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ORIGINAL PAPER

Benzothiazolyl- and benzimidazolyl-substituted 1-iminoisoindolines: synthesis, mechanistic studies, and crystal structure determination

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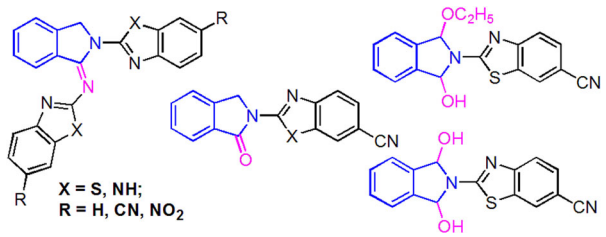
Abstract New benzothiazolyl- and benzimidazolyl-substituted 1-iminoisoindolines are prepared in the reaction of *o*-phthalaldehyde and substituted 2-aminobenzothiazoles and 2-aminobenzimidazoles. The optimization of these reactions is discussed, and the reaction mechanisms are proposed based on the experimental findings. Isoindolines with other heterocyclic substituents are prepared as a confirmation of the proposed mechanisms. Molecular and crystal structures of several prepared compounds are determined by a single crystal X-ray diffraction. These structures are found to be in line with projections based on the chemical and spectroscopic properties, and thus offer an additional confirmation of the proposed reaction mechanisms.

Graphical abstract



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Keywords Heterocycles · Reaction mechanisms · Schiff bases · X-ray structure determination

Introduction

Derivatives of isoindoline have received great attention from synthetic organic and medicinal chemists in recent years due to their wide range of different biological activity, as well as their application in herbicide and dye industries. Natural derivatives of isoindolines that were first isolated in the early 60s showed diverse biological activity [1, 2]; for example, staurosporine isolated from the bacteria *Streptomyces staurosporeus* showed antimicrobial, hypotensive, and cytotoxic activity and acts as a protein kinase C inhibitor [3]. Recently prepared synthetic derivatives of isoindolines exhibit a range of biological activities, such as anti-inflammatory [4], antipsychotic [5, 6], antihypertensive [7, 8], and antitumor [9–11] activity. Moreover, they act as inhibitors of dipeptidilpeptidase [12, 13] and protein kinase [14], in addition to exhibiting a calatase-like activity [15]. Furthermore, derivatives of isoindoline serve as very convenient ligands in coordination and organometallic chemistry [16–18]. Most of the synthetic methods for the preparation of isoindoline skeleton include *o*-phthalaldehyde and corresponding aliphatic and aromatic amines as a starting material [19–21]. Synthetic methods starting from other compounds include phthalonitrile, phthalanhydride, and phthalaldehyde acid as well as multicomponent synthesis [22–24]. It is worth mentioning several papers describing a synthesis of N-substituted isoindolines by one-pot three-component reaction of phthalaldehydic acid or phthalonitrile, primary amine and 2-mercaptobenzimidazole, 1*H*-indole, TMSCN or alcohol [25–28]. These reactions were

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found to be simple and environmentally benign. In the last several years, new methods for the synthesis of 1- and 1,3-substituted isoindolines are developed. For example, 1-isoindolecarboxylic acid esters and the corresponding isoindolines have been selectively synthesized by efficient palladium-catalyzed intramolecular α-arylation reactions of α-amino acid esters, where a slight change of reaction conditions leads to the desired product [29]. Also reported is a synthesis of a series of 1-substituted isoindolines as well as tetrahydro-β-carbolines and tetrahydroisoquinolines via catalyst free [30] or palladium-catalyzed [31, 32] domino Heck-aza-Michael reactions. A stereoselective synthesis of 1,3-disubstituted isoindolines with a wide range of substituents is described as well: a tandem reaction consisting of a nucleophilic addition/intramolecular aza-Michael reaction (IMAMR) on Ellman's *tert*-butylsulfinyl imines, bearing a Michael acceptor in the *ortho* position [33, 34]. Moreover, a synthetic and structural study into bis-imino-substituted diiminoisoindolines, which are synthesized either via $CaCl_2$ mediated reaction of phthalonitrile with primary amines, or via direct reaction of these amines with unsubstituted diiminoisoindoline, was reported [35]. Facile access to enantioenriched isoindolines bearing a quaternary stereogenic centre and a tertiary stereogenic centre was developed via one-pot sequential Cu(I)-catalyzed asymmetric 1,3-dipolar cycloaddition/aromatization of azomethine ylide with quinone derivatives [36]. Most of the synthetic methods described are oriented towards the synthesis of 1- and 1,3-substituted isoindolines and include use of expensive starting material as well as catalysts and a requirement for protection of nitrogen with Boc, Tc, etc. However, there are several papers that describe the synthesis of 1-imino-substituted isoindolines. For example, Takahashi et al. reported a condensation reaction of *o*-phthalaldehyde and substituted aniline to afford 1-imino-substituted isoindolines, but other products were isolated depending on the amine structures [37, 38].

Because of the interesting and diverse biological activity of isoindoline derivatives, we prepared novel benzothiazolyl- and benzimidazolyl-substituted 1-iminoisoindolines starting from *o*-phthalaldehyde and corresponding heterocyclic amines, as a part of our ongoing research to develop novel compounds with potential antitumor activity. We previously reported the condensation reaction of *o*-phthalaldehyde and substituted anilines and aminopyridines, where the isolated products were the expected 2-aryl-1-(*N*-arylimino)isoindolines [39, 40]. The reactions were carried out in absolute ethanol in neutral or acidic reaction conditions. However, in the reaction with bicyclic heteroaromatic amines, such as 2-aminobenzothiazole and 2-aminobenzimidazole derivatives, different products were obtained depending on the solvent and other reaction conditions.

Results and discussion

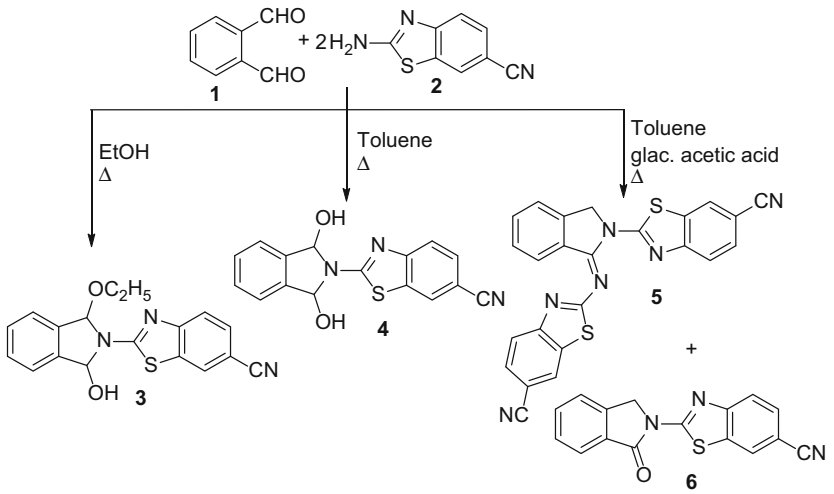
Chemistry

For the synthesis of target compounds first were prepared required precursors. 2-Amino-6-cyanobenzothiazole (**2**) was prepared from 4-aminobenzonitrile in two-step reaction over the corresponding thiocyanate according to the literature [41]. 2-Amino-5-cyanobenzimidazole (**7d**) was prepared in multistep synthesis starting from 4-aminobenzonitrile over acetylamino, nitro compound, and 4-cyano-1,2-phenylenediamine, which was cyclised using BrCN into **7d** according to the literature [42]. 2-Amino-5-nitrobenzimidazole (**7e**) and 2-amino-*N*-phenylbenzimidazole (**10d**) were prepared by cyclisation from 4-nitro-1,2-phenylenediamine and *N*-phenyl-1,2-phenylenediamine, respectively, following the same procedure.

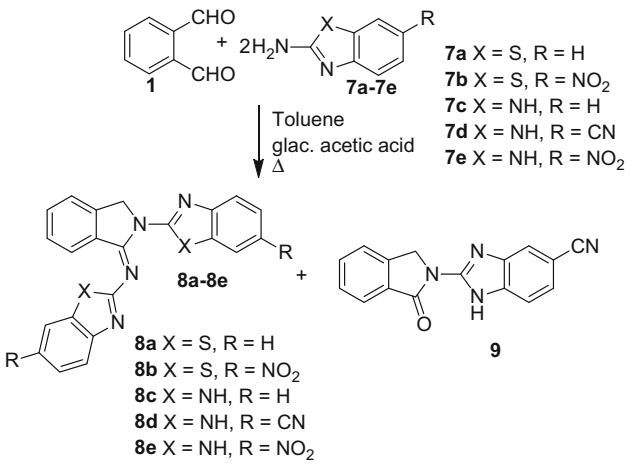
To optimize reaction conditions for the synthesis of target compounds, we used test reaction of *o*-phthalaldehyde and 2-amino-6-cyanobenzothiazole (**2**) (Scheme 1). In our previous report, we presented the synthesis of phenyl- and pyridyl-substituted 1-iminoisoindolines, where reactions were carried out in absolute ethanol in neutral or acidic conditions [40]. The reaction of *o*-phthalaldehyde with two equivalents of 2-amino-6-cyanobenzothiazole (**2**) in absolute ethanol after 24 h of heating gave 2-(1-ethoxy-3-hydroxyisoindolin-2-yl)benzothiazole-6-carbonitrile (**3**) in 73 % yield. In acidic conditions, the reaction product was the same. The structure of compound **3** was also confirmed by X-ray diffraction. Next, we used dry toluene as an aprotic solvent to avoid the reaction with solvent molecule. After 8 h of heating, the product 2-(1,3-dihydroxyisoindolin-2-yl)benzothiazole-6-carbonitrile (**4**) was obtained in 58 % yield. This type of compound was also observed by Takahashi et al. [38]. Finally, when the reaction was carried out in dry toluene in acidic conditions (glacial acetic acid), the target compound 1-imino-substituted-2-*N*-substituted isoindoline **5** was obtained in the mixture with *N*-substituted isoindolin-1-one **6**. The compounds were separated by column chromatography in 35 and 9 % yield, respectively. It seems that, because of lower nucleophilicity of the amino group of 2-amino-6-cyanobenzothiazole, the reaction was successful solely in acidic conditions.

Using the optimized reaction conditions, other target compounds were prepared (Scheme 2). Unsubstituted 2-aminobenzothiazole **7a**, and nitro-substituted 2-aminobenzothiazole **7b** and 2-aminobenzimidazole **7e** in the reaction with *o*-phthalaldehyde gave corresponding 1-imino-substituted-2-*N*-substituted isoindolines **8a** in the yield of 41 %, **8b** in the yield of 28 %, and **8e** (12 %). Unsubstituted 2-aminobenzimidazole **7c** gave mixture of

Scheme 1



Scheme 2

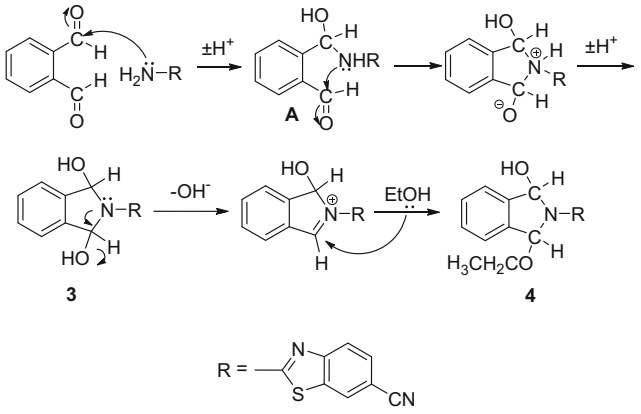


stereoisomers **8c** which were separated based on the difference in solubility. Less soluble *Z* stereoisomer was isolated from the hot DMF solution in the 42 % yield, and *E* stereoisomer was obtained by slow cooling of the solution in the 6 % yield. *Z* and *E* isomers differ in the ^{1}H NMR spectra by the position of NH protons, which are for *Z* isomer 12.48 and 12.15 ppm and for *E* isomer 12.71 and 10.82 ppm. In addition, proton chemical shifts characteristic for aromatic protons were found in the narrow area at 7.80–7.10 ppm for *Z* isomer, while for *E* isomer, two separate signals at lower magnetic field were observed which indicates difference in the surroundings of the aromatic protons. The structure of *E* isomer was also confirmed by X-ray diffraction. In the reactions with unsubstituted and nitro-substituted amines **7a**, **7b**, **7c**, and **7e,** monosubstituted isoindolinone was not detected, while cyano-substituted 2-aminobenzimidazole **7d** gave 1-imino-substituted-2-*N*-substituted isoindoline **8d** (6 %) and *N*-substituted isoindolin-1-one **9** (58 %), the same as cyano-substituted 2-aminobenzothiazole **2**.

All compound structures were confirmed by the analysis of ^{1}H and ^{13}C NMR spectra except nitro-substituted compounds **8b** and **8e** and cyano-substituted compound **8d,** where ^{13}C NMR analysis failed due to their very low solubility in DMSO. Characteristic chemical shifts for isoindoline ring were found at 5.55–4.93 ppm in ^{1}H NMR spectra as well as at 54.12–50.22 ppm in ^{13}C NMR spectra which matches CH_2 group of isoindoline (**5**, **6**, **8a**–**8e**, **9**). The presence of imino group was confirmed by the chemical shift at 157.33–155.36 ppm (**5**, **8a**, **8c**) in ^{13}C NMR spectra characteristic for quaternary carbon atom of imino group. In ^{13}C NMR spectra of isoindolinone **6** and **9** chemical shifts at 167.07 and 167.02 ppm, respectively, support the presence of carbonyl group. Compound structures were also confirmed by the analysis of IR spectra. The main attributes of IR spectra are C=N stretching band of imino group at 1667–1617 cm^{-1} for isoindolines **6** and **8a**–**8e** and C=O stretching band of carbonyl group at 1696 and 1689 cm^{-1} for isoindolinones **6** and **9**. Other bands that are characteristic for different substituents on benzothiazole and benzimidazole ring are C≡N stretching band of cyano group at 2222–2219 cm^{-1} (**5**, **6**, **8d**, **9**), NO_2 asymmetric stretching band of nitro group at 1503 and 1518 cm^{-1}, and NO_2 symmetric stretching bands of nitro group at 1324–1277 cm^{-1} (**8b**, **8e**).

Based on the isolated products **3**–**9** and our previous results [39, 40], mechanisms for the formation of isoindoline derivatives can be proposed. As we have reported, the reaction of *o*-phthalaldehyde with anilines and aminopyridines is unambiguous giving expected

Scheme 3



1-iminoisoindoline. However, when the amino group is less nucleophilic, as in the case of aminobenzothiazole and aminobenzimidazole, and the reaction is performed in neutral conditions, products **3** and **4** were formed. The mechanism for their formation is presented in Scheme 3. Our assumption is that the cyclization to isoindoline ring takes place after the formation of geminal amino alcohol **A**. That is, the elimination of water to give imine cannot take place in the absence of acid. Alcohol **3** is then converted to ether **4** in the presence of ethanol.

When the condensation reaction is carried out under acidic conditions, the elimination of water from the geminal amino alcohol to give imine is possible. The proposed mechanism of the reaction under acidic conditions is shown in Scheme 4.

Probably, the first step is the same as in the neutral conditions; the carbaldehyde reacts with an amine to give the geminal amino alcohol **A**, which could then under acid catalyzed conditions react in two ways, to form 1-iminoisoindoline **E** or isoindolinone **D**. It is presumed that there is a competition between the formation of isoindoline ring by intramolecular reaction and elimination of water to form *o*-formyl-Schiff base. When the isoindoline ring is formed before the elimination of water, the resulting intermediate ultimately gives compound **D** via water elimination and keto-enol tautomerism, as described by Takahashi et al. [38]. If the water molecule is eliminated first, the *o*-formyl-Schiff base **B** is formed which then probably cyclizes to the iminium ion (route a). The iminium is prone to a nucleophilic attack of second amine giving imino-substituted isoindoline **E** via imine-enamine tautomerism. However, the possibility that **E** is formed via intermediate *o*-disubstituted Schiff base **C** (route b) cannot be disregarded, as it has been demonstrated by Chitanda et al. [16]. They described the isolation of *o*-disubstituted Schiff base, where the substituent is sterically hindered highly bulky 2,6-diisopropylaniline.

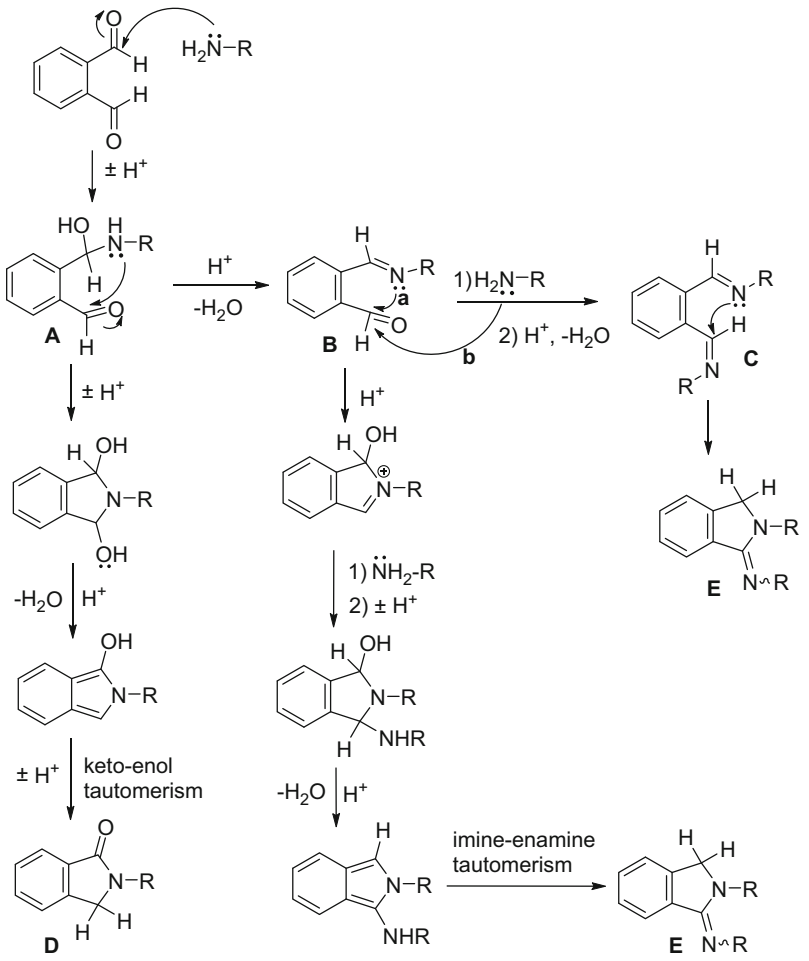
To confirm the proposed mechanistic scenarios, we conducted reactions with some other amino-substituted heterocycles, i.e., thiazole, pyrimidine, and triazole, as well as N-substituted benzimidazoles. Isolated products are given in Fig. 1.

Amino-substituted thiazole gave in the same reaction conditions expected iminoisoindoline **11a** and isoindolinone **11b**, while amino-substituted pyrimidine gave only isoindolinone **11c**. When 4-amino-1,2,4-triazole was introduced, di-Schiff base **11d** was isolated as terminal compound which could be in favour of the assumption that the *o*-disubstituted Schiff base is the intermediate in the formation of isoindoline ring. Nitrogen atom of the imino group in **11d** is probably less nucleophilic and does not react further to give isoindoline ring. Substitution on the nitrogen atom of the benzimidazole ring changes reaction pathway, probably due to a steric hindrance. Reactions were successful only in toluene in neutral conditions. In the case of *N*-phenyl-substituted 2-aminobenzimidazole, the isolated product **11e** is similar to compound **3**, where one OH group is substituted with one molecule of amine and in the case of *N*-methyl-substituted 2-aminobenzimidazole, bicyclic product **11f** was isolated. It is assumed that **10e** is more nucleophilic but sterically hindered and thus isoindoline ring is not formed. Instead, intermediate Schiff base could react in intramolecular cyclization reaction to give **11f** (Scheme 5). All compound structures were confirmed by use of ^{1}H and ^{13}C NMR spectra as well as analysis of IR spectra. Values are given in Experimental part and are in accordance with previously explained findings. Additional confirmation of the structure of compounds **11e** and **11f** was given by X-ray diffraction.

Crystal structure determination

The crystal and molecular structures of **3**, **8a**, **8c**, **11e**, and **11f** were determined by single crystal X-ray diffraction. In all five structures, the bond lengths and angles are normal [43, 44]. Compound **3** crystallises in the orthorhombic *P nma* space group with eight molecules per-unit cell. The dihedral angle between the two ring systems is somewhat larger than in **8a** and **8c** (7.1°), which is in accordance with the fact that the two rings cannot share π electron density as is the case in the other two molecules. The molecule is chiral with two asymmetrically substituted carbon atoms (C1 and C8; Fig. 2), but it crystallises as a racemate in a centrosymmetric space group. Two chiral centres are of opposite absolute configurations, so that the crystal is comprised of equal amounts of (*R*, *S*) and (*S*, *R*) stereoisomers.

Scheme 4



The molecules are interconnected into the crystal structure via O–H···N hydrogen bonds between the hydroxyl group of one molecule and the cyano group of its neighbour (O1—H1o···N3 of 2.94 Å) into chains along the crystallographic *a* axis (Fig. 3). These chains are comprised of homochiral molecules and form elongated helices about the screw axes. Each chain is further connected to two neighbouring chains of opposite chirality via (C15—H15···O2 of 3.25 Å) into layers perpendicular to the crystallographic *c* axis.

Compound **8a** was found to crystallise in the monoclinic $P\ 2_1$ space group with two molecules per-unit cell. The molecular geometry is very similar to that of **8c**, with the benzothiazole system bonded to the isoindoline nitrogen almost coplanar with the isoindoline system (dihedral angle of 1.4°), and the benzothiazole system bonded to the imino group is at a dihedral angle of ca. 66.9° to the isoindoline system (Fig. 4). As there are no strong hydrogen donors or acceptors present in the molecule, the crystal packing is governed only by weak C—H···π interactions (C21—H21···C21 of 3.75 Å and C8—H8b···C6 of 3.58 Å) which interconnect molecules into double chains along the crystallographic *c* axis (Fig. 5).

Compound **8c** (Fig. 6) crystallises as a *N*,*N*-dimethylformamide solvate in the triclinic $P\ \bar{1}$ space group with two molecules of **8c** and two of *N*,*N*-dimethylformamide per-unit cell. The benzimidazole system bonded to the isoindoline nitrogen is almost coplanar with the isoindoline system (dihedral angle of 2.9°), and the benzimidazole system bonded to the imino group is at a dihedral angle of ca. 77.3° to the isoindoline system. The imine group is of *E* configuration. The molecular geometry is stabilised by an intramolecular hydrogen bond N4—H1n···N2 of 2.70 Å between the imino nitrogen atom and a nitrogen atom of the benzimidazole bonded to the isoindoline nitrogen. This hydrogen bond, however, is bifurcated, and the same hydrogen atom is also in contact with the *N*,*N*-dimethylformamide oxygen atom (N4—H1n···O1 of 3.01 Å). The NH group of the other benzimidazole ring forms a hydrogen bond with an isoindoline bound benzimidazole system

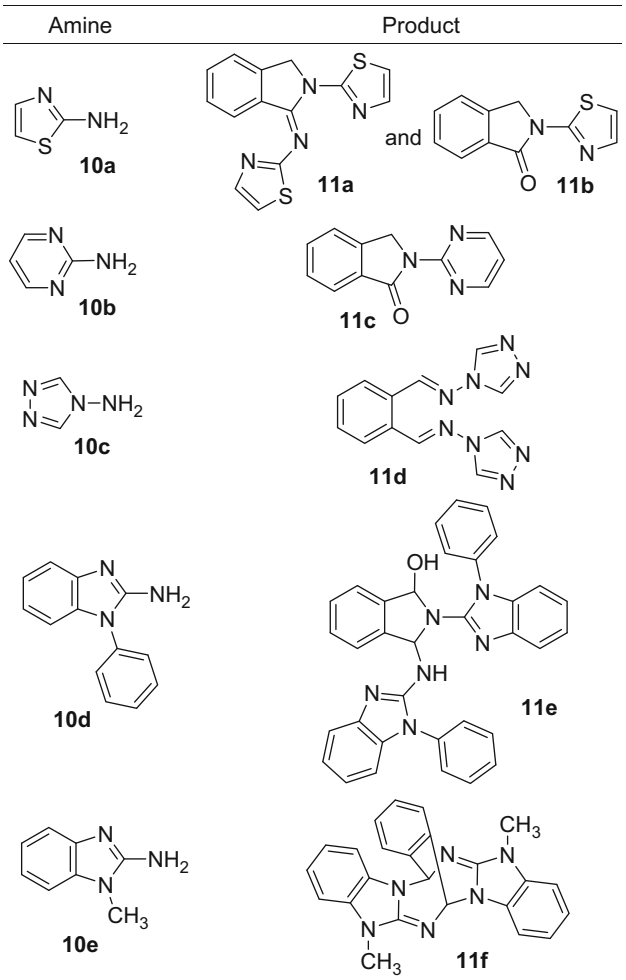


Fig. 1 Amino-substituted heterocycles and corresponding products in the reaction with *o*-phthalaldehyde

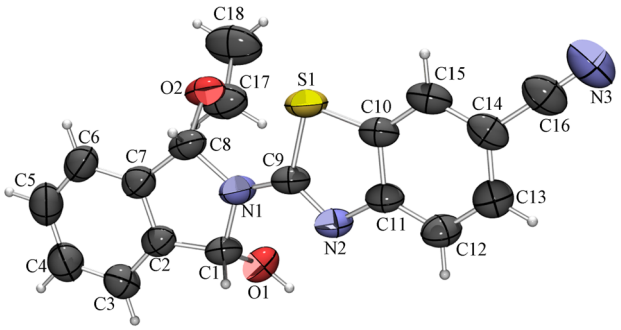


Fig. 2 Molecular structure of **3** with the atom-labelling scheme. Thermal ellipsoids are drawn at the 50 % probability level, and hydrogen atoms are presented as spheres of arbitrary small radii

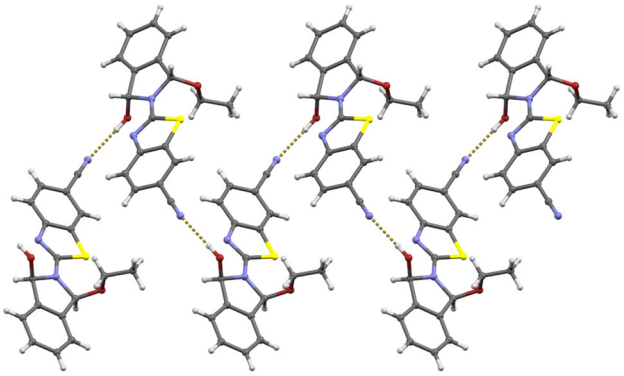
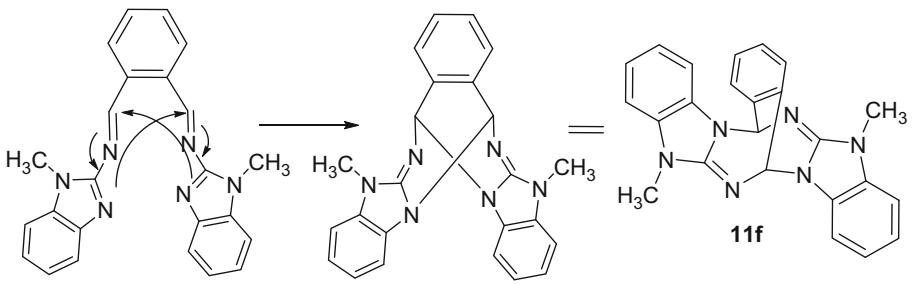


Fig. 3 Hydrogen-bonded chains connected in the crystal structure of **3**

of a neighbouring molecule (N6—H2n···N3 of 2.95 Å), forming a centrosymmetric dimer via a $R_2^2(16)$ hydrogen-bonding motif. The crystal structure, therefore, comprises centrosymmetric hydrogen-bonded complexes of two molecules of **8c** and two *N*,*N*-dimethylformamide molecules (Fig. 7a), which are further connected into chains along the crystallographic axis *c* via weak hydrogen bonds (C23—H23···N5 of 3.55 Å; Fig. 7b). The hydrogen bonding of the solvent molecule to the **8c** molecule also accounts for the observed stability of the crystals (no solvent loss was noticed), similarly as in other Schiff base—*N*,*N*-dimethylformamide solvates [45].

Scheme 5



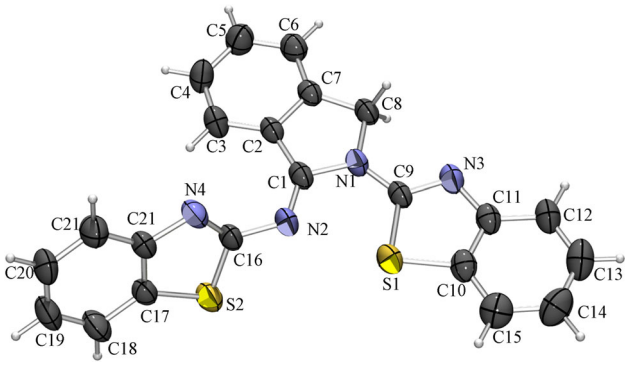


Fig. 4 Molecular structure of **8a** with the atom-labelling scheme. Thermal ellipsoids are drawn at the 50 % probability level, and hydrogen atoms are presented as spheres of arbitrary small radii

Compound **11e** (Fig. 8) crystallises in the monoclinic *P* $2_1/c$ space group with four molecules per-unit cell. The molecule comprises two *N*-phenylbenzimidazole systems of which one is bonded to the isoindoline nitrogen and the other through an amine group. The dihedral angle between the benzimidazole system bonded to the isoindoline nitrogen and the isoindoline system is larger than in **3** (14.82°), and the benzimidazole system bonded to the amino group is at a dihedral angle of ca. 76.64° to the isoindoline system. The molecular geometry is stabilised by an intramolecular hydrogen bond O1—H1o···N3 of 2.80 Å between the hydroxyl group and a nitrogen atom of the benzimidazole bonded to the isoindoline through the amine group. There is also another intramolecular hydrogen bond, N2—H1n···N6 of 2.94 Å between the amine group and a nitrogen atom of the other benzimidazole; however, it is sterically unfavourable with the N–H–N angle of ca. 105°. The molecule is chiral with two asymmetrically substituted carbon atoms (C1 and C8; Fig. 8). While the compound crystallises in a centrosymmetric space group with equivalent amounts of two enantiomers, the stereoisomers present [(*R*, *R*) and (*S*, *S*)] correspond to those found in **3**, with hydrogen atoms on the one side of the isoindoline ring plane, and the hydroxyl group and the other substituent (ethoxy group in **3**, 2-amino-*N*-phenylbenzimidazole in **11e**) on the other. This seems to imply that the hydroxyl group bonded on the atom C1 of the isoindoline controls the chirality on the C8 atom, probably by hydrogen bonding with the incoming nucleophile and thus directing it to the same side of the ring plane. As both the strong hydrogen bond donors of the molecule are employed in intramolecular bonding, the crystal packing is governed only by weak interactions, most notably C—H···N (C34—H34···N6 of 3.53 Å) and C—H···π interactions (C8—H8···C24 of 3.60 Å, C17—H17···C15 of 3.42 Å, and C19—H19···C23 of 3.55 Å) which interconnect the molecules into undulating layers perpendicular to the crystallographic *a* axis. The layers are further connected into a 3D structure by C—H···O interactions (C11—H11···O1 of 3.35 Å).

Compound **11f** (Fig. 9) crystallises in the triclinic *C* 2/*c* space group with four molecules per-unit cell. The molecule possesses *C*2 symmetry that is positioned on the crystallographic twofold axis. Two benzimidazole systems have bonded to the central ring derived from *o*-phthalaldehyde forming a central bicyclic system with C9 carbon atoms bonded to the *o*-phthalaldehyde phenylene (C10), and also bind to a benzimidazole nitrogen (N3) of one benzimidazole system and an imine nitrogen (N1) which connects it to the other benzimidazole system. This renders

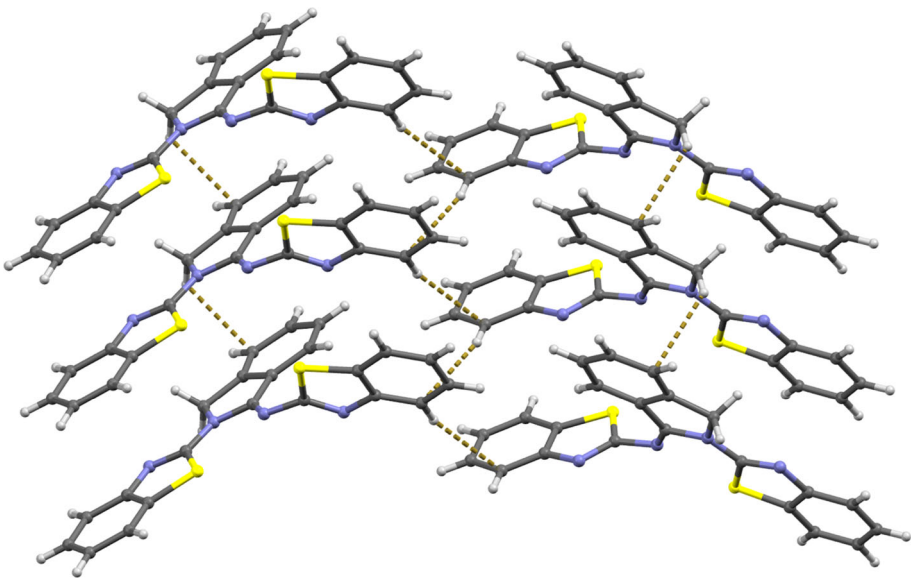


Fig. 5 Double chains connected by C—H···π interactions in the crystal structure of **8a**

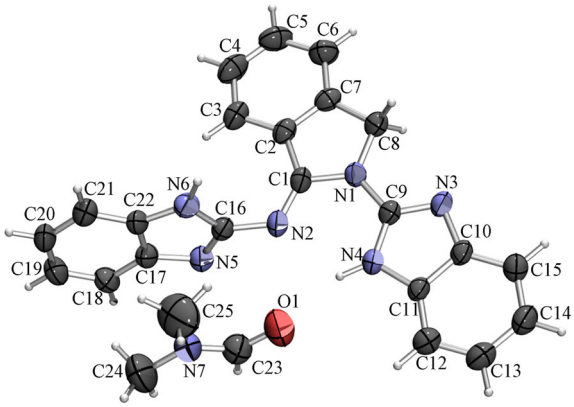


Fig. 6 Molecular structure of **8c** - *N*,*N*-dimethylformamide solvate with the atom-labelling scheme. Thermal ellipsoids are drawn at the 50 % probability level, and hydrogen atoms are presented as spheres of arbitrary small radii

C9 unsymmetrical with both C9 atoms in the molecule of the same chirality, and **11f** crystallises as a racemic mixture of (*R*, *R*) and (*S*, *S*) stereoisomers. The general shape of the molecule is a threefoil with two planar benzimidazole blades and the third phthalaldehyde one. The mean planes of the benzimidazole systems are at a dihedral angle of ca. 66.4° to one another and 57.4° to the mean plane of the *o*-phthalaldehyde phenylene ring. In lieu of strong hydrogen bond donors or acceptors, the crystal packing is governed only by weak C—H···π interactions between the *o*-phthalaldehyde phenylene hydrogen and the imine groups of the neighbouring molecule (C12—H12···N3 of 3.59 Å and C12—H12···N3 of 3.58 Å) which interconnect molecules into chains along the crystallographic *b* axis.

Conclusion

In this paper, we presented synthesis and mechanistic studies of new benzothiazolyl-substituted isoidolines **3**, **4**, **5**, **6**, **8a**, and **8b** and benzimidazolyl-substituted isoindolines **8c**–**8e**, **9**, **11e**, and **11f** in the reaction of *o*-phthalaldehyde and substituted 2-aminobenzothiazoles and 2-aminobenzimidazoles. To obtain 1-imino-substituted isoindoline derivatives, reaction conditions were optimized in the test reaction of *o*-phthalaldehyde with 2-amino-6-cyanobenzothiazole in different solvents (ethanol or toluene, and neutral or acidic conditions). The proposed reaction mechanisms in ethanol and toluene in neutral conditions include the attack of one molecule of amine on aldehyde group of *o*-phthalaldehyde to give geminal amino alcohol followed by cyclization to form isoindoline ring (compounds **3** and **4**). In acidic conditions, the elimination of water from the geminal amino alcohol is possible which leads to the attack of second molecule of amine followed by intramolecular reaction to form 1-imino-substituted-2-*N*-substituted isoindoline (**5**, **8a**–**8e**, **11a**) or intramolecular reaction followed by the elimination of water to form 2-*N*-substituted-isoindolin-1-one (**6**, **9**, **11b**, **11c**). Thiazole, pyrimidine, and triazole heterocycles were also introduced to support proposed mechanisms (**11a**–**11c**). The proposed structures of **3**, **8a**, **8c**, **11e**, and **11f** were also confirmed by single crystal X-ray diffraction. The molecular structures of **8a** and **8c** are very similar with an approximately coplanar isoindoline-benzothiazole (i.e., isoindoline-benzimidazole) system with an *E*-imino-benzothiazole (i.e., *E*-imino-benzimidazole) substituent. Chiral molecules **3**, **11e**, and **11f** were found to crystallise as racemic mixture of (*R*, *S*) and (*S*, *R*) stereoisomers for **3** and (*R*, *R*) and (*S*, *S*) stereoisomers for **11e** and **11f**.

Experimental

Melting points were determined on a Kofler hot stage microscope. IR spectra were recorded on a Bruker Vertex 70 spectrophotometer with diamond crystal. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV300 or Bruker AV600 spectrophotometers at 300 or 600 MHz (^{1}H NMR spectra) and 75 or 150 MHz (^{13}C NMR spectra). All NMR

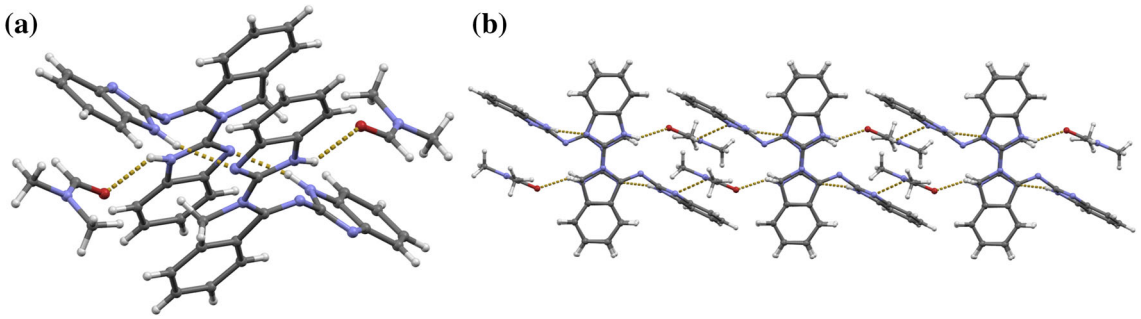


Fig. 7 Crystal structure of **8c**—*N*,*N*-dimethylformamide solvate: **a** a hydrogen-bonded centrosymmetric complex; **b** chain formed from centrosymmetric complex by C—H···N hydrogen bonding

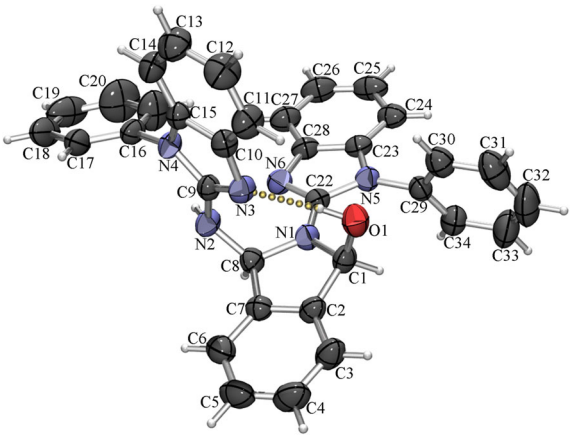


Fig. 8 Molecular structure of **11e** with the atom-labelling scheme. Thermal ellipsoids are drawn at the 50 % probability level, and hydrogen atoms are presented as spheres of arbitrary small radii

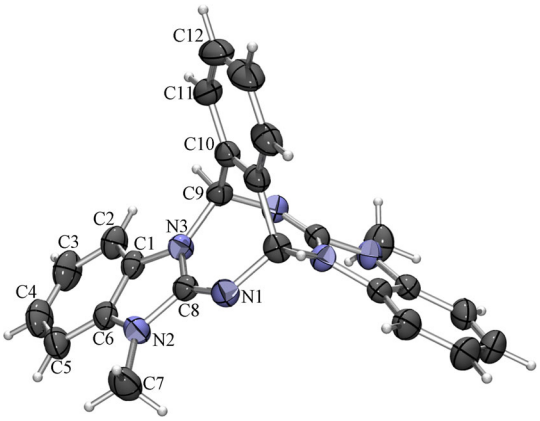


Fig. 9 Molecular structure of **11f** with the atom-labelling scheme. Thermal ellipsoids are drawn at the 50 % probability level, and hydrogen atoms are presented as spheres of arbitrary small radii

spectra were measured in DMSO-d_6 solutions using TMS as an internal standard. Chemical shifts are reported in ppm (δ) relative to TMS. Mass spectra were recorded on an Agilent 1200 series LC/6410 QQQ instrument. Elemental analysis for carbon, hydrogen, and nitrogen was performed on a Perkin-Elmer 2400 Series II CHNS analyzer, and their results were found to be in good agreement with the calculated values. All compounds were routinely checked by thin layer chromatography (TLC) using precoated Merck silica gel 60F-254 plates, and the spots were detected under UV light (254 nm). Column chromatography (CC) was performed using silica gel (0.063–0.2 mm) Fluka; glass column was slurry-packed under gravity.

2-(1-Ethoxy-3-hydroxyisoindolin-2-yl)benzothiazole-6-carbonitrile (**3**, $C_{18}H_{15}N_3O_2S$)

A solution of 0.670 g *o*-phthalaldehyde (**1**, 5.0 mmol) and 1.750 g 2-amino-6-cyanobenzothiazole (**2**, 10.0 mmol) in 50 cm^3 absolute ethanol was refluxed for 24 h. After cooling, the resulting product was filtered off and dried under vacuum to obtain 1.231 g (73 %) of yellow crystalline product. m.p.: 188–190 °C; ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): $\delta = 8.45$ (s, 1H, H_{arom}), 7.74 (s, 2H, H_{arom}), 7.55 (s, 1H, H_{arom}), 7.52 (s, 3H, H_{arom}), 7.13 (s, 1H, H_{isoind}), 6.39 (s, 1H, H_{isoind}), 6.35 (s, 1H, OH), 3.53 (q, $J = 7.1$ Hz, 1H, CH_2), 3.26 (q, $J = 7.1$ Hz, 1H, CH_2), 1.08 (t, $J = 7.0$ Hz, 3H, CH_3) ppm; ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): $\delta = 167.88$, 155.26, 140.41, 136.12, 132.09, 130.26, 130.23, 129.91, 126.59, 124.45, 124.14, 120.14, 119.91, 103.83, 90.94, 85.25, 59.31, 15.69 ppm; IR (diamond): $\bar{\nu} = 3415$ (O–H st), 2231 (C≡N), 1607, 1552, 1515 cm^{-1}; MS (ESI): $m/z = 328.1$ ($[M + 1]^+$).

2-(1,3-Dihydroxyisoindolin-2-yl)benzothiazole-6-carbonitrile (**4**, $C_{16}H_{11}N_3O_2S$)

A solution of 0.175 g *o*-phthalaldehyde (**1**, 1.3 mmol) and 0.456 g 2-amino-6-cyanobenzothiazole (**2**, 2.6 mmol) in 30 cm^3 absolute toluene was refluxed for 8 h. After cooling, the resulting product was filtered off and recrystallised from methanol to obtain 0.235 g (58 %) of yellow powder. m.p.: 151–153 °C; ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): $\delta = 8.44$ (s, 1H, H_{arom}), 8.18 (d, $J = 1.4$ Hz, 1H, H_{arom}), 8.02 (s, 1H, H_{arom}), 7.73 (s, 1H, H_{arom}), 7.61 (dd, $J_1 = 8.3$ Hz, $J_2 = 1.6$ Hz, 1H, H_{isoind}), 7.52 (s, 1H, H_{arom}), 7.51 (s, 2H, H_{arom}), 7.42 (d, $J = 8.4$ Hz, 1H, H_{isoind}), 6.69 (d, $J = 8.9$ Hz, 1H, OH), 6.29 (d, $J = 8.9$ Hz, 1H, OH) ppm; ^{13}C NMR (150 MHz, DMSO-d_6, 25 °C): $\delta = 170.51$, 156.95, 139.70, 132.24, 130.10, 129.77, 126.44, 125.71, 124.18, 124.15, 120.10, 119.87, 118.34, 102.55, 85.56, 85.53 ppm; IR (diamond): $\bar{\nu} = 3353$ (O–H st), 3305, 3059, 2222 (C≡N), 1647, 1605, 1512 cm^{-1}; MS (ESI): $m/z = 310.1$ ($[M + 1]^+$).

2-[1-[(6-Cyanobenzothiazol-2-yl)imino]isoindolin-2-yl]benzothiazole-6-carbonitrile (**5**, $C_{24}H_{12}N_6S_2$) *and 2-(1-oxoisoindolin-2-yl)benzothiazole-6-carbonitrile* (**6**, $C_{16}H_9N_3OS$)

To a solution of 0.123 g *o*-phthalaldehyde (**1**, 0.9 mmol) and 0.320 g 2-amino-6-cyanobenzothiazole (**2**, 1.8 mmol) in 20 cm^3, absolute toluene glacial acetic acid was added and the reaction mixture was refluxed for 8 h. After cooling, the reaction mixture was evaporated to dryness and resulting mixture was purified by column chromatography using dichloromethane/methanol as eluent (gradient elution from 50:1 to 10:1).

5: 0.139 g (35 %) of yellow powder; m.p.: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6, 25 °C): $\delta = 8.66$ (s, 1H, H_{arom}), 8.62 (s, 1H, H_{arom}), 8.02 (d, $J = 8.5$ Hz, 1H, H_{arom}), 7.99 (d, $J = 8.0$ Hz, 1H, H_{arom}), 7.90 (d, $J = 8.0$ Hz, 2H, H_{arom}), 7.82 (s, 1H, H_{arom}), 7.79 (s, 1H, H_{arom}), 7.53 (d, $J = 7.7$ Hz, 1H, H_{arom}), 7.43 (s, 1H,

H_{arom}), 5.54 (s, 2H, H_{isoind}) ppm; ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): $\delta = 169.71$, 160.18, 155.36, 151.51, 142.29, 141.30, 135.18, 133.70, 133.40, 128.37, 127.71, 127.10, 126.82, 126.00 (2C), 124.18 (2C), 122.10, 121.58, 118.95, 118.86, 106.18, 105.77, 53.91 ppm; IR (diamond): $\bar{\nu} = 2221$ (C≡N), 1667 (C=N), 1605, 1505 cm^{-1}; MS (ESI): $m/z = 449.1$ ($[M + 1]^+$).

6: 0.023 g (9 %) of pale yellow powder; m.p.: >300 °C; ^1H NMR (600 MHz, DMSO-d_6, 25 °C): $\delta = 8.63$ (s, 1H, H_{arom}), 7.98 (d, $J = 8.4$ Hz, 1H, H_{arom}), 7.95 (d, $J = 7.6$ Hz, 1H, H_{arom}), 7.88 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.4$ Hz, 1H, H_{arom}), 7.83-7.78 (m, 2H, H_{arom}), 7.63 (t, $J = 7.2$ Hz, 1H, H_{arom}), 5.31 (s, 2H, H_{isoind}) ppm; ^{13}C NMR (150 MHz, DMSO-d_6, 25 °C): $\delta = 167.07$, 160.29, 151.61, 142.31, 134.15, 132.52, 129.84, 129.58, 128.56, 127.18, 124.15, 124.07, 121.50, 119.08, 105.64, 51.01 ppm; IR (diamond): $\bar{\nu} = 2222$ (C≡N), 1696 (C=O), 1660, 1508 cm^{-1}; MS (ESI): $m/z = 292.1$ ($[M + 1]^+$).

General method for the synthesis of compounds 8a–8e, 9, and 11a–11d

A solution of *o*-phthalaldehyde (**1**) and corresponding amines in molar ration 1:2 in absolute toluene was prepared, and glacial acetic acid was added. After refluxing for 24 h, the resulting product was filtered off and recrystallised from the corresponding solvent or purified by column chromatography using dichloromethane/methanol as eluent (gradient elution from 50:1 to 10:1).

N-[2-(Benzothiazol-2-yl)isoindolin-1-ylidene]benzothiazol-2-amine (**8a**, $C_{22}H_{14}N_4S_2$)

From 0.45 g *o*-phthalaldehyde (**1**, 3.3 mmol) and 1.00 g 2-aminobenzothiazole (**7a**, 6.6 mmol), after recrystallisation from ethanol/toluene 0.545 g (41 %) of yellow crystalline product was obtained. m.p.: 257–259 °C; ^1H NMR (300 MHz, DMSO-d_6, 25 °C): $\delta = 8.07$ (d, $J = 7.7$ Hz, 1H, H_{arom}), 8.03 (d, $J = 7.8$ Hz, 1H, H_{arom}), 7.91–7.79 (m, 3H, H_{arom}), 7.72 (t, $J = 7.2$ Hz, 1H, H_{arom}), 7.54–7.47 (m, 2H, H_{arom}), 7.45–7.33 (m, 4H, H_{arom}), 5.51 (s, 2H, H_{isoind}) ppm; ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): $\delta = 167.65$, 157.18, 155.28, 151.95, 148.93, 142.56, 134.83, 133.71, 133.00, 128.67, 128.53, 126.86, 126.74, 126.10, 124.71, 124.53, 124.24, 122.47, 122.43, 121.91, 121.29, 54.12 ppm; IR (diamond): $\bar{\nu} = 3054$, 1665 (C=N), 1591 cm^{-1}; MS (ESI): $m/z = 399.2$ ($[M + 1]^+$).

6-Nitro-N-[2-(6-nitrobenzothiazol-2-yl)isoindolin-1-ylidene]benzothiazol-2-amine (**8b**, $C_{22}H_{12}N_6O_4S_2$)

From 0.67 g *o*-phthalaldehyde (**1**, 5.0 mmol) and 1.95 g 2-amino-6-nitrobenzothiazole (**7b**, 10.0 mmol) after recrystallisation from DMF 0.680 g (28 %) of green powder was obtained. m.p.: >300 °C; ^1H NMR (300 MHz, DMSO-d_6, 25 °C): $\delta = 9.12$ (dd, $J_1 = 8.7$ Hz, $J_2 = 2.4$ Hz, 2H, H_{arom}), 8.35 (t, $J = 2.7$ Hz, 1H, H_{arom}), 8.32 (t, $J = 2.7$ Hz, 1H, H_{arom}), 8.04 (d, $J = 5.6$ Hz, 1H, H_{arom}), 8.01 (d, $J = 5.6$ Hz, 1H, H_{arom}), 7.83 (d, $J = 7.5$ Hz, 1H, H_{arom}), 7.76 (t, $J = 7.4$ Hz, 1H, H_{arom}), 7.55 (d, $J = 8.0$ Hz, 1H, H_{arom}), 7.43 (t, $J = 7.3$ Hz, 1H, H_{arom}), 5.55 (s, 2H, H_{isoind}) ppm; ^{13}C NMR (75 MHz, DMSO-d_6, 80 °C): not soluble enough; IR (diamond): $\bar{\nu} = 1659$ (C=N), 1503 (NO_2 st as), 1323 (NO_2 st sy), 1283 (NO_2 st sy) cm^{-1}; MS (ESI): $m/z = 489.1$ ($[M + 1]^+$).

N-[2-(1H-Benzimidazol-2-yl)isoindolin-1-ylidene]-1H-benzimidazol-2-amine (**8c**, $C_{22}H_{16}N_6$)

From 0.50 g *o*-phthalaldehyde (**1**, 3.7 mmol) and 1.00 g 2-aminobenzimidazole (**7c**, 7.5 mmol) after recrystallisation from toluene two isomers were isolated. From the hot solution, less soluble isomer *Z* was obtained, and after cooling, isomer *E* was obtained.

(*Z*)-Isomer: 0.571 g (42 %) of yellow-green powder; m.p.: 244–247 °C; ^1H NMR (300 MHz, DMSO-d_6, 25 °C): $\delta = 12.48$ (bs, 1H, NH), 12.16 (bs, 1H, NH), 7.75 (d, $J = 7.6$ Hz, 1H, H_{arom}), 7.65 (t, $J = 7.3$ Hz, 1H, H_{arom}), 7.58 (s, 2H, H_{arom}), 7.48 (s, 2H, H_{arom}), 7.39–7.31 (m, 2H, H_{arom}), 7.18–7.11 (m, 4H, H_{arom}) 5.35 (s, 2H, H_{isoind}) ppm; ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): $\delta = 157.33$, 154.23, 147.31, 142.19 (2C), 141.18, 133.50, 133.02, 129.48 (2C), 128.40, 126.04, 124.39, 121.99, 121.60, 121.42 (4C), 117.59, 112.23, 52.45 ppm; IR (diamond): $\bar{\nu} = 3432$, 1646 (C=N), 1589 cm^{-1}; MS (ESI): $m/z = 365.2$ ($[M + 1]^+$).

(*E*)-Isomer: 0.084 g (6 %) of orange crystalline product; m.p.: 229–231 °C; ^1H NMR (300 MHz, DMSO-d_6, 25 °C): $\delta = 12.71$ (s, 1H, NH), 10.82 (s, 1H, NH), 8.47 (t, $J = 4.6$ Hz, 1H, H_{arom}), 8.33 (d, $J = 7.2$ Hz, 1H, H_{arom}), 7.80 (s, 1H, H_{arom}), 7.72 (dd, $J_1 = 7.7$ Hz, $J_2 = 1.9$ Hz, 2H, H_{arom}), 7.67 (dd, $J_1 = 4.1$ Hz, $J_2 = 1.5$ Hz, 1H, H_{arom}), 7.63 (dd, $J_1 = 5.9$ Hz, $J_2 = 1.9$ Hz, 1H, H_{arom}), 7.60 (d, $J = 4.8$ Hz, 1H, H_{arom}), 7.33–7.24 (m, 4H, H_{arom}), 4.93 (s, 2H, H_{isoind}) ppm; ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): $\delta = 163.65$, 156.23, 145.12, 143.84, 141.92, 141.49, 134.38, 132.86, 132.19, 131.70, 128.38, 124.31, 123.84, 123.77, 122.65, 122.48, 122.21, 118.60, 117.51, 114.15, 112.49, 51.05 ppm; IR (diamond): $\bar{\nu} = 3418$, 3356, 1617 (C=N), 1547 cm^{-1}; MS (ESI): $m/z = 365.2$ ($[M + 1]^+$).

2-[1-[(6-Cyano-1H-benzimidazol-2-yl)imino]isoindolin-2-yl]-1H-benzimidazole-6-carbonitrile (**8d**, $C_{24}H_{14}N_8$) *and 2-(1-oxoisoindolin-2-yl)-1H-benzimidazole-6-carbonitrile* (**9**, $C_{16}H_{10}N_4O$)

From 0.123 g *o*-phthalaldehyde (**1**, 0.9 mmol) and 0.320 g 2-amino-5-cyanobenzimidazole (**7d**, 1.8 mmol) after column chromatography two compounds were obtained.

8d: 0.022 g (6 %) of yellow powder; m.p.: 266–269 °C; ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ = 13.08 (s, 1H, NH), 13.01 (s, 1H, NH), 8.56 (s, 1H, H_{arom}), 8.41–8.34 (m, 1H, H_{arom}), 8.28–8.25 (m, 1H, H_{arom}), 7.95 (s, 1H, H_{arom}), 7.91 (s, 1H, H_{arom}), 7.75 (s, 1H, H_{arom}), 7.73–7.71 (m, 1H, H_{arom}), 7.69 (s, 1H, H_{arom}), 7.67–7.65 (m, 2H, H_{arom}), 4.93 (s, 2H, H_{isoind}) ppm; ^{13}C NMR (75 MHz, DMSO-d_6, 80 °C): not soluble enough; IR (diamond): $\bar{\nu}$ = 2924, 2851, 2222 (C≡N), 1659 (C=N), 1582 cm^{-1}; MS (ESI): *m/z* = 415.1 ([M + 1]$^+$).

9: 0.143 g (58 %) of ivory powder; m.p.: >300 °C; ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ = 12.80 (d, 1H, J = 15.2 Hz, NH), 8.02 (s, 1H, H_{arom}), 7.92 (d, J = 6.5 Hz, 1H, H_{arom}), 7.77 (s, 2H, H_{arom}), 7.75–7.66 (m, 1H, H_{arom}), 7.64–7.58 (m, 1H, H_{arom}), 7.55 (d, J = 8.2 Hz, 1H, H_{arom}), 5.18 (s, 2H, H_{isoind}) ppm; ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ = 167.42, 149.13, 148.43, 142.76, 140.88, 137.28, 134.10, 129.06, 125.94, 124.53, 122.09, 120.66, 118.70, 113.41, 104.05, 50.22 ppm; IR (diamond): $\bar{\nu}$ = 3300, 2219 (C≡N), 1689 (C=O), 1626, 1538 cm^{-1}; MS (ESI): *m/z* = 275.1 ([M + 1]$^+$).

6-Nitro-N-[2-(6-nitro-1H-benzimidazol-2-yl)isoindolin-1-ylidene]-1H-benzimidazol-2-amine (**8e**, $C_{22}H_{14}N_8O_4$)
From 0.14 g *o*-phthalaldehyde (**1**, 1.0 mmol) and 0.35 g 2-amino-5-nitrobenzimidazole (**7e**, 2.0 mmol) after column chromatography 0.236 g (52 %) of yellow powder was obtained. m.p.: >300 °C; ^{1}H NMR (600 MHz, DMSO-d_6, 25 °C): δ = 13.17 (bs, 2H, NH), 8.64 (d, J = 16.7 Hz, 1H, H_{arom}), 8.35 (d, J = 1.9 Hz, 1H, H_{arom}), 8.25 (t, J = 9.4 Hz, 1H, H_{arom}), 8.20 (bs, 1H, H_{arom}), 7.95 (s, 1H, H_{arom}), 7.83 (s, 1H, H_{arom}), 7.78–7.74 (m, 2H, H_{arom}), 7.73–7.68 (m, 2H, H_{arom}), 4.97 (s, 2H, H_{isoind}) ppm; ^{13}C NMR (75 MHz, DMSO-d_6, 80 °C): not soluble enough; IR (diamond): $\bar{\nu}$ = 3199, 2896, 1633 (C=N), 1570, 1518 (NO_2 st as), 1324 (NO_2 st sy), 1277 (NO_2 st sy) cm^{-1}; MS (ESI): *m/z* = 455.2 ([M + 1]$^+$).

N-[2-(Thiazol-2-yl)isoindolin-1-ylidene]thiazol-2-amine (**11a**, $C_{14}H_{10}N_4S_2$) *and 2-(thiazol-2-yl)isoindolin-1-one* (**11b**, $C_{11}H_8N_2OS$)
From 0.4 g *o*-phthalaldehyde (**1**, 3.0 mmol) and 0.5 g 2-aminothiazole (**10a**, 6.0 mmol) after column chromatography two compounds were obtained.

11a: 0.370 g (50 %) of yellow powder; m.p.: 205–208 °C; ^{1}H NMR (600 MHz, DMSO-d_6, 25 °C): δ = 7.75 (d, J = 7.7 Hz, 1H, H_{arom}), 7.66 (td, J_1 = 7.6 Hz, J_2 = 0.9 Hz, 1H, H_{arom}), 7.62 (d, J = 3.5 Hz, 1H, H_{arom}), 7.58 (d, J = 3.7 Hz, 1H, H_{arom}), 7.48 (d, J = 3.7 Hz, 1H, H_{arom}), 7.39 (t, J = 7.5 Hz, 1H, H_{arom}), 7.37 (d, J = 3.5 Hz, 1H, H_{arom}), 7.33 (d, J = 8.0 Hz, 1H, H_{arom}), 5.34 (s, 2H, H_{isoind}) ppm; ^{13}C NMR (150 MHz, DMSO-d_6, 25 °C): δ = 168.77, 157.06, 153.93, 141.61, 140.05, 137.94, 132.55, 128.29, 127.81, 125.46, 124.05, 117.04, 114.95, 53.03 ppm; IR (diamond): $\bar{\nu}$ = 1643 (C=N), 1498, 1472 cm^{-1}; MS (ESI): *m/z* = 299.1 ([M + 1]$^+$).

11b: 0.170 g (31 %) of pink powder; m.p.: 190–193 °C; ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ = 7.88 (d, J = 7.6 Hz, 1H, H_{arom}), 7.77-7.73 (m, 2H, H_{arom}), 7.64–7.55 (m, 2H, H_{arom}), 7.39 (d, J = 3.5 Hz, 1H, H_{arom}), 5.18 (s, 2H, H_{isoind}) ppm; ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ = 166.27, 157.46, 142.29, 138.31, 133.78, 130.81, 128.99, 124.49, 124.08, 114.79, 51.07 ppm; IR (diamond): $\bar{\nu}$ = 3106, 1705 (C=O), 1506 cm^{-1}; MS (ESI): *m/z* = 217.1 ([M + 1]$^+$).

2-(Pyrimidin-2-yl)-isoindolin-1-one (**11c**, $C_{12}H_9N_3O$)
From 0.200 g *o*-phthalaldehyde (**1**, 1.6 mmol) and 0.300 g 2-aminopyrimidine (**10b**, 3.2 mmol) after column chromatography 0.060 g (18 %) of white powder was obtained. m.p.: 180–185 °C; ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ = 8.79 (d, J = 4.8 Hz, 2H, H_{arom}), 7.83 (d, J = 7.6 Hz, 1H, H_{arom}), 7.75–7.68 (m, 2H, H_{arom}), 7.58–7.53 (m, 1H, H_{arom}), 7.29 (t, J = 4.8 Hz, 1H, H_{arom}), 5.11 (s, 2H, H_{isoind}) ppm; ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ = 165.90, 158.88 (2C), 157.83, 141.82, 133.46, 132.52, 128.73, 124.22, 124.18, 117.53, 50.66 ppm; IR (diamond): $\bar{\nu}$ = 3040, 2942, 1714 (C=O), 1564 cm^{-1}; MS (ESI): *m/z* = 212.1 ([M + 1]$^+$).

N,N'-Bis(1,2,4-triazol-4-yl)-phthalimine (**11d**, $C_{12}H_{10}N_8$)
From 0.400 g *o*-phthalaldehyde (**1**, 3.0 mmol) and 0.500 g 4-amino-1,2,4-triazole (**10c**, 6.0 mmol) after recrystallisation from ethanol 0.560 g (71 %) of green powder was obtained. m.p.: 252–255 °C; ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ = 9.57 (s, 2H, CH), 9.24 (s, 4H, H_{arom}), 8.12–8.07 (m, 2H, H_{arom}), 7.79–7.73 (m, 2H, H_{arom}) ppm; ^{13}C NMR (150 MHz, DMSO-d_6, 25 °C): δ = 155.65, 139.20, 132.14, 131.96, 128.13 ppm; IR (diamond): $\bar{\nu}$ = 3444, 3121, 3115, 3072, 1611 (C=N), 1584, 1503 cm^{-1}; MS (ESI): *m/z* = 267.2 ([M + 1]$^+$).

2-(N-Phenyl-1H-benzimidazol-2-yl)-3-[(N-phenyl-1H-benzimidazol-2-yl)amino]isoindolin-1-ol (**11e**, $C_{34}H_{26}N_6O$)
A solution of 0.092 g *o*-phthalaldehyde (**1**, 0.7 mmol) and 0.300 g 2-amino-*N*-phenylbenzimidazole (**10d**, 1.4 mmol) in 20 cm^3 absolute toluene was refluxed for 6 h. After cooling, the resulting product was filtered off and dried under vacuum to obtain 0.273 g (73 %) of white powder. White crystals were obtained by slow evaporation of dichloromethane solution. m.p.: 175–176 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.46 (d, J = 10.8 Hz, 1H, NH), 7.66 (d, J = 7.8 Hz, 2H, H_{arom}), 7.60–7.50 (m, 8H, H_{arom}), 7.47–7.41 (m, 2H, H_{arom}), 7.38–7.33 (m, 3H, H_{arom}), 7.20–7.13 (m, 2H, H_{arom}), 7.03–6.90 (m, 3H, H_{arom}), 6.86 (d, J = 7.1 Hz, 1H, H_{arom}), 6.77 (d,

Table 1 Crystallographic data for compounds **3, 8a**, **8c**, **11e**, and **11f**

	3	**8a**	**8c**	**11e**	**11f**
Formula	$C_{18}H_{15}N_3O_2S$	$C_{22}H_{14}N_4S_2$	$C_{22}H_{16}N_6 \cdot C_3H_7NO$	$C_{34}H_{26}N_6O$	$C_{24}H_{20}N_6$
M_r	337.39	398.49	437.5	534.61	392.46
T/K	295 (2)	295 (2)	295 (2)	295 (2)	295 (2)
Crystal system	Orthorhombic	Monoclinic	Triclinic	Monoclinic	Monoclinic
Space group	*P nma*	*P* 2_1	*P* $\bar{1}$	*P* $2_1/c$	*C* 2/*c*
a/Å	9.3795 (3)	11.8505 (7)	8.301 (3)	15.0779 (9)	15.915 (3)
b/Å	14.4178 (8)	4.3945 (4)	10.966 (4)	19.8773 (10)	7.8946 (6)
c/Å	24.6086 (13)	17.8941 (10)	12.561 (5)	9.7120 (6)	16.973 (3)
α/°	90	90	96.85 (3)	90	90
β/°	90	99.931 (6)	100.58 (3)	107.622 (7)	116.93 (3)
γ/°	90	90	99.06(3)	90	90
V/Å^3	3327.9 (3)	917.91 (11)	1097.0 (7)	2774.2 (3)	1901.2 (7)
Z	8	2	2	4	4
ρ_{calc}/g cm^{-3}	1.347	1.442	1.324	1.28	1.371
Radiation	MoK_α	MoK_α	MoK_α	MoK_α	MoK_α
μ/mm^{-1}	0.21	0.306	0.086	0.08	0.085
h, *k*, *l* range	$-11 < h < 11$	$-14 < h < 15$	$-9 < h < 9$	$-19 < h < 17$	$-20 < h < 20$
	$-18 < k < 18$	$-4 < k < 5$	$-13 < k < 13$	$-24 < k < 24$	$-10 < k < 9$
	$-31 < l < 31$	$-22 < l < 22$	$-14 < l < 14$	$-12 < l < 12$	$-21 < l < 21$
Reflections collected	26,914	7148	9882	12,082	7703
Reflections unique	3595	3210	3826	5956	2064
Reflections observed ($I > 2\ \sigma(I)$)	2220	2406	2561	2719	1306
R_1 (obs)	0.0401	0.0546	0.1081	0.0385	0.036
wR_2 (obs)	0.1251	0.1341	0.2534	0.1016	0.089
GooF	0.971	1.029	1.14	0.868	0.88

$J = 7.9$ Hz, 1H, H_{arom}), 6.51 (d, $J = 5.7$ Hz, 1H, OH), 6.43 (d, $J = 5.7$ Hz, 1H, CH), 5.81 (d, $J = 10.8$ Hz, 1H, CH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 151.09$, 150.78, 141.70, 141.28, 140.78, 137.49, 136.58, 136.27, 134.40, 134.20, 131.11, 130.39, 130.38, 129.38, 129.21, 129.09, 128.90, 127.52, 127.05, 126.66, 123.32, 122.46, 122.20, 121.99, 121.76, 120.66, 120.22, 116.57, 115.70, 109.11, 108.44, 108.19, 83.60, 72.36 ppm; IR (diamond): $\bar{\nu} = 3389$, 3058, 2912, 1597, 1555 cm^{-1}; MS (ESI): $m/z = 535.1$ ($[M + 1]^+$).

Bis-N,N′-3,3′-dimethyl-[1,2-a:1′,2′-e]-N(H)benzimidazolyl-9,10-phenylene-1,3,5,7-tetraazabicyclo[2,3]-1,5-octadiene (**11f**, $C_{24}H_{20}N_6$)

A solution of 0.092 g *o*-phthalaldehyde (**1**, 0.7 mmol) and 0.20 g 2-amino-*N*-methylbenzimidazole (**10e**, 1.4 mmol) in 20 cm^3 absolute toluene was refluxed for 6 h. After cooling, the resulting product was filtered off and dried under vacuum to obtain 0.190 g (69 %) of yellow powder. Yellow crystals were obtained by slow evaporation of dichloromethane solution. m.p.: 195–196 °C; ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): $\delta = 7.42$–7.40 (m, 1H, H_{arom}), 7.38–7.35 (m, 4H, H_{arom}), 7.07 (td, $J_1 = 7.7$ Hz, $J_2 = 1.0$ Hz, 2H, H_{arom}), 7.02 (td, $J_1 = 7.6$ Hz, $J_2 = 0.9$ Hz, 2H, H_{arom}), 6.82 (d, $J = 7.3$ Hz, 2H, H_{arom}), 6.54 (s, 2H, CH), 3.31 (s, 6H, CH_3) ppm; ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C): $\delta = 150.89$, 134.09, 132.09, 130.61, 128.51, 125.45, 120.76, 119.86, 106.39, 105.93, 69.22, 27.52 ppm; IR (diamond): $\bar{\nu} = 3435$, 2934, 1629, 1602, 1494 cm^{-1}; MS (ESI): $m/z = 393.1$ ($[M + 1]^+$).

X-ray structure determination

The crystal and molecular structures of **3**, **8a**, **8c**, **11e**, and **11f** were determined by single crystal X-ray diffraction. The diffraction data were collected at 295 K for all five crystals. Diffraction measurements were made on an Oxford Diffraction Xcalibur Kappa CCD X-ray diffractometer with graphite-monochromated MoK_α ($\lambda = 0.71073$ Å) radiation [46]. The data sets were collected using the ω scan mode over the 2θ range up to 54°. The structures were solved by the direct methods and

refined using SHELXS and SHELXL programs [47]. The structural refinement was performed on F^2 using all data. The hydrogen atoms were placed in calculated positions and treated as riding on their parent atoms [C–H = 0.93 Å and $U_{iso}(H) = 1.2\ U_{eq}(C)$; C–H = 0.97 Å and $U_{iso}(H) = 1.2\ U_{eq}(C)$]. All calculations were performed, and the drawings were prepared using WINGX crystallographic suite of programs [48]. The crystal data are listed in Table 1. Supplementary crystallographic data for this paper can be obtained from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk. CCDC 1412953–1412954 contain the supplementary crystallographic data for this paper.

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