58] Such examples where multiple polymorphic structures exhibit conglomerate behaviors are exceptionally rare and are ideal case studies for the study of conglomerate crystallization.

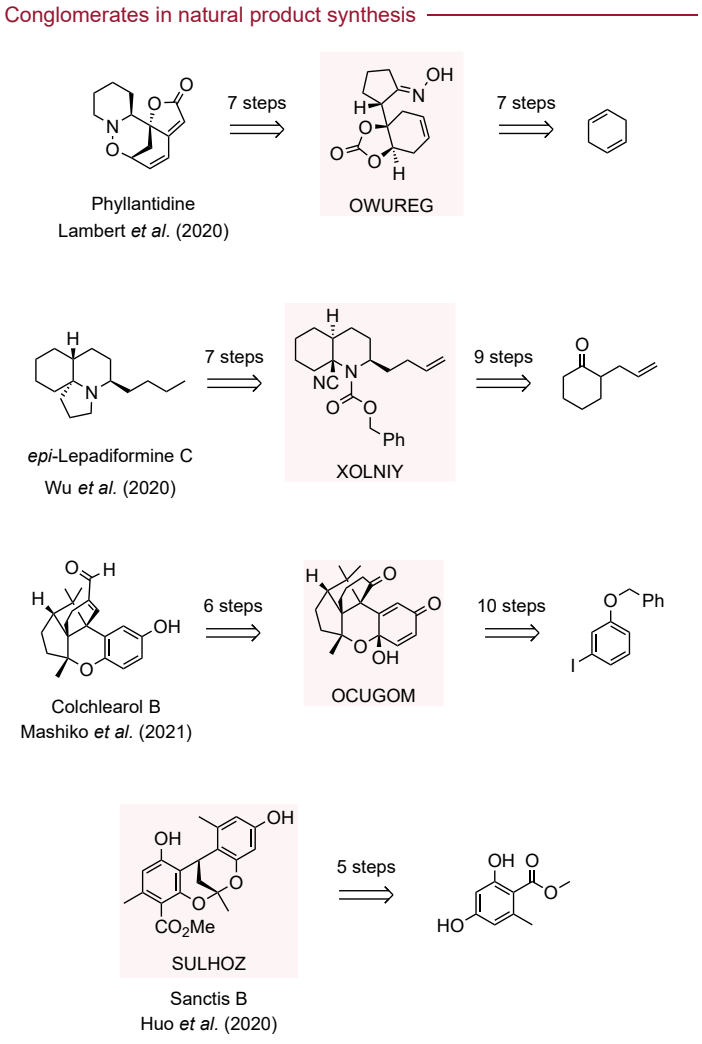

Figure 4: Natural product syntheses with conglomerate crystals identified in the published synthetic routes. The identified conglomerate structures are labelled with their associated CSD Refcodes: OWUREG,[49] XOLNIY,[50] OCUGOM,[51] SULHOZ.[52]

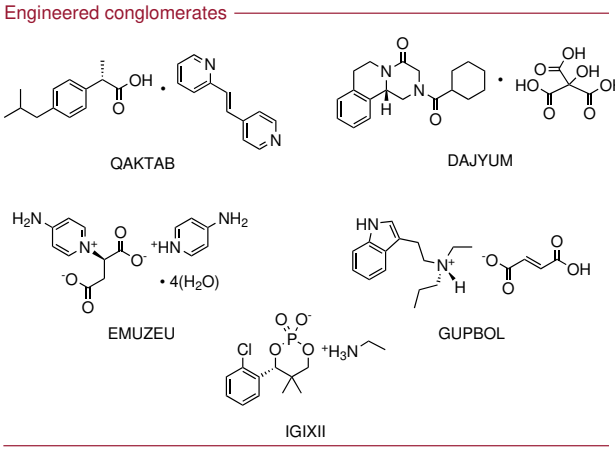

Figure 5: Chiral conglomerates crystals formed by crystal engineering. The conglomerate structures are labelled with their associated CSD Refcodes: QAKTAB,[53] DAJYUM,[54] EMUZEU,[55] GUPBOL,[56] IGIXII.[57]

Hypothesised deracemizations. The most exciting potential of discovering a conglomerate crystallization from the point of view of a synthetic chemist is the possibility of combining it with racemization conditions in order to facilitate a spontaneous deracemization of the bulk material. It is hoped that once armed with this list of potential substrates, synthetic chemists can begin to hypothesize which conglomerate substrates can be paired with known racemization conditions. Figure 6 presents an example of how new substrates may be selected from the list of chiral conglomerates (see *Supporting Information*) as candidates for spontaneous deracemization. Overcoming the lack of documentation of this crystallization phenomenon will lower the barrier to entry for synthetic chemists to develop new protocols for this form of chiral amplification in their syntheses.

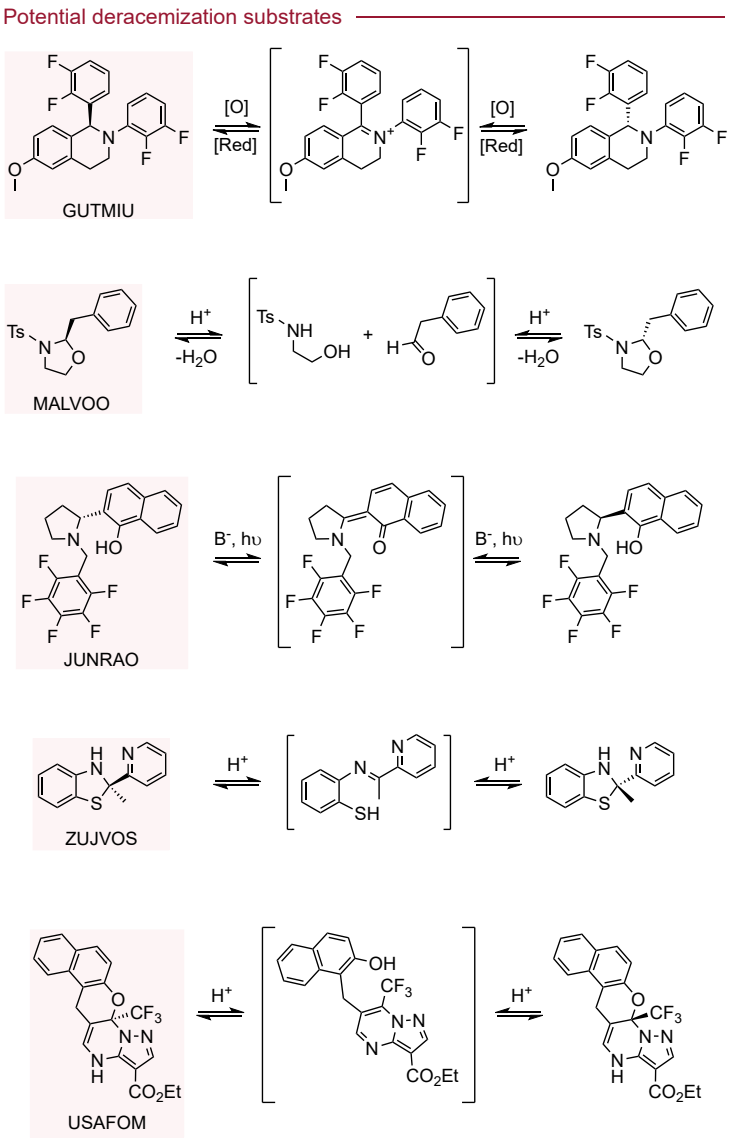

Figure 6: Hypothesised substrates and conditions for spontaneous deracemization. Conglomerate substrates are labelled by their CSD Refcodes: GUTMIU,[59] MALVOO,[60] JUNRAO,[61] ZUJVOS,[62] USAFOM.[63]

Future reporting. The presence of unidentified conglomerates within the CSD is symptomatic of communication between two traditionally separate disciplines – namely the synthetic and the structural communities. To take full advantage of this phenomenon, information transfer between these groups needs to be facilitated. Nowhere can this difference be seen more clearly than when considering CSD communications as a publication avenue. The fastest growing component in the CSD is the use of *CSD Communications* for publication of individual crystal structures.[64] In 2021, 5,110 structures were published as *CSD Communications*, making it the top journal in the CSD, with 9.3% of the total structures published that year. For comparison, 1,645 structures were published in the CSD with *Cryst. Growth Des.* and 1,530 structures with *CrystEngComm*. The publishing mechanism offered by *CSD Communications* achieves its admirable aim of the rapid communication of crystal structures. However, there is no consensus on how to identify conglomerate behavior within a CIF and publishing a crystal structure within *CSD Communications* alone does not allow authors to report the synthetic route of the material, thereby obscuring the identification of conglomerate behaviors by manual inspection. This has been the most accessible method of publishing a lone crystal structure for a synthetic chemist, but ultimately it is both the synthetic and the crystallographic communities that suffer from the loss of information by not identifying the conglomerate behavior within the CIF or not reporting a synthetic protocol for the material. As such, the optimal solution is to capture the conglomerate crystallization behavior during the deposition process to a crystallographic database. This might be achieved by prompting the user to consider if the chiral material had originated from a racemic process by means of a checkbox and creating a searchable identifier associated with the deposited CIF if the conditions for a conglomerate crystal are met. This has the advantage of capturing conglomerate behavior without requiring the user to be familiar with the crystallographic terminology. Without the intervention of the crystallographic databases, the crystallographic community could adopt the inclusion of a searchable identifier within the CIF prior to deposition to a crystallographic database either by including a text string or

by utilizing the "_chemical_enantioexcess_*" CIF fields in order to allow for the identification and automatic searching of conglomerate crystallization. It will be the wider crystallographic community which ultimately decides on the standard practice to record this metadata.

Conclusion

By conducting a manual search of the distribution of the CSD version 5.43 (November 2021) an additional 343 chiral conglomerate crystallizations have been identified to have been published between 2020–2021. This list is presented in full within the *Supporting Information*. Trends in the journals that contained chiral conglomerate crystallization reinforced the previous observations that the majority of examples of this behavior appear in non-crystallographic journals. By manually curating the structures which are capable of undergoing this form of crystallization, substrates which may be paired with racemization conditions can be identified by synthetic chemists in order to mediate new spontaneous deracemization protocols.

Abbreviations: CCDC, Cambridge Crystallograpic Data Center; CIF, Crystallographic Information File; CSD, Cambridge Structural Database; IUCr, International Union of Crystallography; XRD, X-ray diffraction.

Conflict of interests: The authors have no conflict of interests to declare.

Author contributions: James A. Barclay, Callum S. Begg, and Jinyi Xuan have contributed equally to this paper.

Acknowledgement

We thank the EPSRC for PhD studentship to C.S.B. (EP/T518001/1, project reference 2456710) and PhD studentship to J.X. through the SOFI^2 CDT programme (EP/S023631/1, project reference 2531010); the Royal Society for PhD studentship for J.A.B. (RGF/EA/180312) and a research fellowship to M.O.K. (UF150536).

Supporting Information Available

The full curated list of chiral conglomerate crystals published between 2020–2021, along with their chemical structures and their associated references, are available within Supporting Information (.pdf). The annotated output from *Conquest* is available with the resulting classification for each crystal (.xlsx). The chiral conglomerate crystals identified in this work have been collated as CIF and Refcode list formats (.cif, .txt, .gcd) and are freely available from the *Zenodo* data repository (`https://doi.org/10.5281/zenodo.7473978`).

References

(1) Taylor, R.; Kennard, O. Crystallographic Evidence for the Existence of C–H···O, C–H···N, and C–H···Cl Hydrogen Bonds. *J. Am. Chem. Soc.* **1982**, *104*, 5063–5070, DOI: 10.1021/ja00383a012.

(2) Taylor, R. The hydrogen bond between N-H or O-H and organic fluorine: Favourable yes, competitive no. *Acta Crystallogr. B* **2017**, *73*, 474–488, DOI: 10.1107/S2052520617005923.

(3) Bishop, R.; Scudder, M. L. Multiple molecules in the asymmetric unit ($Z' > 1$) and the formation of false conglomerate crystal structures. *Cryst. Growth Des.* **2009**, *9*, 2890–2894, DOI: 10.1021/CG9002143.

(4) Bernal, I.; Watkins, S. A list of organometallic kryptoracemates. *Acta Crystallographica Section C: Structural Chemistry* **2015**, *71*, 216–221, DOI: 10.1107/S2053229615002636.

(5) Clevers, S.; Coquerel, G. Kryptoracemic compound hunting and frequency in the Cambridge Structural Database. *CrystEngComm* **2020**, *22*, 7407–7419, DOI: 10.1039/D0CE00303D.

(6) Cole, J. C.; Yao, J. W.; Shields, G. P.; Motherwell, W. D.; Allen, F. H.; Howard, J. A. Automatic detection of molecular symmetry in the Cambridge Structural Database. *Acta Crystallogr. B* **2001**, *57*, 88–94, DOI: 10.1107/S010876810001380X.

(7) Pidcock, E. Achiral molecules in non-centrosymmetric space groups. *Chem. Commun.* **2005**, 3457–3459, DOI: 10.1039/b505236j.

(8) Rekis, T. Crystallization of chiral molecular compounds: What can be learned from the Cambridge Structural Database? *Acta Crystallogr. B* **2020**, *76*, 307–315, DOI: 10.1107/S2052520620003601.

(9) Galek, P. T.; Fábián, L.; Allen, F. H. Universal prediction of intramolecular hydrogen bonds in organic crystals. *Acta Crystallogr. B* **2010**, *66*, 237–252, DOI: 10.1107/S0108768110003988.

(10) Galek, P. T.; Chisholm, J. A.; Pidcock, E.; Wood, P. A. Hydrogen-Bond coordination in organic crystal structures: statistics, predictions and applications. *Acta Crystallogr. B* **2014**, *70*, 91–105, DOI: 10.1107/S2052520613033003.

(11) Brock, C. P. High-Z structures of organic molecules: Their diversity and organizing principles. *Acta Crystallogr. B* **2016**, *72*, 807–821, DOI: 10.1107/S2052520616017297.

(12) Steed, K. M.; Steed, J. W. Packing problems: High Z' crystal structures and their

relationship to cocrystals, inclusion compounds, and polymorphism. *Chem. Rev.* **2015**, *115*, 2895–2933, DOI: 10.1021/cr500564z.

(13) Walsh, M. P.; Barclay, J. A.; Begg, C. S.; Xuan, J.; Johnson, N. T.; Cole, J. C.; Kitching, M. O. Identifying a Hidden Conglomerate Chiral Pool in the CSD. *JACS Au* **2022**, DOI: 10.1021/jacsau.2c00394.

(14) Flack, H. D. Louis Pasteurs discovery of molecular chirality and spontaneous resolution in 1848, together with a complete review of his crystallographic and chemical work. *Acta Crystallogr. A* **2009**, *65*, 371–389, DOI: 10.1107/S0108767309024088.

(15) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*; Wiley: New York, 1994; pp 43–88.

(16) Buhse, T.; Cruz, J. M.; Noble-Terán, M. E.; Hochberg, D.; Ribó, J. M.; Crusats, J.; Micheau, J. C. Spontaneous deracemizations. *Chem. Rev.* **2021**, *121*, 2147–2229, DOI: 10.1021/acs.chemrev.0c00819.

(17) Washio, A.; Hosaka, M.; Uemura, N.; Yoshida, Y.; Mino, T.; Kasashima, Y.; Sakamoto, M. Asymmetric Anisoin Synthesis Involving Benzoin Condensation Followed by Deracemization. *Cryst. Growth Des.* **2021**, *21*, 2423–2428, DOI: 10.1021/acs.cgd.1c00036.

(18) Valenti, G.; Tinnemans, P.; Baglai, I.; Noorduin, W. L.; Kaptein, B.; Leeman, M.; ter Horst, J. H.; Kellogg, R. M. Combining Incompatible Processes for Deracemization of a Praziquantel Derivative under Flow Conditions. *Angew. Chem. Int. Ed.* **2021**, *60*, 5279–5282, DOI: 10.1002/anie.202013502.

(19) Uemura, N.; Toyoda, S.; Shimizu, W.; Yoshida, Y.; Mino, T.; Sakamoto, M. Absolute asymmetric synthesis involving chiral symmetry breaking in diels-alder reaction. *Symmetry* **2020**, *12*, 910, DOI: 10.3390/SYM12060910.

(20) Uemura, N.; Hosaka, M.; Washio, A.; Yoshida, Y.; Mino, T.; Sakamoto, M. Chiral Symmetry Breaking of Thiohydantoins by Attrition-Enhanced Deracemization. *Cryst. Growth Des.* **2020**, *20*, 4898–4903, DOI: 10.1021/acs.cgd.0c00829.

(21) Uemura, N.; Toyoda, S.; Shimizu, W.; Yoshida, Y.; Mino, T.; Sakamoto, M. Absolute asymmetric synthesis involving chiral symmetry breaking in Diels-Alder reaction. *Symmetry* **2020**, *12*, 910, DOI: 10.3390/SYM12060910.

(22) Nakamura, T.; Ban, K.; Yoshida, Y.; Mino, T.; Kasashima, Y.; Sakamoto, M. Asymmetric Synthesis of Indoline from Achiral Phthalimide Involving Crystallization-Induced Deracemization. *Chem. Eur. J.* **2021**, *27*, 16338–16341, DOI: 10.1002/chem.202103345.

(23) Sanada, K.; Washio, A.; Nishihata, K.; Yagishita, F.; Yoshida, Y.; Mino, T.; Suzuki, S.; Kasashima, Y.; Sakamoto, M. Chiral Symmetry Breaking of Racemic 3-Phenylsuccinimides via Crystallization-Induced Dynamic Deracemization. *Cryst. Growth Des.* **2021**, *21*, 6051–6055, DOI: 10.1021/acs.cgd.1c01010.

(24) Shimizu, W.; Uemura, N.; Yoshida, Y.; Mino, T.; Kasashima, Y.; Sakamoto, M. Attrition-enhanced deracemization and absolute asymmetric synthesis of flavanones from prochiral precursors. *Cryst. Growth Des.* **2020**, *20*, 5676–5681, DOI: 10.1021/acs.cgd.0c00955.

(25) Ishikawa, H.; Ban, K.; Uemura, N.; Yoshida, Y.; Mino, T.; Kasashima, Y.; Sakamoto, M. Attrition-Enhanced Deracemization of Axially Chiral Nicotinamides. *Eur. J. Org. Chem.* **2020**, 1001–1005, DOI: 10.1002/ejoc.201901826.

(26) Belletti, G.; Tortora, C.; Mellema, I. D.; Tinnemans, P.; Meekes, H.; Rutjes, F. P.; Tsogoeva, S. B.; Vlieg, E. Photoracemization-Based Viedma Ripening of a BINOL Derivative. *Chem. Eur. J.* **2020**, *26*, 839–844, DOI: 10.1002/chem.201904382.

(27) Sakamoto, M.; Uemura, N.; Saito, R.; Shimobayashi, H.; Yoshida, Y.; Mino, T.; Omatsu, T. Chirogenesis and Amplification of Molecular Chirality Using Optical Vortices. *Angew. Chem. Int. Ed.* **2021**, *60*, 12819–12823, DOI: 10.1002/anie.202103382.

(28) de Jesús Cruz, P.; Cassels, W. R.; Chen, C. H.; Johnson, J. S. Doubly stereoconvergent crystallization enabled by asymmetric catalysis. *Science* **2022**, *376*, 1224–1230, DOI: 10.1126/science.abo5048.

(29) de Jesús Cruz, P.; Johnson, J. S. Crystallization-Enabled Henry Reactions: Stereoconvergent Construction of Fully Substituted [N]-Asymmetric Centers. *J. Am. Chem. Soc.* **2022**, *144*, 15803–15811, DOI: 10.1021/jacs.2c06669.

(30) Guillot, M.; de Meester, J.; Huynen, S.; Collard, L.; Robeyns, K.; Riant, O.; Leyssens, T. Cocrystallization-Induced Spontaneous Deracemization: A General Thermodynamic Approach to Deracemization. *Angew. Chem. Int. Ed.* **2020**, *59*, 11303–11306, DOI: 10.1002/anie.202002464.

(31) Guillot, M.; De Meester, J.; Collard, L.; Riant, O.; Leyssens, T. Co-Crystallization-Induced Spontaneous Deracemization: An Optimization Study. *Org. Process Res. and Dev.* **2021**, *25*, 884–891, DOI: doi.org/10.1021/acs.oprd.0c00538.

(32) Walsh, M. P.; Phelps, J. M.; Lennon, M. E.; Yufit, D. S.; Kitching, M. O. Enantioselective synthesis of ammonium cations. *Nature* **2021**, *597*, 70–76, DOI: 10.1038/s41586-021-03735-5.

(33) Zhou, F.; Shemchuk, O.; Charpentier, M. D.; Matheys, C.; Collard, L.; ter Horst, J. H.; Leyssens, T. Simultaneous Chiral Resolution of Two Racemic Compounds by Preferential Cocrystallization. *Angew. Chem. Int. Ed.* **2021**, *60*, 20264–20268, DOI: 10.1002/anie.202107804.

(34) Zhou, Z.; Kawade, R. K.; Wei, Z.; Kuriakose, F.; Üngör, Ö.; Jo, M.; Shatruk, M.; Gershoni-Poranne, R.; Petrukhina, M. A.; Alabugin, I. V. Negative Charge as

a Lens for Concentrating Antiaromaticity: Using a Pentagonal Defect and Helicene Strain for Cyclizations. *Angew. Chem. Int. Ed.* **2020**, *59*, 1256–1262, DOI: 10.1002/anie.201911319.

(35) Martin, J. S.; Zeng, X.; Chen, X.; Miller, C.; Han, C.; Lin, Y.; Yamamoto, N.; Wang, X.; Yazdi, S.; Yan, Y.; Beard, M. C.; Yan, Y. A Nanocrystal Catalyst Incorporating a Surface Bound Transition Metal to Induce Photocatalytic Sequential Electron Transfer Events. *J. Am. Chem. Soc.* **2021**, *143*, 11361–11369, DOI: 10.1021/jacs.1c00503.

(36) Fischer, M.; Hering-Junghans, C. On 1,3-phosphaazaallenes and their diverse reactivity. *Chem. Sci.* **2021**, *12*, 10279–10289, DOI: 10.1039/d1sc02947a.

(37) Shirbhate, M. E.; Kwon, S.; Song, A.; Kim, S.; Kim, D.; Huang, H.; Kim, Y.; Lee, H.; Kim, S. J.; Baik, M. H.; Yoon, J.; Kim, K. M. Optical and Fluorescent Dual Sensing of Aminoalcohols by in Situ Generation of BODIPY-like Chromophore. *ACS Appl. Mater. Interfaces* **2020**, DOI: 10.1021/jacs.9b13232.

(38) Kim, S. M.; Kang, O. Y.; Lim, H. J.; Park, S. J. Selective Synthesis of N-Cyano Sulfilimines by Dearomatizing Stable Thionium Ions. *ACS Omega* **2020**, *5*, 10191–10199, DOI: 10.1021/acsomega.0c01086.

(39) Wang, X.; Wang, H. R.; Xu, X.; Zhao, D. Ring Expansion to 8-Membered Silacycles through Formal Cross-Dimerization of 5-Membered Palladacycles with Silacyclobutanes. *Eur. J. Org. Chem.* **2021**, *2021*, 3039–3042, DOI: 10.1002/ejoc.202100535.

(40) Ishijima, K.; Tanaka, S.; Imoto, H.; Naka, K. 2-Arylbenzo[: B] arsoles: An experimental and computational study on the relationship between structural and photophysical properties. *Dalton Trans.* **2020**, *49*, 15612–15621, DOI: 10.1039/d0dt02669g.

(41) Shen, J.; Ye, R.; Romanies, A.; Roy, A.; Chen, F.; Ren, C.; Liu, Z.; Zeng, H. Aquafoldmer-Based Aquaporin-like Synthetic Water Channel. *J. Am. Chem. Soc.* **2020**, *142*, 10050–10058, DOI: 10.1021/jacs.0c02013.

(42) Kamble, S. B.; Maliekal, P. J.; Dharpure, P. D.; Badani, P. M.; Karnik, A. V. Synthesis of Concave and Vaulted 2 H-Pyran-Fused BINOLs and Corresponding [5] and [7]-Oxahelicenoids: Regioselective Cascade-Concerted Route and DFT Studies. *J. Org. Chem.* **2020**, *85*, 7739–7747, DOI: 10.1021/acs.joc.0c00363.

(43) Wang, M.; Zhang, M.; Luo, Y.; Liu, Z.; Yang, C.; Lan, J.; Wu, D.; You, J. Pd(II)-Catalyzed Regioselective Multiple C-H Arylations of 1-Naphthamides with Cyclic Diaryliodonium Salts: One-Step Access to [4]- And [5]Carbohelicenes. *Org. Lett.* **2020**, *22*, 135–139, DOI: 10.1021/acs.orglett.9b04046.

(44) Purtsas, A.; Kataeva, O.; Knölker, H. J. Iron-Catalyzed Oxidative CC Cross-Coupling Reaction of Tertiary Anilines with Hydroxyarenes by Using Air as Sole Oxidant. *Chem. Eur. J.* **2020**, *26*, 2499–2508, DOI: 10.1002/chem.201905595.

(45) Karishma, P.; Gogia, A.; Mandal, S. K.; Sakhuja, R. Ruthenium Catalyzed CH Amidation and Carbocyclization using Isocyanates: An Access to Amidated 2-phenylphthalazine-1,4-diones and Indazolo[1,2-b]phthalazine-triones. *Adv. Synth. Catal.* **2021**, *363*, 762–775, DOI: 10.1002/adsc.202001146.

(46) Taj Muhammad, M.; Jiao, Y.; Ye, C.; Chiou, M. F.; Israr, M.; Zhu, X.; Li, Y.; Wen, Z.; Studer, A.; Bao, H. Synthesis of difluoromethylated allenes through trifunctionalization of 1,3-enynes. *Nat. Commun.* **2020**, *11*, 1–8, DOI: 10.1038/s41467-019-14254-3.

(47) Wang, F.; Gan, F.; Qiu, H. Amplifiable Symmetry Breaking in Aggregates of Vibrating Helical Molecules . *J. Am. Chem. Soc.* **2020**, *142*, 16167–16172, DOI: 10.1021/jacs.0c06932.

(48) Hu, Y.; Teat, S. J.; Gong, W.; Zhou, Z.; Jin, Y.; Chen, H.; Wu, J.; Cui, Y.; Jiang, T.; Cheng, X.; Zhang, W. Single crystals of mechanically entwined helical covalent polymers. *Nat. Chem.* **2021**, *13*, 660–665, DOI: 10.1038/s41557-021-00686-2.

(49) Lambert, K. M.; Cox, J. B.; Liu, L.; Jackson, A. C.; Yruegas, S.; Wiberg, K. B.; Wood, J. L. Total Synthesis of ()-Phyllantidine: Development and Mechanistic Evaluation of a Ring Expansion for Installation of Embedded Nitrogen-Oxygen Bonds. *Angew. Chem. Int. Ed.* **2020**, *59*, 9757–9766, DOI: 10.1002/anie.202003829.

(50) Wu, J. L.; Chiou, W. H. Diastereocontrolled Formal Syntheses of ()-Lepadiformines A, B, and C and the Divergent Synthesis of 2- epi-Lepadiformine C through Unexpected Double Consecutive Epimerizations. *J. Org. Chem.* **2020**, *85*, 9051–9063, DOI: 10.1021/acs.joc.0c00964.

(51) Mashiko, T.; Shingai, Y.; Sakai, J.; Kamo, S.; Adachi, S.; Matsuzawa, A.; Sugita, K. Total Synthesis of Cochlearol B via Intramolecular [2+2] Photocycloaddition. *Angew. Chem. Int. Ed.* **2021**, *60*, 24484–24487, DOI: 10.1002/anie.202110556.

(52) Huo, L.; Dong, C.; Wang, M.; Lu, X.; Zhang, W.; Yang, B.; Yuan, Y.; Qiu, S.; Liu, H.; Tan, H. Biomimetic Total Syntheses of Sanctis A-B with Structure Revision. *Org. Lett.* **2020**, *22*, 934–938, DOI: 10.1021/acs.orglett.9b04486.

(53) Li, W.; De Groen, M.; Kramer, H. J.; De Gelder, R.; Tinnemans, P.; Meekes, H.; Ter Horst, J. H. Screening Approach for Identifying Cocrystal Types and Resolution Opportunities in Complex Chiral Multicomponent Systems. *Cryst. Growth Des.* **2021**, *21*, 112–124, DOI: 10.1021/acs.cgd.0c00890.

(54) Liu, Q.; Yang, D.; Chen, T.; Zhang, B.; Xing, C.; Zhang, L.; Lu, Y.; Du, G. Insights into the Solubility and Structural Features of Four Praziquantel Cocrystals. *Cryst. Growth Des.* **2021**, *21*, 6321–6331, DOI: 10.1021/acs.cgd.1c00785.

(55) Chitra, R.; Choudhury, R.; Capet, F.; Roussel, P.; Bhatt, P. Crystal structure of 4-aminopyridinium 3-(4-aminopyridinium) succinate tetra hydrate: A new salt from 4-aminopyridine and maleic acid crystallization. *J. Mol. Struct.* **2021**, *1234*, 130142, DOI: 10.1016/j.molstruc.2021.130142.

(56) Chadeayne, A. R.; Pham, D. N.; Golen, J. A.; Manke, D. R. DMT analogues: N-ethyl-N-propyltryptamine and N-allyl-N-methytryptamine as their hydrofumarate salts. *Acta Crystallogr. E* **2020**, *76*, 1201–1205, DOI: 10.1107/S2056989020008683.

(57) Mbodji, A.; Gbabode, G.; Sanselme, M.; Cartigny, Y.; Couvrat, N.; Leeman, M.; Dupray, V.; Kellogg, R. M.; Coquerel, G. Evidence of Conglomerate with Partial Solid Solutions in Ethylammonium Chlocyphos. *Cryst. Growth Des.* **2020**, *20*, 2562–2569, DOI: 10.1021/acs.cgd.9b01699.

(58) Gerasimova, D. P.; Saifina, A. F.; Zakharychev, D. V.; Fayzullin, R. R.; Kurbangalieva, A. R.; Lodochnikova, O. A. The second example of doubly enantiophobic behavior during crystallization: a detailed crystallographic, thermochemical and spectroscopic study. *CrystEngComm* **2021**, *23*, 3907–3918, DOI: 10.1039/d1ce00227a.

(59) Singla, L.; Yadav, H. R.; Choudhury, A. R. Evaluation of fluorine-mediated intermolecular interactions in tetrafluorinated tetrahydroisoquinoline derivatives: Synthesis and computational studies. *Acta Crystallogr. B* **2020**, *76*, 604–617, DOI: 10.1107/S2052520620006873.

(60) Yang, S.; Chen, Y.; Yuan, Z.; Bu, F.; Jiang, C.; Ding, Z. Divergent synthesis of oxazolidines and morpholines: via PhI(OAc)2-mediated difunctionalization of alkenes. *Organic and Biomolecular Chemistry* **2020**, *18*, 9873–9882, DOI: 10.1039/d0ob01987a.

(61) Cao, L.; Zhao, H.; Tan, Z.; Guan, R.; Jiang, H.; Zhang, M. Ruthenium-Catalyzed Hydrogen Evolution o-Aminoalkylation of Phenols with Cyclic Amines. *Org. Lett.* **2020**, *22*, 4781–4785, DOI: 10.1021/acs.orglett.0c01580.

(62) Acevedo-García, Á.; Alvarado-Rodríguez, J. G.; Andrade-López, N.; Álvarez-Hernández, J. A. Reactivity of dihydrobenzothiazole heterocycles: Synthesis, molecular and crystal structure of an organotin compound containing a tridentate Schiff ligand. *Inorg. Chem. Commun.* **2020**, *112*, 107750, DOI: 10.1016/j.inoche.2019.107750.

(63) Osyanin, V.; Osipov, D. V.; Korzhenko, K. S.; Demidov, O. P.; Klimochkin, Y. N. Reactions of β-Carbonyl-Substituted 4H-chromenes and 1H-benzo[f]Chromenes with 5-aminopyrazoles. *Chem. Heterocycl. Compounds* **2021**, *57*, 305–313, DOI: 10.1007/s10593-021-02908-4.

(64) CSD Statistics and Insights - The Cambridge Crystallographic Data Centre (CCDC). https://www.ccdc.cam.ac.uk/CCDCStats/.

Graphical TOC Entry

Conglomerates in the CSD (2020–2021)

INETON	JUPBAA	OBONOM	ORIVUJ	PUGHUX	QUZMIK
INICIU	JUPBEE	OBOPEE	ORIWEU	PUGJAF	QUZQUA
INIDOA	JUPKEN	OBOSIL	OROQIY	PUGLEL	QUZTOX
INIHIZ	JUPKOX	OBOTEI	OSARUY	PUGLIP	QUZYOC
INILAV	JUPLEO	OBOVOU	OSAZEQ	PUGMOW	QUZYUI
INIYOW	JUPLIS	OBOVUA	OSEGEB	PUGMUC	QUZZAP
INIYUC	JUPTAS	OBUBIA	OSEGIF	PUGNAJ	RABCEG
INODUN	JUPWAV	OBUNOS	OSEGOL	PUGNIR	RABCIK
INOLOP	JUPWID	OBUZEU	OSEGUR	PUGNUD	RABCOQ
INOREL	JUPYUR	OCAQES	OSEHAY	PUGQEQ	RABKAK
INOTUD	JUQBOP	OCAQIW	OSEJII	PUGTUJ	RABKEO
INOWAM	JUQJAJ	OCARAO	OSEYAP	PUGVUL	RABKIS
INUNAJ	JUQLOZ	OCAROD	OSOQIZ	PUGXAT	RABKOY
IPABAF	JUQYIG	OCEKAM	OSOQOF	PUGYIC	RACFEK