ABSTRACT: In this work, we design and synthesize supramolecular 2,5-substituted chalcogenazolo[5,4-\(\beta\)]pyridine (CGP) synthons arranging in supramolecular ribbons at the solid state. A careful choice of the combination of substituents at the 2- and 5-positions on the CGP scaffold is outlined to accomplish supramolecular materials by means of multiple hybrid interactions, comprising both chalcogen and hydrogen bonds. Depending on the steric and electronic properties of the substituents, different solid-state arrangements have been achieved. Among the different moieties on the 5-position, an oxazole unit has been incorporated on the Se- and Te-congeners by Pd-catalyzed cross-coupling reaction and a supramolecular ribbon-like organization was consistently obtained at the solid state.

INTRODUCTION

In recent years, crystal engineering has soared interest in the scientific community, given its valuable implications in the rational design of functional materials.\(^1\)\(\text{−}\)\(^5\) Several studies have focused on the use of supramolecular bonds, selectively involving recognition motifs to generate stable and predictable multidimensional networks in the solid state.\(^6\)\(\text{−}\)\(^10\) Among the several noncovalent interactions, hydrogen bonds embody the main interaction occurring in biological systems,\(^11\)\(\text{−}\)\(^12\) as well as being used for many applications in chemistry and materials science.\(^13\)\(\text{−}\)\(^16\) However, over the past decades, there has been a flourishing interest for a class of exotic noncovalent interactions, namely, Secondary Bonding Interactions (SBIs),\(^17\) as attractive alternatives to the ubiquitous hydrogen bond in crystal engineering. SBIs’ nature relies on electrostatic (explained in terms of \(\sigma\)-holes)\(^18\) and van der Waals contributions, as well as on orbital mixing described as \(n(Y)\rightarrow\sigma^*(E-X)\) donation (X-E\(\cdots\)Y), which involves non-bonding electrons of the electron-donating atom Y and the empty antibonding \(\sigma^*\) located on the E atom.\(^19\) When the central polarizable E atom belongs to Group VI of the periodic table, the term chalcogen bonding (EB, known also as ChB) is used to describe the interaction between a positively polarized chalcogen atom and a Lewis base.\(^20\)\(\text{−}\)\(^22\) Despite recent developments in catalysis\(^23\)\(\text{−}\)\(^28\) and sensing\(^25\),\(^29\) EB interactions have been mainly exploited in crystal engineering,\(^30\),\(^31\) providing a distinctive series of persistent recognition motifs.\(^32\)\(\text{−}\)\(^35\) The structure of the most part of these chalcogen-bonding synthons builds on a heterocyclic scaffold, in which the chalcogen bond donors and acceptors are proximal to each other,\(^36\)\(\text{−}\)\(^38\) thus effectively developing macroyclic\(^39\)\(\text{−}\)\(^41\) and wire-like\(^42\),\(^43\) supramolecular architectures. Previous work done in our group with 2-substituted benzo-1,3-chalcogenazoles described the formation of polymeric structures achieved through single EB interactions.\(^44\),\(^45\) When using the chalcogenazolo[5,4-\(\beta\)]pyridine (CGP) module, frontal double chalcogen bonds are obtained in the solid state with high recognition fidelity when the Te chalcogen is used.\(^36\) Notably, changing the derivatization in the 2-position of the CGP ring has allowed the complexity of the molecular assembly to be expanded, engineering organic solids through...
the co-crystallization of heteromolecular supramolecular polymers, held by concurring chalcogen- and halogen-bonding interactions.47 Building on these results, in this work, we pursue the idea of expanding the functionalization space of the CGP module in the 5-position. This would allow face-to-face dimer association to be disrupted and originate new recognition modes in the solid state (see Figure 1).

**Design of 2- and 5-Substituted CGP Derivatives.** We conjectured that, depending on the electronic and steric properties of the substituents in the 2- and 5-positions, one could disrupt the typical doubly chalcogen-bonded recognition of a CGP-based derivative (recognition mode A, Figure 1) and force the module to associate in a different fashion. For instance, if the substituent in the 5-position (orange) sterically clashes with that in the 2-position (green) in the frontal arrangement, one could envisage that a head-to-tail recognition mode is favored (e.g., B and C modes displayed in Figure 1).

In this arrangement, an EB is established between the N atom of the chalcogenazole ring (Nc) and the chalcogen atom of a neighboring CGP moiety. If no homo-repulsions are present between the substituents in the 2-position (green), a noncovalent ribbon-like organization, held together by a combination of frontal hydrogen- and chalcogen-bonding interactions, is expected to develop (mode B, Figure 1). Finally, if all substituents would undergo homo- and hetero-repulsions in the frontal arrangements, then the only possibility would be for the motif to assemble into nonplanar chalcogen-bonded wire-like assemblies (mode C, Figure 1), as previously observed by us.45

![Figure 1](https://dx.doi.org/10.1021/acs.cgd.0c01318)

**Figure 1.** Representation of the design of 2- and 5-substituted CGP scaffold with the recognition modes expected by modulating the repulsive interactions (e.g., steric or electrostatic) between the 2- and the 5-substituents (i.e., green and orange): frontal EB dimers (A), head-to-tail ribbon (B) and wire-like (C) organizations.

**RESULTS AND DISCUSSION**

**Synthesis.** The synthesis started with the selective bromination of the commercially available amines 1Me and 1Cl using N-bromo succinimide (NBS) in MeCN, which provided compounds 2Me and 2Cl, respectively, in good and excellent yields. Brominated amines 2Me and 2Cl were treated with 1 equiv of n-BuLi, followed by the addition of 1 equiv of...
trialkyl magnesiumate (freshly prepared by mixing i-PrMgCl with 2 equiv of n-BuLi). Subsequent addition of the relevant freshly grounded elemental chalcogen powder to the reaction mixture led to the corresponding bischalcogenides $^{3X-E}$ in significantly improved yields (28–55%) when compared to synthetic protocols previously implemented by our group. The synthesis of derivatives $^{4X-E}$ was completed by the reductive cleavage of the dichalcogenide bond using NaBH4 and MeOH in THF, followed by addition of MeI. To insert the CF3 moiety in the 2-position, a one-pot amidation/dehydrative cyclization reaction was performed on $^{4X-E}$ using Tf2O in a 1:1 mixture of CH2Cl2 and pyridine, followed by the addition of POCl3 in a 1:1 DIPEA/dioxane solution under refluxing conditions to give $^{X-E-CF3}$. In parallel, Te-bearing amine $^{4Cl-Te}$ was converted into amides $^{5Cl-R}$ upon reaction with the relevant acyl chloride which, followed by cyclization in the presence of POCl3 in DIPEA and dioxane, afforded $^{CI-Te-R}$ in excellent yields. Given the proved chemical compatibility of the CGP moiety with Pd-catalyzed cross-coupling conditions, a Negishi cross-coupling reaction was attempted to prepare Ox-Te-Ph starting from chloro-derivative $^{Cl-Te-Ph}$. Nevertheless, no conversion was observed.

Thus, we moved our attention to the iodo-bearing congeners as electrophilic substrates. As a result, cyclized products bearing chlorine in the 5-position, i.e., $^{CI-E-CF3}$ and $^{CI-Te-Ph}$, were transformed into iodo-containing $^{I-E-CF3}$ and $^{I-Te-Ph}$ using NaI in the presence of AcCl in MeCN at 80 °C under microwave irradiation. Finally, reaction between the iodinated derivatives and oxazol-2-ylzinc(II) chloride using [Pd(PPh3)4] in THF at reflux afforded targeted molecules Ox-E-R in good yields (Scheme 1).

### Scheme 1. Synthetic Pathway to 2,5-Functionalized CGP Derivatives

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| Reagents and conditions: (a) NBS, MeCN, r.t., 5 min; (b) 1. n-BuLi, THF, 0 °C, 10 min; 2. i-PrBu2MgLi-LiCl, 0 °C, 1 h; 3. E0, r.t., overnight; 4. Se: K2Fe(CN)6, H2O, r.t., 10 min; Te: NH4Cl, H2O, air, r.t., 2 h; (c) 1. NaBH4, MeOH, THF, r.t., 1 h; 2. Mel, r.t., 1.5 h; (d) 1. (CF3CO)2O, CH2Cl2, pyridine, 0 °C to r.t., overnight; 2. POCl3, DIPEA, 1,4-dioxane, reflux, overnight; (e) acyl chloride, CH2Cl2, pyridine, 0 °C to r.t., overnight; (f) POCl3, DIPEA, 1,4-dioxane, reflux, overnight; (g) AcCl, NaI, MeCN, 80 °C, MW, 12 h; (h) oxazol-2-ylzinc(II) chloride, [Pd(PPh3)4] 10 mol %, THF, reflux, 2 h. |
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Solid-State Self-Assembly. The association properties of the 2,5-functionalized CGP derivatives in the solid state were probed by X-ray analysis of single crystals, generally obtained
by slow evaporation of a CHCl₃ solution. Governed by fluorophilic domains established by the CF₃ moiety in the 2-position, crystals of Me-Te-CF₃ and Cl-E-CF₃ are isomorphs, despite bearing either a Me or Cl atom in the 5-position, either Se or Te atoms. Te-congeners Me-Te-CF₃ (Figure 2a) and Cl-Te-CF₃ (Figure 2e) develop in a ribbon-like arrangement, in which each molecule is involved in frontal interactions comprising a chalcogen bond (dNc···Te = 3.423 and 3.406 Å for Me-Te-CF₃ and Cl-Te-CF₃, respectively) and a hydrogen bond, with the latter established between the pyridyl H and N atoms (dNp···C = 3.420 and 3.385 Å, respectively, for Me-Te-CF₃ and Cl-Te-CF₃). Surprisingly, the Se-based congener, Cl-Se-CF₃, arranges in an analogue ribbon-like orientation (Figure 2c), though held together only by hydrogen-bonding interactions (dNp···C = 3.351 Å). Additional π−π stacking interactions, governing the columnar stacking arrangement in a head-to-tail fashion, are also observed (dπ−π = 3.529 Å, dπ−π = 3.464 Å, and 3.484 Å; Figure 2b,d,f respectively), with the longest distance reported for Me-Te-CF₃.

Moving to the crystal structure of iodo-derivative I-Te-CF₃, a different molecular packing could be observed. Interestingly, doubly chalcogen-bonded, distorted noncovalent dimers are observed (dNp···Te = 3.217 Å). Given the low electronegativity and high polarizability of the I atom, the solid-state arrangement suggests the presence of a weaker repulsion between the CF₃ and I atoms, compared to that between CF₃ and Cl (Figure 3a). Moreover, each dimer associates through double hydrogen bonds involving the Nc atom (dNc···Te = 3.486 Å), hence generating a kinked ribbon at the solid state (Figure 3b). π−π stacking interactions are also observed (dπ−π = 3.824 Å with an offset of 2.585 Å), with each column interconnected by multiple halogen bonds (dI···I = 3.482 Å). In this arrangement, each I atom acts simultaneously as both halogen-bonding acceptor and donor (Figure 3c).

As previously observed for compound Cl-Se-CF₃, also I-Se-CF₃ crystallizes through the formation of ribbon-like structures with no detectable chalcogen-nitrogen contacts. In these crystals, the monomers organize through hydrogen-bonding interaction (dNp···C = 3.418 Å), which are considerably longer than those observed for Cl-Se-CF₃ (Figure 3d). Notably, I-Se-CF₃ forms columns through π−π stacking interactions (estimated dπ−π = 3.489 Å), having the CF₃ moieties segregated in fluorinated domains (dF···F = 2.573 and 2.933 Å; Figure 3e). The functionalization of the 2-position with the thiophenyl unit for Cl-Te-Th and the phenyl ring for Cl-Te-
Ph and 1-Te-Ph leads to the growth of wire-like supramolecular structures, held together by single EB between the N$_c$ atom and the Te atom of each neighboring molecule. Notably, the asymmetric unit of compound Cl-Te-Th includes two molecules, building a wire-like supramolecular assembly through single EB interactions involving the tellurazole N atom ($d_{N_c\cdots Te} = 3.385 \, \text{Å}$; Figure 4a). A similar solid-state organization, as that obtained for Cl-Te-Th, was observed for Cl-Te-Ph. In this case, both Te $\sigma$-holes are involved in EB interactions (Figure 4b). Specifically, the $\sigma$-hole($\alpha$) engages with the tellurazole N$_c$ atom, developing the wire-like arrangement ($d_{N_c\cdots Te} = 3.464 \, \text{Å}$; Figure 4d), whereas the $\sigma$-hole($\beta$) bridges the neighboring supramolecular wires through the interaction with the N$_p$ atom ($d_{N_p\cdots Te} = 3.431 \, \text{Å}$). Furthermore, the molecules are held together through $\pi-\pi$ stacking interactions in a quasi-parallel fashion (estimated $d_{\pi-\pi} = 3.460 \, \text{Å}$), with halogen–halogen interactions connecting the columnar architectures ($d_{C\cdots Cl} = 3.244 \, \text{Å}$; Figure 4c).

In the case of iodo-derivative I-Te-Ph, the asymmetric unit contains two molecules, each interacting with a nearby module through single EB with the N$_c$ atom ($d_{N_c\cdots Te} = 3.464$ and 3.582 Å). The resulting wire-like organization is further strengthened by weak hydrogen contacts established between the N$_c$ atom and one of the H atoms of the phenyl ring ($d_{N_c\cdots H} = 3.237$ and 3.321 Å; Figure 4e). In contrast to chlorinated analogue Cl-Te-Ph, $\pi-\pi$ stacking interactions govern the formation of columnar arrangements in a quasi-parallel head-to-tail fashion (estimated $d_{\pi-\pi} = 3.542 \, \text{Å}$), with I-Te interactions ($\sigma^* \pi$, $d_{C\cdots I} = 3.505 \, \text{Å}$) bridging the columns (Figure 4f).

Building on these observations, one can notice that wire-like structures are consistently attained over ribbon and dimeric arrangements with 5-functionalized CGP modules bearing a phenyl moiety in the 2-position. Remarkably, a shortening of the N$_c\cdots$Te distance can be observed when passing from phenyl-substituted Cl-Te-Ph and I-Te-Ph to Cl-Te-Th.

Aiming at validating the occurrence of recognition motifs with multiple intermolecular interactions in the solid state, several crystallization attempts for oxazole derivatives Ox-Te-Ph and Ox-E-CF$_3$ have been performed. However, only the CF$_3$-containing compounds provided single crystals suitable for X-ray diffraction analysis. Notably, Te-congener Ox-Te-CF$_3$ develops HB/EB ribbons in the solid state. These structures differentiate from those described so far because the O atom of the oxazole and the N atom of the pyridyl moiety both engage in two hydrogen bonds with the H atoms in positions 6 and 7 of a neighboring molecule ($d_{O\cdots C} = 3.211 \, \text{Å}$ and $d_{N\cdots C} = 3.423 \, \text{Å}$, respectively). A frontal chalcogen bond is also established between the N$_c$ and Te atoms of two adjacent molecules ($d_{N_c\cdots Te} = 3.355 \, \text{Å}$; Figure 5a). Considering that the length of this EB is shorter ($d_{N_c\cdots Te} = 3.355 \, \text{Å}$) than those found in the crystal structures of Me-Te-CF$_3$ and Cl-Te-CF$_3$ ($d_{N_c\cdots Te} = 3.423$ and 3.406 Å, respectively), it is suggested that two HB interactions synergistically strengthen the association between the two molecular modules. Supplementary $\pi-\pi$ stacking interactions can be discerned in the molecular packing ($d_{\pi-\pi} = 3.392 \, \text{Å}$; Figure 5b), with each molecular module arranged in an antiparallel fashion. An analogue supramolecular organization is observed for Se-based congener Ox-Se-CF$_3$, having the O atom involved in a hydrogen bond.

Figure 3. X-ray structures and their ESP maps of (a) 1-Te-CF$_3$ and (d) I-Se-CF$_3$; (b) kinked ribbon of 1-Te-CF$_3$; columnar orientations of (c) 1-Te-CF$_3$ and (e) I-Se-CF$_3$ (the halogen-bonding and F···F contacts are also displayed). Space groups: C2/c for 1-Te-CF$_3$, Cmca for I-Se-CF$_3$. Crystallization solvent: CHCl$_3$. 

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as well as the Np atom, with the H atoms in 6- and 7-positions of the facing molecular neighbor (\(d_{O-C} = 3.201 \text{ Å}, d_{N-C} = 3.418 \text{ Å}\)). This governs the arrangement of the synthons in ribbons at the solid state (Figure 5c). Similarly to Cl-Se-CF3 and I-Se-CF3, no chalcogen bond could be observed for Ox-Se-CF3, given that the Se····N distance was longer than the sum of their van der Waals radii (\(d_{Se-N} = 3.514 \text{ Å} > 3.45 \text{ Å}\)). In addition, the crystal packing develops through antiparallel \(\pi-\pi\) stacking (\(d_{\pi-\pi} = 3.369 \text{ Å}\); Figure 5d).

\section*{CONCLUSIONS}

In this paper, we have expanded the recognition space of the CGP moiety in the solid state. By combining the substituents in positions 2 (phenyl, thiophenyl, and CF3 moieties) and 5 (Me group, Cl and I atoms), a large variety of supramolecular assemblies in the solid state could be obtained by modulating the substituents’ steric and electronic properties. Aiming at developing a recognition pattern based on multiple HB and simultaneous single EB interactions, oxazolyl-bearing CGP molecules Ox-Te-CF3 and Ox-Se-CF3 have been prepared, with the latter used as reference compound to study the role of the chosen chalcogen atom in the new recognition systems. As expected, the choice of a small moiety as CF3 in the 2-position, combined with Me, Cl, and oxazole substituents in the 5-position, governed the formation of supramolecular head-to-tail HB/EB ribbons. Replacing Cl with an I atom in the 5-position in Te-congener I-Te-CF3 led to the formation of distorted EB dimers, arranged into a kinked ribbon in the solid state. Furthermore, derivatives bearing sterically demanding phenyl and thiophenyl groups showed the typical wiring organization. These results could open the road toward the engineering of a large variety of materials marked by tunable molecular arrangements, as well as depicting heteromolecular recognition systems involving HB and EB interactions. The encoding of concomitant weak interactions at the solid state could allow the design of multiresponsive materials for applications in optoelectronics and sensing.
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.cgd.0c01318.

Synthetic protocols and spectroscopic data for all molecules, computational studies, X-ray data (PDF)

Accession Codes
CCDC 1954271, 1954273—1954278, and 2015556—2015558 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes
The authors declare no competing financial interest.

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