Colorimetric detection of achiral anions and chiral carboxylates by a chiral thiourea–phthalimide dyad†

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The chiral chemosensor **1**, based on a thiourea-activated phthalimide, is available by four reaction steps from 4-nitrophthalimide. **1** detects fluoride, chloride, acetate, and dihydrogen phosphate anions by changes in UV-vis absorption. Fluoride in excess induces deprotonation whereas the other anions show only complex formation in the ground state. ^{1}H-NMR studies confirm the formation of these H-bonded complexes and the fluoride-induced receptor deprotonation in the recognition process. Moderate chiral recognition was observed for sodium D/L-lactate with K_{ass}(D)/K_{ass}(L) = 1.93.

Introduction

In chemical and biological processes, anions act as nucleophiles, bases, redox agents, or catalysts.[1] Sensors that allow the sensitive and selective recognition of these species are of current interest in analytic and mechanistic studies.[2]

A typical colorimetric sensor for anions is designed by a modular approach, attaching an appropriate chromophore either covalently or non-covalently to the receptor fragment with high affinity for the desired analyte.[3] Following the receptor–anion interaction, an appropriate signalling process must take place. The mechanisms for anion sensing signalling processes are generally photoinduced electron transfer (PET),[4–8] excited-state proton transfer.[9,10] excimer/exciplex formation,[11,12] metal-to-ligand charge transfer,[9] or modulation of efficiency of interchromophore energy transfer.[13] Thioureas are currently used for the design of neutral receptors for anions and neutral donors due to their ability to act as strong H-bond donors in sensor design and in asymmetric organocatalysis.[14,15] We have intensively investigated the phthalimide chromophore in recent years and tuned these compounds from non-fluorescent to highly fluorescent by specific substitution.[16,17] Recently, chiral photocages were developed on the phthalimide basis, both non-fluorescent[18] and fluorescent with fluorescence up/down reporter function,[19] as well as a phthalimide-urea sensor for fluoride.[20]

Concerning asymmetric guest–host interactions, it is well known that chemical properties and biological activity of chiral compounds are strongly dependent on their absolute configuration in chiral environments; enantiomers have different pharmacological properties in terms of activity, potency, toxicity, transport mechanisms or metabolic routes.[21] Thus, the development of artificial chiral receptors, which show properties of strong chiral recognition and chiral catalysis, attracts considerable attention because recognition and catalysis are fundamental characteristics of biochemical systems and could contribute to the development of pharmaceuticals, enantioselective sensors, catalysts, enzyme models, respectively, as well as other molecular devices.[22,23] With this premise, we became motivated in developing a new modular receptor–chromophore system (Fig. 1) based on thiourea–phthalimide conjugates in order to observe sensing of halide ions, acetate, dihydrogen phosphate as well as the enantioselective recognition of chiral carboxylates.

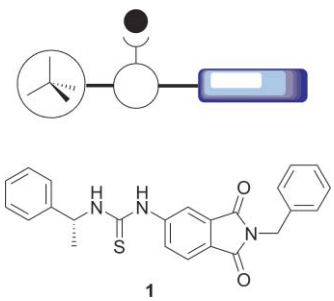

Fig. 1 Chiral phthalimide–thiourea conjugate **1**.

Herein, we report the synthesis of **1** and the investigation of its absorption properties in the presence of anions F^-, Cl^-, AcO^-, $H_2PO_4^-$, and D/L-lactate by absorption studies and by confirmation of the H-bonding interaction between **1** and anions by ^{1}H-NMR titration experiments.

Results and discussion

The synthesis of the chiral thiourea–phthalimide pair was performed from phthalimide following a five-step synthetic route shown in Scheme 1. The first step is the selective C-4 nitration which yields **3** in 58%.[24] 2-Benzyl-5-nitroisoindoline-1,3-dione (**4**) was obtained in the second step by nucleophilic substitution in 47%.[25] Catalytic hydrogenation of **4** with Pd/C in EtOH gave 5-amino-2-benzylisoindoline-1,3-dione (**5**) in 78% yield.[26] 2-Benzyl-5-isothiocyanatoisoindoline-1,3-dione **6** was obtained from **5** by reaction with thiosphosgene in 57% yield,[27] and coupling with (*S*)-1-phenylethylamine gave 1-(2-benzyl-1,3-dioxoisoindolin-5-yl)-3-(phenylethyl) thiourea (**1**) in 81% yield.

The absorption spectra of sensor **1** were measured in the absence of anions in different solvents and show two bands centered at 272 and 350 nm. These bands correspond to the two characteristic

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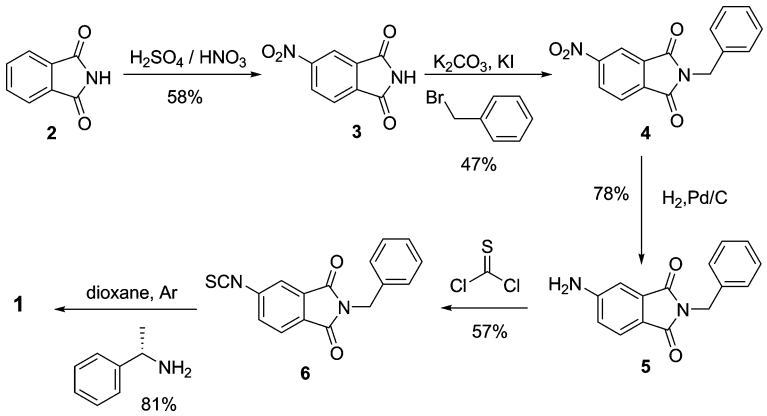
† Electronic supplementary information (ESI) available: Absorption spectra changes in the presence of chloride, iodide, DBU and complexing anions with an excess of methanol; proton NMR spectra changes of the sensor in the presence of acetate, dihydrogenphosphate, L-lactate and chloride. See DOI: 10.1039/c0pp00175a



Scheme 1 Synthesis of the thiourea–phthalimide dyad **1**.

Table 1 Absorption of sensor **1** in different solvents

Solvent[a]	π,π*/nm	n,π*/nm	log ε (n,π*)
DCM	274	351	3.87
MeCN	271	347	3.73
DMSO	276	356	3.82
MeOH	270	348	3.88

[a] DCM = dichloromethane; 10^{-5} M solutions.

electronic transitions, π,π* at higher and n,π* transition at lower energy. Table 1 lists these absorption bands of **1** in different solvents with the π,π* transition between 270 and 276 nm and the n,π* transition between 347 and 356 nm. The magnitude of the 350 nm transition also confirm the n,π* configuration. No significant changes were observed with increasing solvent polarity and also the protic solvent methanol does not significantly change the absorption behavior. Sensor **1** shows zero fluorescence even under basic conditions in protic solvents, an unusual property when considering other compounds with the thiourea group not directly connected to the chromophore.[28]

The degree and selectivity of anion recognition was studied by absorption spectra. The sensor solution was titrated with the different anions F^-, Cl^-, Br^-, I^-, AcO^- and $H_2PO_4^-$, each applied as tetrabutylammonium salts (TBA^+X^-) in acetonitrile. The less strongly binding anions sulfate and nitrate were not investigated. The water content of these solution was approx. 1% which did not disturb the association analysis. The spectra in the presence of an additional equivalent of water (with respect to the sensor concentration) did not lead to a change in the absorption spectra.

Consecutive titration with fluoride affects the ground state and shifts the absorption at 347 nm bathochromic due to anion recognition. Furthermore, two isosbestic points appeared at 286 and 367 nm and a new absorption band at 434 nm. These changes in absorption behaviour confirm the formation of a new species after recognition of F^- by sensor **1**. Fig. 2 shows the UV spectra during titration with F^- in acetonitrile solution of the sensor, the inset shows the 433 nm absorption change / concentration (A_0 = absorbance without added anion; C_A/C_H = anion *versus* host concentration) correlation for this specific recognition.

This curve can be interpreted as the superposition of two processes, complex formation and subsequent deprotonation. The

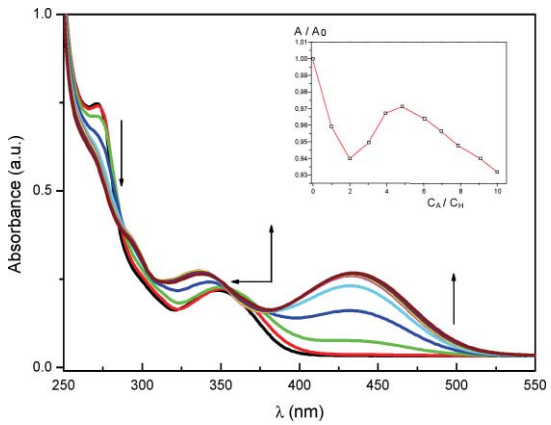


Fig. 2 Absorption spectra of **1** (3.3×10^{-5} M) in the presence of increasing amounts of fluoride (0.033 → 0.3 mM) in acetonitrile. Inset: changes in the absorption intensity at 433 nm upon addition of fluoride (non-line-fitted curve).

absorption data were used to calculate the association constant as applied[14] and described by Fabbrizzi and coworkers.[29] These consecutive equilibria in solution can be described involving the neutral receptor LH and the anion X^-:

$$LH + X^- \rightleftharpoons [LH \cdots X]^- \quad (1)$$

$$[LH \cdots X]^- + X^- \rightleftharpoons L^- + [HX_2]^- \quad (2)$$

The first equilibrium (eqn (1)) results in a more or less stable hydrogen-bonded complex for all investigated anions. The second equilibrium (eqn (2)) is related to both the intrinsic acidity of LH and the stability of $[HX_2]^-$ where LH corresponds to the sensor and X to the anion. Our results suggest that complex formation can be ruled out as the only recognition mechanism for fluoride. Taken into consideration the literature results,[29] the possible mechanism for sensor system **1** could be related to a deprotonation reaction of the NH group of the thiourea (receptor part) to F^-. The potential deprotonated species are shown in Fig. 3.

Taking into account the two extreme early and late absorption change regions corresponding to association and deprotonation, data evaluation resulted in two equilibrium constants: 6.7×10^5 for eqn (1) and 3.0×10^4 for eqn (2) (Table 2).

Table 2 Association constants of sensor **1** with the different anions and enantioselectivites (K_{ass}(D)/K_{ass}(L) for lactate)[a]

	F^- (×10⁴)	Cl^- (×10³)	AcO^- (×10³)	$H_2PO_4^-$ (×10³)	D-lact. (×10³)	L-lact (×10³)	D/L
K_{ass} (eqn (1))	67.7 ± 8.6	1.37 ± 0.82	21.79 ± 5.26	7.48 ± 2.11	4.03 ± 0.76	2.07 ± 0.58	1.93
K_{ass} (eqn (2))	3.0 ± 0.43						

[a] 3.3×10^{-5} M in **1** in CH_3CN.

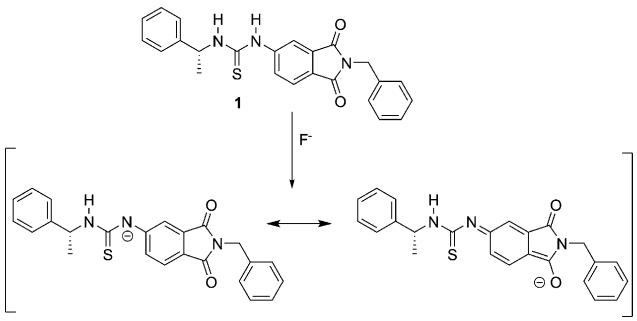


Fig. 3 Resonance structure of the sensor **1** after deprotonation.

To confirm the second deprotonation process of **1**, ^{1}H NMR titration experiments were performed in DMSO-d_6. The thiourea protons appear at 8.36 (H^2) and 9.35 (H^1) ppm (Fig. 4). In the presence of increasing equivalents of F^-, the H^1 signal disappeared and the H^2 signal was gradually shifted to higher fields with progressively reduced intensity. The deprotonation of H^1 did also affect the proton signals H_a, H_b and H_c: urea anion formation led to a highfield shift of all of these three aromatic proton signals.

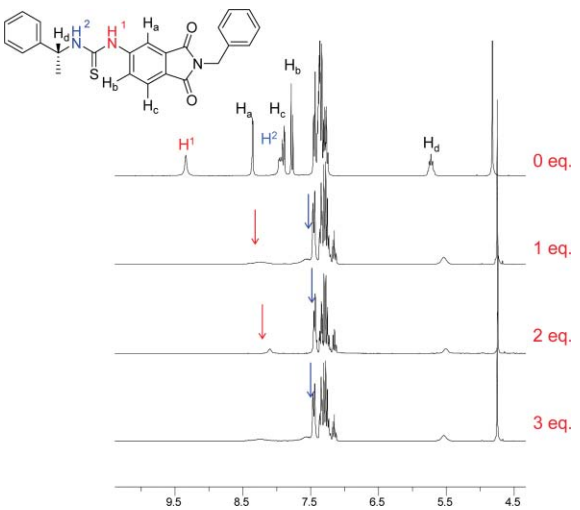


Fig. 4 Changes in ^{1}H NMR (300 MHz) spectra of **1** in DMSO upon addition of fluoride.

Other anions such as chloride, acetate, and dihydrogen phosphate were also recognized by the sensor **1**. In the absorption spectra, one isosbestic point at 353 nm appeared with increasing concentration of acetate and the nπ* transition at 347 nm is weakly red-shifted by 19 nm. Fig. 5 shows the absorption spectra following titration with acetate.

The absorption shift indicates that the ground state of sensor **1** is affected, *i.e.* these changes in the absorption spectra are the consequence of complex formation or deprotonation process of the thiourea protons (Fig. 6). In this case it was possible to calculate the association constant from the absorption intensity/concentration plot by a non-linear least-squares method,[30] the inset in Fig. 5 shows the corresponding plot (Table 2).

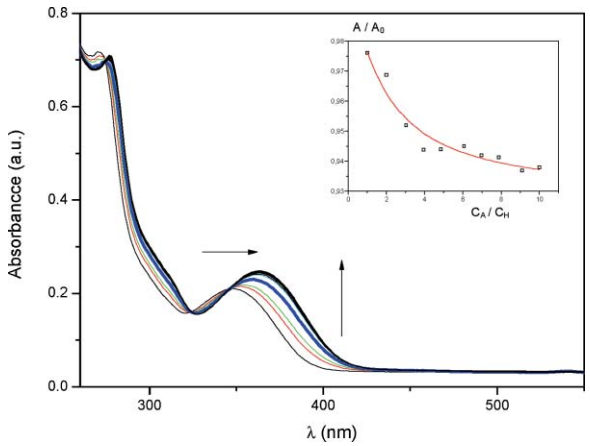


Fig. 5 Absorption spectra of **1** (3.3×10^{-5} M) in the presence of increasing amounts of AcO^- (0.033 → 0.3 mM) in acetonitrile. Inset: changes in the absorption intensity at 380 nm upon addition of acetate.

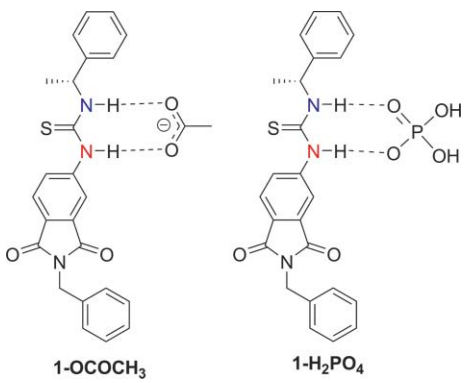


Fig. 6 Association complexes between sensor **1** and the anions AcO^- and $H_2PO_4^-$.

With increasing amounts of $H_2PO_4^-$, in the absorption spectra of **1** an isosbestic point appeared at 323 nm and the band at 347 nm is weakly red-shifted by 13 nm. The absorption spectra of **1** with large amounts of Cl^- are shown in the ESI.† The spectra of **1** showed an isosbestic point at 321 nm and an increasing band at 350 nm.

The results of the titration process with acetate and dihydrogen phosphate and the other anions are shown in Fig. 7. The absorption spectra thus obtained allow the assumption that a

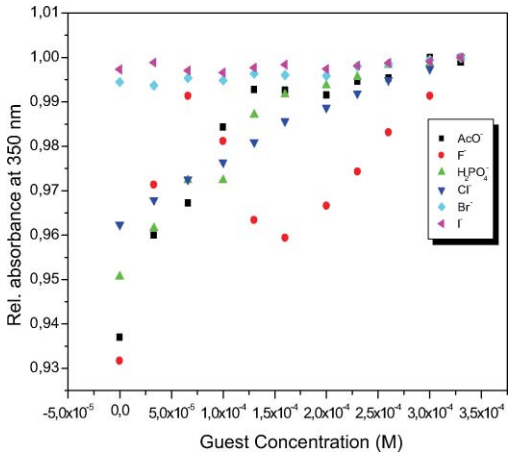


Fig. 7 Changes in the absorption of **1** at 350 nm upon titration of F^-, Cl^-, Br^-, I^-, AcO^- and $H_2PO_4^-$.

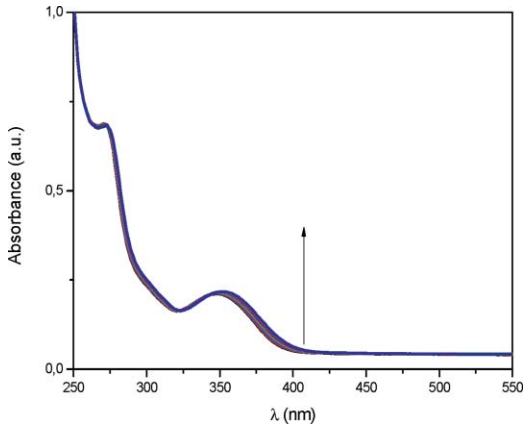


Fig. 8 Absorption spectra of **1** (3.3×10^{-5} M) in the presence of increasing amounts of L-lactate (0.033 → 0.3 mM) in acetonitrile.

charge transfer complex (CT) is primarily formed with each anion. To confirm these processes, NMR titration experiments were performed and compared with the distinct deprotonation process induced by a non-nucleophilic base (DBU, see ESI). The perturbation and partial reversibility of the process was demonstrated by addition of a protic solvent like methanol or ethanol, respectively (see ESI).

For bromide and iodide, no changes in absorption lines or intensities of **1** were observed. The slopes corresponding to Br^- and I^- addition are nearly identical. The slope for the recognition of Cl^-, AcO^- and $H_2PO_4^-$, respectively, increases gradually upon rising concentration (Fig. 7). Fluoride, as already discussed, displays a special behavior, in that the absorption spectra change is highly non-linear and points to two processes that are highly different in their equilibrium constants. These changes can be associated with the deprotonation of H^1 and the hydrogen bonding with H^2.

A comparison of the behaviour of AcO^- with F^- shows that the complex formed with AcO^- is more stable than the F^- complex. The small fluoride ion interacts with H^1 to release HF that in presence of F^- forms HF_2^-. The reason for this is the relatively low stability of the intermediate complex $[^1H \cdots F]^-$ in comparison to the stability of HF_2^-. The sensors studied by Fabbrizzi *et al.* presented the same behavior as sensor **1** in the presence of F^-.[14] For all complexes, the association constants K_{ass} were calculated by using the equation published by Qing *et al.*[30]

Chiral recognition experiments were also carried out. The absorption spectra of sensor **1** in the presence of D- and L-lactate did not show significant changes (see ESI). Fig. 8 shows the absorption spectra of **1** in the presence of L-lactate. Only a weak increase of the absorption band at 373 nm was observed. This can be interpreted again as complex formation in the ground state. The analogous behaviour was obtained for D-lactate.

Fig. 9 shows the plot of the absorption changes of **1** in the presence of D- and L-lactate. The difference between both anions can be observed in the plot especially at lower concentrations of the chiral anions.

For these complexes, the association constants K_{ass} (Table 2) were calculated by using the following equation and coefficient optimization:[30,31]

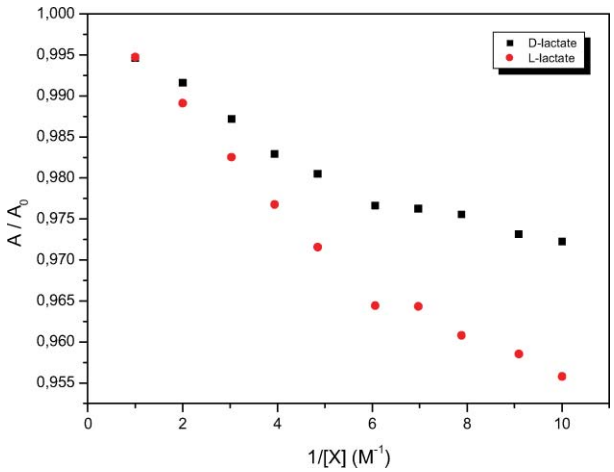


Fig. 9 Changes in the absorption of **1** at 373 nm upon addition of D- and L-lactate.

$$A/A_0 = 1 + \frac{A_{lim}/A_0 - 1}{2}\left[1 + \frac{C_A}{C_H} + \frac{1}{K_a C_H} - \sqrt{\left(1 + \frac{C_A}{C_H} + \frac{1}{K_a C_H}\right)^2 - 4\frac{C_A}{C_H}}\right]$$

A_0 is the absorption intensity of the host in the absence of anions, A_{lim} is the absorption intensity reaching a limit by adding excessive anions, C_A is the concentration of anions added. C_H is the concentration of the host molecule and A is the absorption intensity of the complex. By allowing $1/K_a C_H$ to be varied, the K_a values can be obtained by non-linear least-squares analysis of A/A_0 *vs.* C_A/C_H.

From the two association constants for D- and L-lactate, an enantioselectivity coefficient of 1.93 results, which corresponds to moderate chiral differentiation between lactate enantiomers.

In summary, a new sensor for F^-, Cl^-, AcO^- and $H_2PO_4^-$ is described. F^- recognition involves two consecutive association/deprotonation processes and the recognition of Cl^-, AcO^- and $H_2PO_4^-$ shows formation of CT complexes. Sensor **1** exhibits a moderate chiral discrimination between D- and L-lactate.

Conclusion

In summary, the acidity of the NH protons of sensor **1** gives rise to the different interactions between sensor and anions. The recognition of these anions through hydrogen bonding and deprotonation were observed by absorption spectra and ^{1}H NMR. The sensor showed efficient recognition of $AcO^- > H_2PO_4^- > Cl^-$ through hydrogen bonding and for F^- as a combination of association and deprotonation of the receptor. The sensor **1** can be used as a basic model for a chiral absorption chemosensor for chiral carboxylic acids.

Experimental

Materials

The starting materials thiophosgene, benzylbromide and phthalimide, as well as (*S*)-phenylethylamine were commercially available and used without further purification. Spectroscopic grade acetonitrile (MeCN), dimethylsulfoxide (DMSO), methanol (MeOH) and dichloromethane (DCM) were used as solvents. Commercial TBA salt solutions were used.

^{1}H NMR. The spectra were recorded on Bruker AC 300 and Bruker AV 600 spectrometers (300/600 MHz). Chemical shifts are reported as δ in ppm and the coupling constant, *J*, in Hz. In all spectra solvent peaks were used as internal standard. Solvent used are DMSO-d_6 (δ = 2.49 ppm) and CD_3CN (δ = 1.94 ppm). Splitting patterns are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quintet; m, multiplet. **^{13}C NMR**. The spectra were recorded either on a Bruker AC 300 spectrometer instrument operating at 75 MHz or on a Bruker AV 600 spectrometer instrument operating at 126 MHz. **Absorption spectroscopy**. Absorption spectra were recorded using Perkin-Elmer Lambda 35 UV/vis spectrometer. The samples were placed into quartz cells of 1 cm path length. Compound concentrations were fixed as indicated.

Synthesis of the chemosensor 1

5-Nitroisoindoline-1,3-dione (3)[24]. At 15 °C, 10 g (68.0 mmol) of phthalimide (**2**) was added in ten portions over a 15 min interval to 62.5 mL of a mixture of concentrated sulfuric acid and 100% nitric acid (4 : 1 v / v) under vigorous stirring. The temperature was raised slowly to 35 °C and held for 45 min whereby the solution turned yellow. The reaction mixture was subsequently cooled to 0 °C, slowly poured into 250 g of ice at such a rate that the temperature was kept below 15 °C. The precipitate was collected by vacuum filtration and washed with cold water. Product **3** was recrystallized from EtOH to give colorless crystals in 58% yield. m.p. 194–195 °C, ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.07 (d, 1H, J = 8.2, CH_{ar}), 8.44 (d, 1H, J = 1.9, CH_{ar}), 8.61 (dd, 1H, J_1 = 8.2, J_2 = 2.0, CH_{ar}), 11.38 (s, 1H, NH).

2-Benzyl-5-nitroisoindoline-1,3-dione (4)[25]. In a 100 mL round flask 2.00 g (10.4 mmol) of 4-nitrophthalamide (**3**), 0.90 g (6.51 mmol) of anhydrous potassium carbonate and 0.20 g potassium iodide were placed. Then 12.4 mL benzylbromide and 20 mL of dry DMF were added. The mixture was heated at 140 °C for 1.5 h. The cooled reaction mixture was poured into 150 mL of cold water. After collecting the solid, it was washed successively with 40 mL portions of water, 2% sodium hydroxide solution, and water. The dried crude product **4** was recrystallized from EtOH (the solution was concentrated and water was added dropwise until the turbidity just disappeared) and filtered while hot: 47% yield. M.p. 164–165 °C, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.89 (s, 2H, CH_2), 7.32 (m, 3H, CH_{ar}), 7.44 (m, 2H, CH_{ar}), 8.04 (d, 1H, J = 8.1, CH_{ar}), 8.59 (dd, 1H, J_1 = 8.1, J_2 = 1.8, CH_{ar}), 8.66 (d, 1H, J = 1.7, CH_{ar}).

5-Amino-2-benzylisoindoline-1,3-dione (5)[26]. A mixture of 2.09 mmol of **4**, 5% Pd/C in 20 mL of EtOH was vigorously stirred at room temperature under a hydrogen atmosphere for 4 h. The reaction mixture was then filtered over celite and concentrated *in vacuo*. The residue was recrystallized from EtOH to give **5** in 78% yield. m.p. 126–127 °C, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.33 (s, 2H, NH_2), 4.81 (s, 2H, CH_2), 6.82 (dd, 1H, J_1 = 8.1, J_2 = 2.1, CH_{ar}), 7.03 (d, 1H, J = 2.0, CH_{ar}), 7.34 (m, 5H, CH_{ar}), 7.61 (d, 1H, J = 8.1, CH_{ar}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.3 (CH_2), 108.5 (CH_{ar}), 117.8 (CH_{ar}), 120.5 (C_{ar}), 125.1 (CH_{ar}), 127.6 ($CH_{ar} \times 2$), 128.4 (CH_{ar}), 128.5 ($CH_{ar} \times 2$), 134.9 (C_{ar}), 136.7 (C_{ar}), 152.2 (C_{ar}), 168.1 (C═O), 168.3 (C═O).

2-Benzyl-5-isothiocyanatoisoindoline-1,3-dione (6)[27]. To a stirred solution of 126 mg (0.50 mmol) of 5-amino-2-benzylisoindoline-1,3-dione (**5**) in 2 mL of CH_2Cl_2, 46.0 µL of thiophosgene (69.0 mg, 0.60 mmol) was added in one portion *via* syringe. After 10 min of stirring, 0.15 mL of Et_3N was added in one portion. The whole mixture was stirred at room temperature for additional 4 h. Next, CH_2Cl_2 (2 mL) and water (5 mL) were added to the mixture. The layers were separated, the organic layer was washed with 1 N HCl (2 × 5 mL), dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by column chromatography, R_f 0.90 (SiO_2, CH_2Cl_2), to give **6** in 57% yield. M.p. 155–156 °C, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.83 (s, 2H, CH_2), 7.34 (m, 5H, CH_{ar}), 7.47 (dd, 1H, J_1 = 7.9, J_2 = 1.8, CH_{ar}), 7.63 (d; 1H, J = 1.7, CH_{ar}), 7.82 (d; 1H; J = 7.9 Hz; CH_{ar}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.9 (CH_2), 120.5 (CH_{ar}), 124.7 (CH_{ar}), 127.9 ($CH_{ar} \times 2$), 128.6(C_{ar}), 128.7 ($CH_{ar} \times 2$), 129.6 (CH_{ar}), 130.8 (CH_{ar}), 133.9 (C_{ar}), 135.9 (C_{ar}), 137.4 (C_{ar}), 140.2 (S═C═N), 166.5 (C═O), 166.7 (C═O).

1-(2-benzyl-1,3-dioxoisoindolin-5-yl)-3-((*R*)-1-phenyl-ethyl) thiourea (1). (*S*)-1-phenylethylamine (18.3 µL, 17.3 mg, 0.143 mmol) was added into an argon filled reactor containing 42.2 mg of 2-benzyl-5-isothiocyanatoisoindoline-1,3-dione (**6**) (0.143 mmol) in dry dioxane (10 mL). The mixture was heated at 100 °C under stirring for 24 h. The solvent was evaporated and the crude product **1** was purified by column chromatography, R_f 0.42 (SiO_2, EtOAc / cyclohexane, 2 : 3), in 81% yield. M.p: 171–173 °C, ^{1}H NMR (acetone-d_6, 300 MHz) δ 1.57 (d, 3H, J = 6.9, CH_3), 4.80 (s, 2H, CH_2), 5.71 (m, 1H, CH), 7.34 (m, 10H, CH_{ar}), 7.75 (d; 1H, J = 8.1, CH_{ar}), 7.89 (dd, 1H, J_1 = 8.1, J_2 = 1.8, CH_{ar}), 7.95 (d, 1H, J = 7.7, NH), 8.36 (m, 1H, CH_{ar}), 9.35 (s, 1H, NH).^{13}C NMR (acetone-d_6, 75 MHz) δ 22.9 (CH_3), 42.9 (CH_2), 55.0 (CH), 117.9 (CH_{ar}), 125.4 (CH_{ar}), 128.0 (CH_{ar}), 128.2 (CH_{ar}), 128.9 (CH_{ar}), 129.3 ($CH_{ar} \times 2$), 129.7 ($CH_{ar} \times 2$), 130.3 ($CH_{ar} \times 2$), 130.4 ($CH_{ar} \times 2$), 134.8 ($C_{ar} \times 2$), 139.0 (C_{ar}), 145.2 (C_{ar}), 147.5 (C_{ar}), 168.1 (C═O), 168.2 (C═O), 180.9 (C═S). IR ν 3306(w), 2920 (w), 1769 (m), 1697 (s), 1614 (m), 1530 (s) cm^{-1};

$C_{24}H_{21}N_3O_2S$ (415.1354) HRMS: 415.136; calculated: C 69.37, H 5.09, N 10.11%; found: C 69.39, H 5.13, N 10.06%.

Acknowledgements

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