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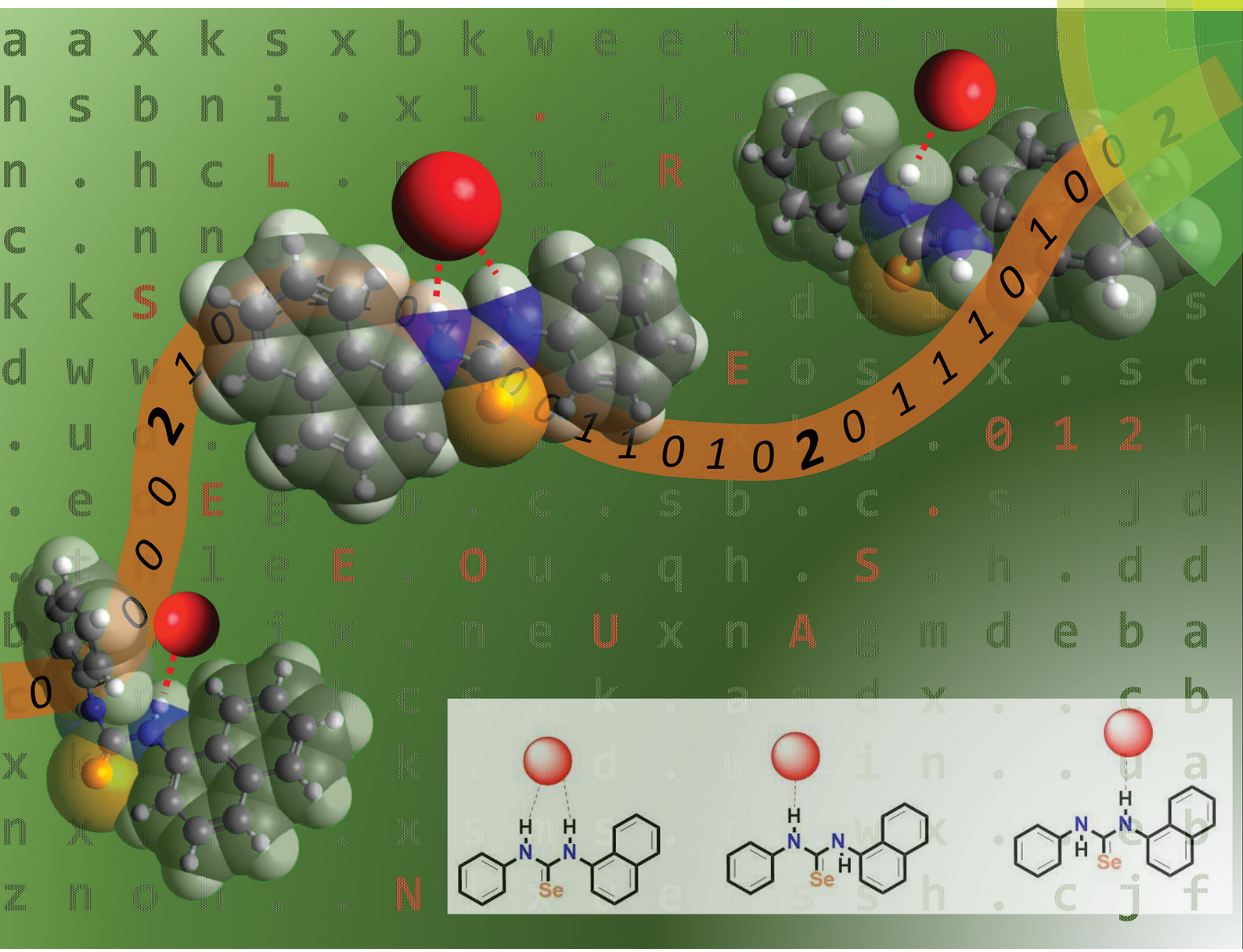

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Selenoureas for anion binding as molecular logic gates†

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The first example of a molecular logic gate based on selenourea/anion host–guest interaction that performs a ternary logic operation using an ^{1}H-NMR easy to read response output is described here. Selenoureas are very versatile receptors for anion binding, capable of forming both mono- and bi-coordinated adducts at room temperature in solution.

Classic molecular logic gates are based on molecules which are able to perform a logic operation when one (or more) chemical process acts as an input and one (or more) easily detectable analytical signal acts as an output. The first pioneering studies in this field were reported by Aviram[1] and de Silva[2] almost 30 years ago. In particular, de Silva *et al.* realised that the binary notation, zeros and ones, and the principles of Boolean language, could be applied to chemical systems and they reported the first molecular logic AND gate using protons and sodium ions as chemical inputs and fluorescence as optical output.[2] Since then, many examples of molecular logic gates have been developed and the complexity of the realized logic functions has dramatically increased.[3–8] Most of the described molecular logic gates are based on fluorescent chemosensors because the "OFF" or "ON" fluorescent status can be straightforwardly translated into the "0" or "1" Boolean operations. Nevertheless, Keinan *et al.* demonstrated that chemical shift and peak integration in ^{1}H-NMR spectra can be efficiently used as measurable parameters to develop an infochemical device able to perform three different operations, (i) text encoding, (ii) encryption of 21-digit binary numbers and their addition and subtraction, and (iii) encryption of 21-digit decimal numbers.[9] Jurczak proposed a novel strategy for the classification of guest chirality based on the combination of artificial neural networks and anion-receptor chemistry using ^{1}H-NMR spectroscopy.[10]

Urea and thiourea moieties have been widely used for the design of artificial receptors for anion binding and sensing.[11–13] Recently, we proposed for the first time selenoureas as a new binding motif for anion recognition and sensing.[14] Normally, ureas and thioureas act, at least in solution, as bidentate ligands for anions forming an eight-membered ring with oxoanions or six-membered rings with spherical anions such as halides,[15,16] while, to the best of our knowledge, stable mono-coordinated adducts are unknown. Following our interest in the development of selenourea-based receptors for anion binding, we designed and synthesised a new family of aromatic selenoureas **L1–L3** and we compared their anion binding properties with those of the corresponding thioureas (**L4–L6**) and ureas (**L7–L9**) using ^{1}H-NMR spectroscopy in DMSO-d_6 (Fig. 1). We wanted to explore the possibility for selenoureas of forming mono-coordinated adducts in solution along with classic bi-coordinated ones and, therefore, the possibility to construct molecular logic gates based on the nature of the adduct formed, as illustrated hereinafter.

The synthesis of the selenoureas **L1–L3** is based on the reaction of phenyl isoselenocyanate (for **L1**) or 1-naphthyl isoselenocyanate (for **L2** and **L3**) with aniline (for **L1** and **L2**) and 1-naphtylamine (for **L3**) in a 1 : 1 mixture of dry DCM and EtOH under an inert atmosphere in the dark at room temperature to give the desired product in good yields (84%, 79%, and 55%, for **L1**, **L2**, and **L3**, respectively, see the ESI,† for synthetic details). The synthesis of the isoselenocyanates was previously reported

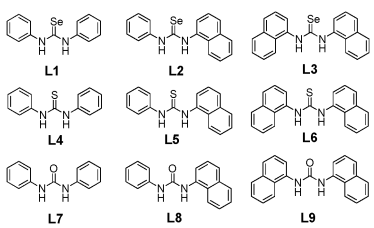

Fig. 1 Receptors presented in the paper.

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by Fernández-Bolaños *et al.*[17] Receptors **L4–L9** were already described in the literature.[18–22]

In order to evaluate the anion binding modes of **L1–L3**, as well as those of the other receptors, 1D-NMR titrations in DMSO-d_6 were performed with chloride, dihydrogenphosphate, acetate, and benzoate as their tetrabutylammonium salts. Resonances due to the selenourea NH protons were found to shift from 10–11 ppm to higher frequencies as a consequence of the anion coordination event. In addition, the appearance of multiple resonances in the range 10–12 ppm and of new resonances both in the aromatic range and at lower frequencies (5–6 ppm), was observed in a number of instances, suggesting the presence of more than one adduct species in solution. In order to rationalize this behaviour and to assign the new resonances, both 1D and 2D-NMR experiments were carried out in DMSO-d_6, starting from the case of the structurally asymmetric **L2** and acetate as guest anion species. This prototypical study case was chosen because during the titration, for a relatively wide range of anion added equivalents, four ^{1}H singlets were simultaneously present in the 10–12 ppm range together with two new singlets in the 5–6 ppm range (Fig. 2a and Fig. S1 ESI,† for a complete stack plot).

Due to the asymmetric structure of **L2** the two signals observed at ~10 ppm in the free receptor are due to the two selenourea NH protons. After the coalescence regime at the beginning of the titration, up to six different singlets attributable to NH protons were observed (Fig. 2a) which could be categorized into three couples of resonances on the basis of their frequency: high (>10.5 ppm), intermediate (9.5–10.5 ppm) and low (4.5–6.0 ppm) (Fig. S2, ESI†). g-COSY, TOCSY and ROESY were carried out on **L2** in DMSO-d_6 in the presence of 2.5 equivalents of acetate (under these conditions all the six singlets were well-resolved, see the ESI† and Fig. S2 for a detailed description) with the aim of identifying all the species present in solution. From the results of these experiments we concluded that three different adduct species were present in solution: a bi-coordinated and two different mono-coordinated adducts of **L2** with acetate as shown in Fig. 2. Attribution of the

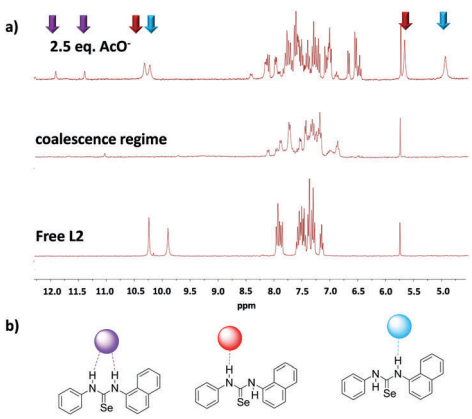

Fig. 2 (a) ^{1}H-NMR spectra of free **L2**, upon addition of 0.5 equivalents of TBAAcO (tetrabutylammonium acetate), and in the presence of 2.5 equivalents of TBAAcO in DMSO-d_6; (b) structures of the proposed mono and bi-coordinated adducts. Colour code: purple indicates bi-coordinated adduct, red and light blue indicate mono-coordinated adducts and the corresponding ^{1}H-NMR signals.

NH signals for the two mono-coordinated adducts, which are marked in red and blue in Fig. 2, is inherently ambiguous, but it is important to stress here that the presence of the bi-coordinated adduct is clearly demonstrated by the presence of resonances above 11 ppm, while the presence of mono-coordinated species is unambiguously supported by resonances in the 4.5–6.0 ppm range. Among the two signals assigned to each mono-coordinated adduct, the one at higher frequency (10–10.5 ppm) is attributed to the selenourea NH proton coordinating the anion, and the one at the lower frequency is attributed to the non-coordinating NH (see the ESI,† Fig. S3).

This interpretation is also strongly supported by a previous study reported by Roberts *et al.*[23] on the interaction of simple urea, thiourea, 1,1-dimethylurea and 1,1-dimethylthiourea with acetate. It was demonstrated that the resonance frequency of the urea protons depended on their localization in space with respect to the chalcogen, with *cis* NH protons characterized by a remarkably lower frequency than *trans* NH protons.

At room temperature, rotation around C–N bonds was fast enough to observe only a single time averaged resonance but, by decreasing the temperature, the two separate signals were visible in the spectrum, after the coalescence regime was overcome.[23] It was also demonstrated that by moving from oxygen to sulfur, the coalescence temperature increased as well as the frequency separation between *cis* and *trans* NH proton signals.[23] Our results seem to be consistent with this evidence and show that the trends (coalescence temperature and frequency separation) on changing the chalcogen continue also by moving further along group 16 down to selenium. In fact, even increasing the temperature up to 330 K to speed up the rotation around the C–N bonds, we did not reach the coalescence regime for **L2** (it should also be noted that our substituents in the selenourea moiety are bulkier than Robert methyls).

After these findings, we moved on to evaluate the effect of the chalcogen on the binding modes by using the asymmetric receptors **L2**, **L5**, and **L8** and acetate as an anion (see the ESI,† Fig. S1 and S4). In the case of **L8**, upon addition of increasing amounts of acetate, the usual progressive shift of the two NH signals was previously reported,[21] which clearly indicated the formation of a bi-coordinated adduct and the fast (on the NMR time scale) exchange rate between the adduct and the free receptor. In the case of **L5**, the behaviour appeared the same (Fig. S4, ESI†) but the system immediately showed a coalescence regime, indicating that the exchange rate significantly decreased when compared to **L8**. As reported above, in the case of **L2** (Fig. S1, ESI†), we observed the formation of both the bi- and mono-coordinated adducts in equilibrium with a slow exchange rate. In light of the above-mentioned evidence from the literature (and the correlations we found with substituents' size in the receptors as reported hereinafter), the observed differences between **L8**, **L5**, and **L2**, could be reasonably explained considering the increasing size of the van der Waals radius of the chalcogen, which could change the rotation barrier around the C–N bonds following the order **L2** > **L5** > **L8**. The effect of the chalcogen on the binding modes was also confirmed in the case of the symmetric diphenyl-substituted **L1**, **L5**, and **L7** (see the ESI,† Fig. S5).

Table 1 Type of adducts observed for **L2** with different anions in DMSO-d_6

Anion	Mono-coordination	Bi-coordination
Cl^-	✘	✔
$H_2PO_4^-$	✘	✔
AcO^-	✔	✔
BzO^-	✔	✔

Table 2 Type of adducts observed for **L1–L3** with acetate in DMSO-d_6

Receptor	Mono-coordination	Bi-coordination
L1	✔	✔
L2	✔	✔
L3	✔	✘

We then evaluated the role of the anion size and geometry on the coordination modes of selenoureas **L1–L3** by comparing chloride, dihydrogenphosphate, acetate, and benzoate. The results obtained for the prototypical case of **L2** are summarised in Table 1 and in the stack plots in the ESI† (Fig. S6). The results for **L1** and **L3** are shown in Fig. S9 and S10 (ESI†), respectively.

In the case of the relatively small and spherical chloride anion, the usual progressive shift of the two selenourea NHs to higher frequency was observed only at high anion equivalents added, indicating a low binding affinity. No coalescence regime was observed, while the resonance shift presumably reflected the fast exchange rate between the free receptor and the bi-coordinated adduct.

In the case of dihydrogenphosphate, after a first coalescence regime the two signals reappeared in the spectrum but located at lower frequency than those of the free receptor. Upon addition of further increasing amounts of anion, the progressive shift of the two NHs was observed, up to frequency values higher than those observed for the free receptor. This peculiar behaviour can be explained with a fast exchange rate between the two possible mono-coordinated species and the bi-coordinated adduct. The absence of resonances in the 4.5–6.0 ppm range, characteristic of mono-coordinated adducts, showed that the bi-coordinated species is the dominating one, to which dihydrogenphosphate anions can evolve very rapidly from any of the two mono-coordinated forms. This is absolutely reliable if one considers the tetrahedral geometry of the anion. The presence of four oxygen atoms pointing to different directions should be able to facilitate the second coordination event even if the receptor adopts a "distorted" non-planar conformation.

The observation of distinct resonances for both mono- and bi-coordinated adducts in the case of the Y-shape anions acetate and benzoate reflected the slower exchange rate between the different species formed in solution. The bulky selenium atom in the receptor should limit rotations around the C–N bonds, thus limiting the accessible conformations. As a consequence, the complementarity between the directionality of the two NH hydrogen bond donors and the Y-shape of these anions is more difficult to be achieved when selenoureas are compared to ureas and thioureas (see the ESI,† Fig. S7). The bulkier benzoate, indeed, formed only one of the two possible mono-coordinated adducts with **L2** because of its increased steric hindrance, which determined the preferential coordination direction on the less cluttered phenyl side of the receptor.

Finally, we evaluated the effect of the substituent size in the receptors on the anion binding ability of selenoureas **L1–L3**, by using acetate as a prototypical anion. The results are summarised in Table 2 and in the stack plots in the ESI† (Fig. S9 and S10).

Both in the case of the di-phenyl (**L1**) and phenyl-naphthyl (**L2**) substituted receptors, resonances corresponding to both mono- and bi-coordinated adducts were observed, with the difference in the total number of NH singlets simply due to the symmetry of the receptor itself (Fig. S8a and b, ESI†). Differently, in the case of 1,3-dinaphthylselenourea **L3** we observed only the mono-coordinated species (Fig. S8c, ESI†). In light of all the collected evidence, this difference is clearly due to the increased steric hindrance provided by the two aryl substituents, making the formation of the bi-coordinated adduct particularly unfavourable. We performed ^{1}H-NMR titrations also with receptors **L4–L9** and all the anions considered and we observed only the formation of the bi-coordinated adducts. It is worth noticing that we did not observed any relevant variation in the UV-Vis and the fluorescent properties of receptors **L1–L3** upon addition of the anions investigated.

The results obtained can be summarised in a truth table (Table 3) where the inputs are (i) the nature of the chalcogen (0, 1, and 2 for oxygen, sulphur and selenium, respectively), (ii) the steric hindrance of the aryl substituents at the urea moiety (0, 1, and 2 for diphenyl, phenyl-naphthyl, and di-naphthyl, respectively), and (iii) the geometry of the anion (0, 1, 2, and 3, for spherical chloride, tetrahedral dihydrogenphosphate, Y-shape acetate, and bulky Y-shape benzoate, respectively), while the outputs are the type of adducts formed identified on the base of ^{1}H-NMR signals (0, 1, and 2, for only mono-coordinated, both mono- and bi-coordinated, and only bi-coordinated, respectively). It is clear, that only selenoureas are able to give multiple

Table 3 Truth table based on the interactions between receptors and anions investigated in this work

Input			
Chalcogen[a]	Substituents[b]	Anion shape[c]	Output[d]
0	0, 1, 2	0, 1, 2, 3	2
1	0, 1, 2	0, 1, 2, 3	2
2	0	0	2
2	0	1	2
2	0	2	1
2	0	3	1
2	1	0	2
2	1	1	2
2	1	2	1
2	1	3	0
2	2	0	2
2	2	1	2
2	2	2	0

[a] Ternary input: 0, oxygen; 1, sulfur; 2, selenium. [b] Ternary input: 0, di-phenyl; 1, phenyl-naphthyl; 2, di-naphthyl. [c] Quaternary input: 0, spherical; 1, tetrahedral; 2, small Y-shaped; 3, bulky Y-shaped. [d] Ternary output: 0, only mono-coordination; 1, both mono- and bi-coordination; 2, only bi-coordination.

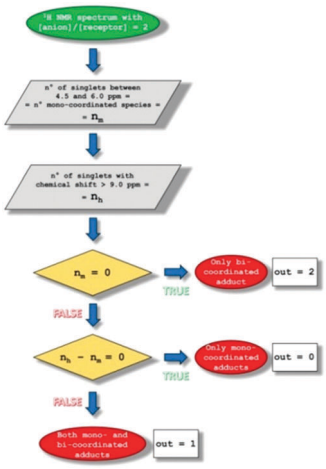

Fig. 3 Explicative flowchart to implement automatic spectra analysis of the receptors **L1–L3** in the presence of Cl^-, $H_2PO_4^-$, CH_3COO^- and Ph-COO^-.

response depending on the anion and on the aryl substituents considered. The output type in Table 3 can be easily determined using the flowchart in Fig. 3, which also provides the basis to implement the automatic NMR spectral analysis for the interactions of the receptors and anions investigated in this communication.

In conclusion, we showed that when compared to ureas and thioureas, selenoureas appear to be more versatile receptors for anion binding, capable of forming at room temperature in solution both mono- and bi-coordinated adducts depending on the geometry of the bound anion and the steric hindrance exerted by the chalcogen itself and the substituents on the urea moiety. This is reflected also on the increase of the NMR coalescence temperature that facilitates the easy detection of the mono-coordinated adduct in solution at room temperature. As a consequence, on using (i) the steric hindrance of the aryl substituents in selenoureas, and (ii) the geometry of the anion guest as inputs, a molecular logic gate can be easily developed following ^{1}H-NMR signals of the adducts formed as chemical outputs.

The investigated series of selenoureas/anions thus, represents, to the best of our knowledge, the first example of a molecular logic gate using the urea-based receptors for anions, that performs a ternary logic operation based on an ^{1}H-NMR easy to read response.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 A. Aviram, *J. Am. Chem. Soc.*, 1988, **110**, 5687–5692.
2 P. A. de Silva, N. H. Q. Gunaratne and C. P. McCoy, *Nature*, 1993, **364**, 42–44.
3 J. Andréasson and U. Pischel, *Chem. Soc. Rev.*, 2015, **44**, 1053–1069.
4 A. Credi, *Angew. Chem., Int. Ed.*, 2007, **46**, 5472–5475.
5 B. Daly, J. Ling and A. P. de Silva, *Front. Chem. Sci. Eng.*, 2014, **8**, 240–251.
6 A. P. De Silva and N. D. McClenaghan, *Chem. – Eur. J.*, 2004, **10**, 574–586.
7 Madhuprasad, M. P. Bhat, H. Y. Jung, D. Losic and M. D. Kurkuri, *Chem. – Eur. J.*, 2016, **22**, 6148–6178.
8 U. Pischel, *Aust. J. Chem.*, 2010, **63**, 148–164.
9 T. Ratner, O. Reany and E. Keinan, *ChemPhysChem*, 2009, **10**, 3303–3309.
10 J. M. Granda and J. Jurczak, *Chem. – Eur. J.*, 2014, **20**, 12368–12372.
11 N. Busschaert, C. Caltagirone, W. Van Rossom and P. A. Gale, *Chem. Rev.*, 2015, **115**, 8038–8155.
12 P. A. Gale and C. Caltagirone, *Chem. Soc. Rev.*, 2015, **44**, 4212–4227.
13 P. A. Gale and C. Caltagirone, *Coord. Chem. Rev.*, 2017, DOI: 10.1016/j.ccr.2017.05.003.
14 A. Casula, A. Llopis-Lorente, A. Garau, F. Isaia, M. Kubicki, V. Lippolis, F. Sancenón, R. Martínez-Máñez, A. Owczarzak, C. Santi, M. Andrea Scorciapino and C. Caltagirone, *Chem. Commun.*, 2017, **53**, 3729–3732.
15 V. Amendola, L. Fabbrizzi and L. Mosca, *Chem. Soc. Rev.*, 2010, **39**, 3889–3915.
16 A.-F. Li, J.-H. Wang, F. Wang and Y.-B. Jiang, *Chem. Soc. Rev.*, 2010, **39**, 3729–3745.
17 J. G. Fernández-Bolaños, Ó. López, V. C. Ulgar, I. Maya and J. Fuentes, *Tetrahedron Lett.*, 2004, **45**, 4081–4084.
18 N. Busschaert, I. L. Kirby, S. Young, S. J. Coles, P. N. Horton, M. E. Light and P. A. Gale, *Angew. Chem., Int. Ed.*, 2012, **51**, 4426–4430.
19 P. P. Deohate, J. P. Deohate and B. N. Berad, *Asian J. Chem.*, 2004, **16**, 255–260.
20 S. A. Kadam, K. Haav, L. Toom, T. Haljasorg and I. Leito, *J. Org. Chem.*, 2014, **79**, 2501–2513.
21 S. A. Kadam, K. Martin, K. Haav, L. Toom, C. Mayeux, A. Pung, P. A. Gale, J. R. Hiscock, S. J. Brooks, I. L. Kirby, N. Busschaert and I. Leito, *Chem. – Eur. J.*, 2015, **21**, 5145–5160.
22 A. Tarai and J. B. Baruah, *J. Mol. Struct.*, 2015, **1091**, 147–151.
23 K. A. Haushalter, J. Lau and J. D. Roberts, *J. Am. Chem. Soc.*, 1996, **118**, 8891–8896.

