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Article

Access to N-thioalkenyl and N-(o-thio)aryl-Benzimidazol-2-ones by Ring Opening of Thiazolobenzimidazolium and Benzimidazobenzothiazolium Salts and C-O Bond Cleavage of an Alkoxide

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Access to *N*-thioalkenyl and *N*-(*o*-thio)aryl-Benzimidazol-2-ones by Ring Opening of Thiazolobenzimidazolium and Benzimidazobenzothiazolium Salts and C-O Bond Cleavage of an Alkoxide

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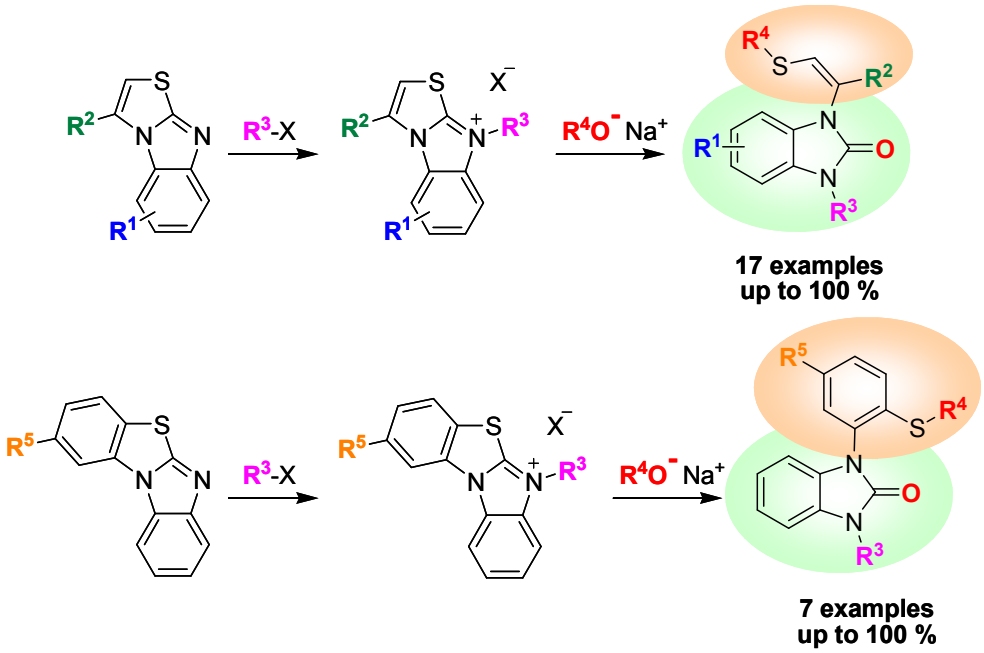
Scheme of abstract:



Abstract: We report herein the synthesis of highly functionalized 1,3-dihydro-*2H*-benzimidazol-2-ones *via* a ring opening of thiazolo[3,2-*a*]benzimidazolium or benzimidazo[2,1-*b*][1,3]benzothiazol-6-ium salts and an unusual C-O bond cleavage of an alkoxide. A large variety of benzimidazolones bearing an original *N*-thioalkenyl or *N*-(*o*-thio)aryl group was obtained in high yields. The developed chemistry provides efficient and rapid access to the privileged benzimidazol-2-one scaffold.

Introduction

Benzimidazol-2-one is a common molecular framework which belongs to privileged structures, i.e. compounds able of providing useful ligands for more than one type of receptor or enzyme target by judicious structural modifications.[1] Indeed, 1,3-dihydro-*2H*-benzimidazol-2-one derivatives exhibit a broad scope of pharmacological properties, including opioid receptor-like agonists[2] and antagonists,[3] reverse transcriptase inhibitors,[4] p38

kinase inhibitors,[5] respiratory syncytial virus fusion inhibitors[6] and progesterone receptor antagonists.[7] A survey of recent literature indicates that investigations in these fields remain an active and crucial area of research.[8] Furthermore, besides all these biological activities, this class of compounds also constitute attractive building blocks in crystal engineering[9] as well as thermoplastic[10] and conducting[11] polymers.

Conventional synthesis of benzimidazol-2-ones bearing two different substituents on each nitrogen atom requires multi-step manipulations, and three pathways can be envisioned. The first strategy involves the formation of the benzimidazole core followed by regioselective alkylation of either nitrogen atom.[7b,12] The requirement of protecting groups is mandatory in such method. Another typical approach consists in the nucleophilic displacement of 2-fluoronitrobenzenes with primary amines, subsequent reduction and cyclization using 1,1'-carbonyldiimidazole[5a,13] or triphosgene.[14] In this case, the scarce commercially availability of diversely substituted starting material represents a limitation. Finally, alternative procedures have been reported by cyclization of *o*-haloarylureas using palladium[15] or copper catalysis.[16] Although these methodologies offer certain advantages, each suffers from some drawback (*e.g.* low yield, reaction sequence not straightforward, only few described examples, harsh conditions) and generates a single functionalized nitrogen atom.

Access to new therapeutic entities depends greatly on the discovery of original and pertinent scaffolds, connected with the development of innovative synthetic reactions. In this paper, we report a straightforward synthesis of unsymmetrically *N,N'*-disubstituted 1,3-dihydro-*2H*-benzimidazol-2-ones **1** and **2** *via* ring opening of thiazolo[3,2-*a*]benzimidazolium **3** and benzimidazo[2,1-*b*][1,3]benzothiazol-6-ium **4** quaternary salts respectively (Figure 1).[17] The strategy described here allows modulation of four substituents on the benzimidazole scaffolds. Interestingly, this work represents the first example of installation of a *N*-thioalkenyl or *N*-(*o*-thio)aryl substituent on these relevant nitrogen-containing heterocycles and only two synthetic

pathways to *N*-alkenyl-benzimidazol-2-ones, simpler structures, are described in the literature.[18]

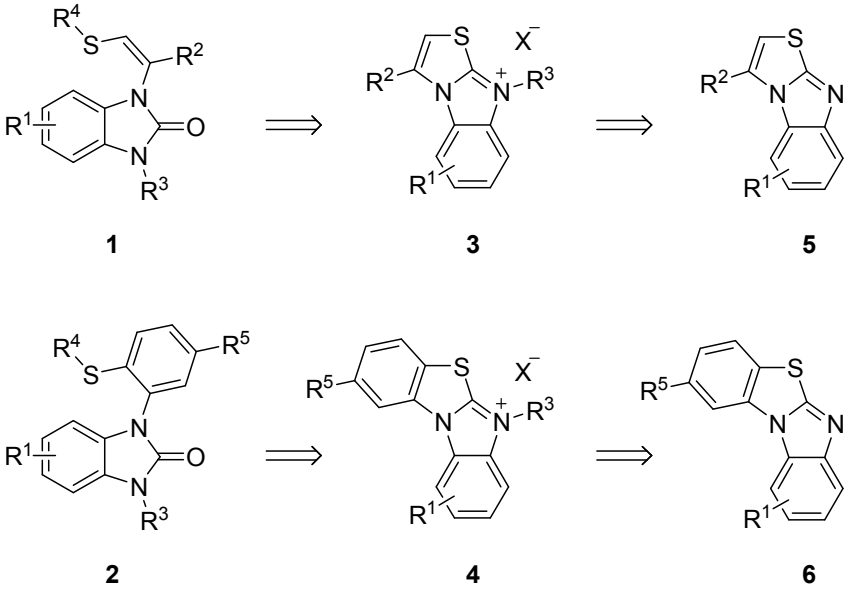


Figure 1. Synthesis of *N*-thioalkenyl and *N*-(*o*-thio)aryl benzimidazol-2-ones starting from thiazolobenzimidazole and benzo[*d*]imidazo-[2,1-*b*]benzothiazole respectively

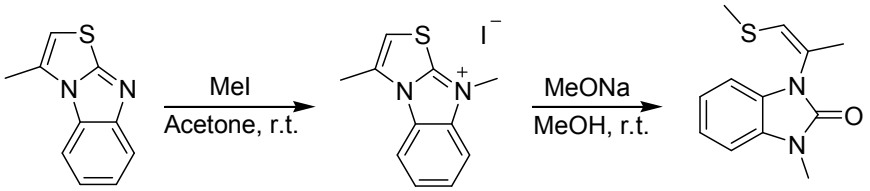
Results and Discussion

1,3-Dihydro-*2H*-benzimidazol-2-ones **1** were prepared using thiazolo[3,2-*a*]benzimidazoles **5** as starting materials. Several thiazolobenzimidazoles **5** are commercially available or can be obtained from 2-mercaptobenzimidazoles.[19] In this work, heterocycles **5** were efficiently synthesised using a one pot procedure starting from *N*-(2-aminophenyl)-thiazoline-2-thiones as we have previously reported.[20] This protocol led to a broad structural diversity: R^1 represents a hydrogen, a fluorine or a trifluoromethyl group, and R^2 can be an alkyl or an aryl substituent.[21]

With compounds **5** in hand, we first examined the sequence leading to benzimidazol-2-one **1a** (Scheme 1). The simplest thiazolobenzimidazole **5a** (R^1 = H; R^2 = Me) was easily converted

into its corresponding quaternary salt **3a** using methyl iodide in acetone. After solubilisation in methanol, this salt was reacted with sodium methoxide at room temperature and we were delighted to observe a ring opening generating the 1,3-dihydro-*2H*-benzimidazol-2-one **1a** as a white powder in 71% overall isolated yield.

Scheme 1. Synthesis of benzimidazol-2-one **1a** *via* ring opening of thiazolobenzimidazolium salt **2a**



5a **3a** (89%) **1a** (80%)

Compound **1a** is remarkable for the simplicity of the synthesis route and for the unprecedented access to (thio)vinyl substituent in benzimidazol-2-one series. The formation of **1a** emphasizes also an uncommon phenomenon: the H_3C-*O* bond of the alkoxide is cleaved to provide the oxygen of the benzimidazolone core and the *C*H_3 group bonded to the sulphur atom. It means that, in this process, the methoxide anion acts as a source of methyl group and oxygen atom.

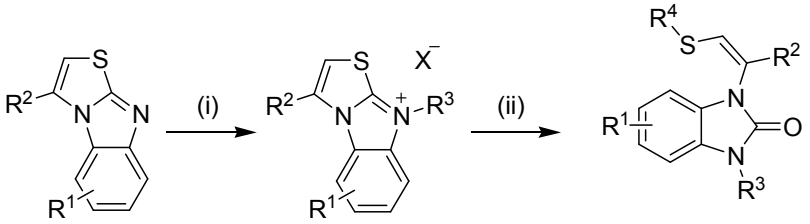
Benzimidazol-2-one **1a** was isolated as a single isomer and a NOESY experiment was carried out in order to establish the stereochemistry of C=C double bond.[21] This 2D NMR spectrum revealed that the vinylic hydrogen atom is close to those belonging to the methyl group located on the double bond. It clearly indicates that both heteroatoms are on the same side of the C=C bond, i.e. a Z configuration issuing from the thiazole moiety.

The study was then directed towards the access to a focused library of benzimidazol-2-ones **1** with the aim to extend the scope of our methodology (Table 1). Heterocycles **5** were allowed

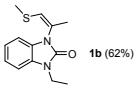
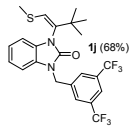
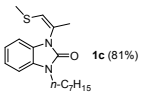
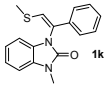
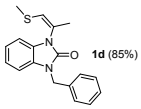
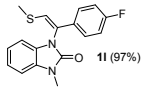
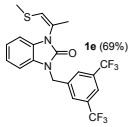
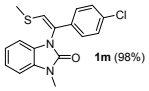
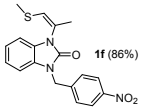
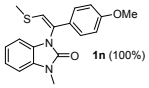
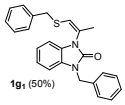
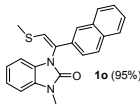
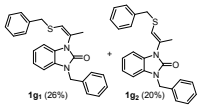
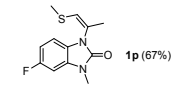
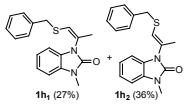
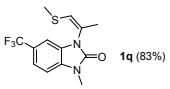
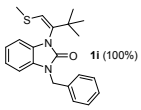
to react with a range of halogenated derivatives R^3-X (iodomethane, iodoethane, 1-iodoheptane, benzyl chloride, 3,5-bis(trifluoromethyl)benzyl chloride or 4-nitrobenzyl chloride) to furnish the corresponding *N*-alkylated salts **3** in 68-100% yield after a simple filtration.

In the presence of MeONa or BnONa, **3** underwent a ring opening and we obtained single stereomers of 1,3-dihydro-*2H*-benzimidazol-2-ones **1** (R^4 = Me) with good to excellent overall yields (Table 1, entries 1-5 and 9-17). This unprecedented sequence enabled the preparation of a large series of *N*-thioalkenyl benzimidazolones **1** with control of four substituents on the heterocyclic ring. Pure products were isolated without tedious purification since the work-up consisted in an extraction in dichloromethane sometimes followed by a quick filtration on a pad of silica. It is noteworthy that the protocol utilizes cheap chemicals and allows high atom efficiency.

Table 1. Synthesis of benzimidazol-2-ones **1** starting from thiazolobenzimidazoles **5**[a]



5 **3** **1**

Entry	**1**[b]	Entry	**1**[b]
1	 **1b** (62%)	10	 **1j** (68%)
2	 **1c** (81%)	11	 **1k** (100%)
3	 **1d** (85%)	12	 **1l** (97%)
4	 **1e** (69%)	13	 **1m** (98%)
5	 **1f** (86%)	14	 **1n** (100%)
6	 **1g**$_1$ (50%)	15	 **1o** (95%)
7	 **1g**$_1$ (26%) **1g**$_2$ (20%)	16	 **1p** (67%)
8	 **1h**$_1$ (27%) **1h**$_2$ (36%)	17	 **1q** (83%)
9	 **1i** (100%)		

[a] Reagents and conditions: (i) R^3-X, acetone (entries 1, 3, 5-8 and 11-17) or none solvent (entries 2 and 9) or acetonitrile (entries 4 and 10), reflux (entries 1-8 and 10-15) or 100°C (entry 9) or room temperature (entries 16 and 17); (ii) MeONa, MeOH, r.t. (entries 1-5 and 9-16) or BnOH/Na, r.t. (entry 6) or BnOH, NaOH, reflux (entries 7-8) or MeONa, MeOH, reflux (entry 17). [b] Overall isolated yield between brackets.

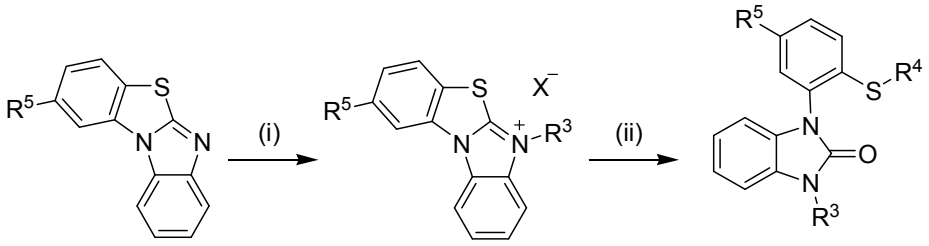
In order to confirm the cleavage of the alkoxide species, salt **3d** (R^1 = H, R^2 = Me, R^3 = Bn) were treated at room temperature by a freshly prepared solution of sodium benzylate (Table 1, entry 6). As expected, addition of BnO^- provided the anticipated *cis* benzimidazolone with subsequent transfer of the benzyl group to sulfur. This unambiguously demonstrates that the R^4 moiety and the oxygen of the carbonyl on the final heterocycle come from the same alkoxide anion. Furthermore, salts **3d** (R^1 = H, R^2 = Me, R^3 = Bn) and **3a** (R^1 = H, R^2 = Me, R^3 = Me) were allowed to react with BnOH/NaOH at reflux (Table 1, entries 7-8). Interestingly, the two geometric isomers of **1g** and **1h** have been obtained in a 45/55 (Z/E) ratio (determined by ^{1}H NMR on the crude material). We assume that the occurrence of both isomers probably resulted from isomerisation of the double bond during heating. However, they were easily separated by column chromatography so that this procedure provided access to the *trans* stereomer of benzimidazolone.

Compound **1k** was crystallised and a suitable crystal was used for X-ray diffraction.[21] The chemical structure of the isolated benzimidazol-2-ones and the stereochemistry of C=C double bond were confirmed. Some insight at the solid state can be gleaned from this analysis: the conformation adopted is characterized by a dihedral angle of 126° between the plane containing the original *N*-thioalkenyl substituent and the plane containing the heterocyclic ring. In addition, the crystal packing revealed the presence of two frozen atropisomers about N-$C_{vinylic}$ bond axis. During HPLC analysis, neither plateau nor peak separation were observed, meaning that the exchange between these atropisomeric forms is fast in solution.

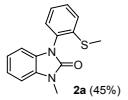
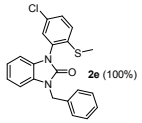
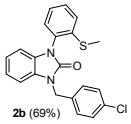
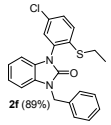
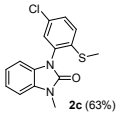
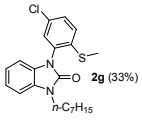
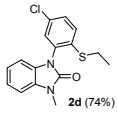
During the development of this work, novel efficient methodologies to generate benzo[d]imidazo[2,1-*b*]thiazoles **6** have been published in literature.[22] These structures are similar to thiazolobenzimidazoles **5** and this encouraged us to perform a parallel treatment in these series, i.e. synthesis of the corresponding quaternary salts **4**, followed by a ring opening

promoted by an alkoxide (Table 2). This sequence would lead to *N*-aryl benzimidazol-2-ones **2** which belong to a class of molecules possessing pharmacological activities such as heat shock protein 90 inhibitors,[23] serotonin 5-HT ligands,[24] farnesyltransferase inhibitors[13a] and maxi-K channel openers.[25]

Table 2. Synthesis of benzimidazol-2-ones **2** starting from benzo[*d*]imidazo-[2,1-*b*]benzothiazoles **6**[a]



6 **4** **2**

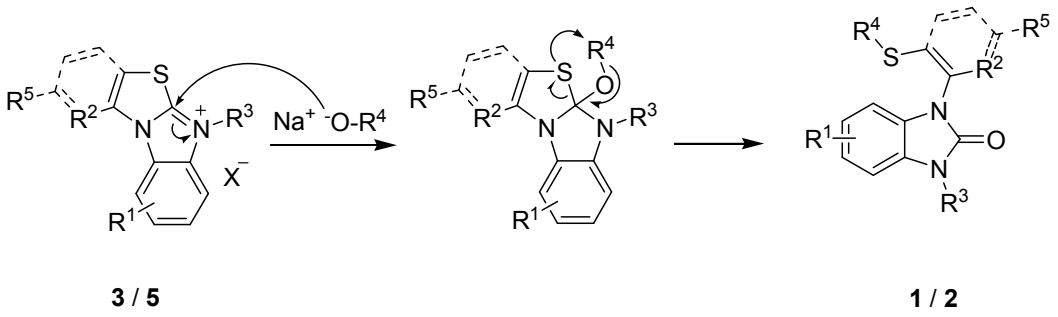
Entry	**2**[b]	Entry	**2**[b]
1	 **2a** (45%)	5	 **2e** (100%)
2	 **2b** (69%)	6	 **2f** (89%)
3	 **2c** (63%)	7	 **2g** (33%)
4	 **2d** (74%)		

[a] Reagents and conditions: (i) R^3-X, pentan-3-one (entries 1-4 and 7) or none solvent (entries 5 and 6), reflux (entries 1-4 and 7) or 90°C (entries 5 and 6); (ii) MeONa/MeOH (entries 1-3, 5 and 7) or EtOH/Na (entries 4 and 6), 40°C (entries 1, 2 and 7) or reflux (entries 3 and 5) or room temperature (entries 4 and 6). [b] Overall isolated yield between brackets.

6a (R^5 = H) and **6c** (R^5 = Cl) were directly obtained according to a reported protocol from 2-mercaptobenzimidazole which is commercially available.[22c] *N*-(*p*-chloro)benzyl **4b** (R^3 = *p*-Cl-Bn, R^5 = H), *N*-benzyl **4e** (R^3 = Bn, R^5 = Cl) and *N*-heptyl **4g** (R^3 = *n*-C_7H_{15}, R^5 = Cl) quaternary salts were then prepared using analogous procedures to that described for compounds **3**. Interestingly, the treatment of **6a** and **6c** with methyl iodide did not proceed quantitatively, even under harsh conditions (large excess of reagent; heating). TLC of the crude revealed the presence of a significant amount of starting material indicating a reversible reaction. We hypothesized that this was probably due to the lower basicity of the involved nitrogen atom and/or to the nucleophilicity of the iodine counterion which could provide a demethylation reaction.[26] To tackle this issue, methyl *p*-toluenesulfonate was chosen as alkylating agent and the desired salts **4a** (R^3 = Me, R^5 = H) and **4c** (R^3 = Me, R^5 = Cl) were isolated in 77% and 87% yield respectively after purification.

Sodium methoxide was then allowed to react with [3,1]benzimidazo[2,1-*b*][1,3]benzothiazol-6-ium **4a-c**, **4e** and **4g** (Table 2, entries 1-3, 5 and 7 respectively) leading to the corresponding *N*-aryl benzimidazolones **2** with good to excellent yields, excepting **2g** for which we were not able to optimize the purification step on column chromatography. Moreover, sodium ethoxide was tested on derivatives **4c** (Table 2, entry 4) and **4e** (Table 2, entry 6). Preliminary attempt on **4c** was carried out at 70°C and furnished a mixture of **2c** (R^3 = Me, R^4 = Me, R^5 = Cl) and **2d** (R^3 = Me, R^4 = Et, R^5 = Cl). We postulated that the formation of compound **2c** probably resulted from a demethylation of the starting quaternary salts. Consequently, the ring opening was performed at room temperature yielding the sole compound **2d**. Similar experimental conditions were used for the synthesis of **2f** which was isolated in very good yield.

Scheme 2. Possible mechanism for the ring opening



A plausible mechanism of this unprecedented ring opening is depicted in Scheme 2. In a first step, the nucleophilic alcoholate species attacks the quaternary sp^2 carbon bonded to three heteroatoms. The R^4-O bond of the alcoholate is then cleaved to provide the oxygen atom of the benzimidazolone core and R^4 bonded to the sulphur atom. Based on the observed results, scheme 2 provides a postulated mechanism as a concerted process. However, depending on the actual bond breaking, the formation of thiolate and oxonium as an intimate ion-pair can be also envisioned. Further studies are underway to trace the occurrence of disulfide moieties which would indicate a stepwise process accompanying the concerted one.

Conclusion

In summary, we have developed and exemplified a powerful sequence for accessing unprecedented *N*-thioalkenyl and *N*-(*o*-thio)aryl 1,3-dihydro-*2H*-benzimidazol-2-ones. The process involves a ring opening of a quaternary salt (thiazolo[3,2-*a*]benzimidazolium or benzimidazo[2,1-*b*][1,3]benzothiazol-6-ium) and a concomitant C-O bond cleavage of the addition product. Taking into account that the 1,3-dihydro-*2H*-benzimidazol-2-one scaffold belongs to the few privileged structures, this study opens the way to an unexplored chemical space for future biological screenings.

Experimental section

General information

Commercially reagent grade chemicals were used as received without additional purification. All reactions were followed by TLC (Kieselgel 60 F-254). TLC spots were visualized with UV light and/or by staining with potassium permanganate or phosphomolybdic acid solution followed by heating. Column chromatography was performed on silica gel (60-200 mesh). Melting points are uncorrected. Chemicals shifts in ^{1}H NMR and ^{13}C NMR spectra are reported as part per million downshift from tetramethylsilane and coupling constants are reported in hertz. When necessary, resonances were assigned using two-dimensional experiments (COSY, HMBC, HSQC). HRMS (ESI) were recorded on a TOF mass spectrometer.

Synthesis of 3-(2-aminophenyl)-1,3-thiazole-2(3*H*)-thione 7

General procedure for compounds **7k-o**: Triethylamine (20 mmol) was added dropwise to a suspension of 1,2-diaminobenzene (10 mmol) in CS_2 (23 mL). After 2 hours, the precipitate was filtered, washed with Et_2O and dried to yield quantitatively the dithiocarbamate salt. This solid was then suspended in ethanol (30 mL) and a solution of α-halogenated ketone (10 mmol; 2-bromoacetophenone for **7k**; 2-bromo-4'-fluoroacetophenone for **7l**; 2-bromo-4'-chloroacetophenone for **7m**; 2-bromo-4'-methoxyacetophenone for **7n**; 2-bromo-2'-acetonaphthone for **7o**) in ethanol (30 mL) was added dropwise at 0°C, followed by an addition of HCl 37% (3 mL) dropwise at 0°C. The mixture was then heated at reflux for 1 hour whereupon water (100 mL) was added. The mixture was then extracted with dichloromethane (3 x 100 mL) and the organic layer was washed with water (3 x 100 mL), dried on $MgSO_4$ and evaporated under reduced pressure. The desired compound was then isolated after crystallisation in ethanol.

3-(2-Aminophenyl)-4-phenyl-1,3-thiazole-2(3*H*)-thione **7k**. Yield: 86% (2.620 g); White solid; Mp = 189°C; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 5.12 (2H, br s, NH_2), 6.42-6.47 (1H, m, arom), 6.70-6.76 (2H, m, arom), 6.99-7.05 (1H, m, arom), 7.17 (1H, s, H5), 7.21-7.31 (5H, m, arom); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 110.3, 116.0, 116.2, 122.9, 128.1 (2C), 128.4 (2C), 129.0, 129.2, 129.8, 130.6, 144.5, 145.0, 188.5; HRMS *m/z* calcd $C_{15}H_{13}N_2S_2$ $[M+H]^+$: 285.0514; found: 285.0514.

3-(2-Aminophenyl)-4-(4-fluorophenyl)-1,3-thiazole-2(3*H*)-thione **7l**. Yield: 77% (2.477 g); White solid; Mp = 139°C; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 5.09 (2H, br s, NH_2), 6.44-6.49 (1H, m, arom), 6.70-6.76 (2H, m, arom), 6.77-6.81 (2H, m, arom), 7.00-7.09 (2H, m, arom+H5), 7.15-7.21 (2H, m, arom); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 109.3, 113.5, 113.8, 116.0, 116.2, 122.9, 129.2, 129.8, 129.9 (2C), 130.5, 144.4, 145.0, 159.6, 188.4; HRMS: ionization of the sample under various conditions failed.

3-(2-Aminophenyl)-4-(4-chlorophenyl)-1,3-thiazole-2(3*H*)-thione **7m**. Yield: 61% (2.730 g); White solid; Mp = 231°C; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 5.15 (2H, br s, NH_2), 6.44-6.50 (1H, m, arom), 6.72 (1H, dd, *J* = 8.2, *J* = 1.2, arom), 6.77 (1H, dd, *J* = 7.9, *J* = 1.5, arom), 7.01-7.07 (1H, m, arom), 7.22 (1H, s, H5), 7.24-7.36 (4H, m, arom); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 110.9, 116.0, 116.2, 122.5, 128.2 (2C), 129.2, 129.4, 130.0, 130.3 (2C), 133.8, 143.2, 145.0, 188.6; HRMS *m/z* calcd $C_{15}H_{12}N_2S_2Cl$ $[M+H]^+$: 319.0124; found: 319.0126.

3-(2-Aminophenyl)-4-(4-methoxyphenyl)-1,3-thiazole-2(3*H*)-thione **7n**. Yield: 75% (6.660 g); White solid; Mp = 164°C; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 3.69 (3H, s, OCH_3), 5.09 (2H, br s, NH_2), 6.43-6.50 (1H, m, arom), 6.70-6.75 (2H, m, arom), 6.77-6.82 (2H, m, arom), 7.00-7.06 (1H, m, arom), 7.07 (1H, s, H5), 7.16-7.21 (2H, m, arom); ^{13}C NMR (100 MHz,

DMSO-*d6*) δ 55.1, 109.3, 113.5 (2C), 116.0, 116.2, 122.9 (2C), 129.2, 129.8, 129.9 (2C), 144.4, 145.0, 159.6, 188.4; HRMS *m/z* calcd $C_{16}H_{15}N_2OS_2$ $[M+H]^+$: 315.0620; found: 315.0622.

3-(2-Aminophenyl)-4-(naphthalen-2-yl)-1,3-thiazole-2(3*H*)-thione **7o**. Yield: 49% (3.900 g); White solid; Mp = 163°C; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 5.20 (2H, br s, NH_2), 6.39-6.45 (1H, m, arom), 6.73 (1H, dd, *J* = 8.2, *J* = 1.2, arom), 6.79 (1H, dd, *J*= 7.8, *J* = 1.4, arom), 6.97-7.03 (1H, m, arom), 7.31 (1H, dd, *J* = 8.6, *J* = 1.7, arom), 7.31 (1H, s, H5), 7.48-7.55 (2H, m, arom), 7.76 (1H, d, *J* = 12.4, arom), 7.76-7.87 (2H, m, arom), 7.90 (1H, s, arom); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 110.8, 116.1, 116.2, 122.9, 125.5, 126.6, 127.0, 127.5 (2C), 128.1 (2C), 128.1, 129.2, 129.9, 132.2, 132.6, 144.5, 145.1, 188.6; HRMS *m/z* calcd $C_{19}H_{15}N_2S_2$ $[M+H]^+$: 335.0671; found: 335.0669.

Synthesis of [1,3]thiazolo[3,2-a]benzimidazole 5

General procedure: Compound **7** (2 mmol) was solubilised in acetone (10 mL) and methyl iodide (20 mmol) was added. After 12 hours, the solvent was removed under reduced pressure to afford quantitatively the corresponding thiazolium iodide. The residue was heated at reflux for 12-24 hours in methanol (20 mL) whereupon the solvent was removed under reduced pressure to afford quantitatively the corresponding thiazolo[3,2-*a*]benzimidazolium iodide. The crude was then treated with a saturated solution of $NaHCO_3$ (20 mL). The mixture was extracted with dichloromethane (3 x 10 mL) and the organic layer was dried on $MgSO_4$ and evaporated to give the desired compound.

3-Phenyl[1,3]thiazolo[3,2-*a*]benzimidazole **5k**. Yield: 69% (603 mg); White solid; Mp = 147°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (1H, s, H5), 7.08-7.14 (1H, m, arom), 7.23 (1H, d, *J* = 8.2, arom), 7.34-7.40 (1H, m, arom), 7.56-7.69 (5H, m, arom), 7.82 (1H, d, *J* = 8.2, arom);

^{13}C NMR (100 MHz, $CDCl_3$) δ 108.3, 112.1, 118.8, 121.2, 124.2, 129.0, 129.1 (2C), 129.2 (2C), 129.7, 130.5, 134.6, 146.7, 156.8; HRMS *m/z* calcd $C_{15}H_{11}N_2S$ $[M+H]^+$: 251.0637; found: 251.0638.

3-(4-Fluorophenyl)[1,3]thiazolo[3,2-*a*]benzimidazole **5l**. Yield: 91% (300 mg); White solid; Mp = 152°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (1H, s, H5), 7.12-7.20 (2H, m, arom), 7.27-7.34 (2H, m, arom), 7.37-7.43 (1H, m, arom), 7.63-7.69 (2H, m, arom), 7.85 (1H, d, *J* = 8.3, arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.3, 111.9, 116.5, 116.7, 118.5, 121.7, 124.7, 124.9, 129.4, 131.2, 131.3, 133.6, 145.4, 156.3, 164.1 (d, *J* = 251); HRMS *m/z* calcd $C_{15}H_{10}N_2SF$ $[M+H]^+$: 269.0543; found: 269.0543.

3-(4-Chlorophenyl)[1,3]thiazolo[3,2-*a*]benzimidazole **5m**. Yield: 86% (160 mg); White solid; Mp = 200°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (1H, s, H5), 7.16-7.25 (2H, m, arom), 7.41-7.47 (1H, m, arom), 7.58-7.65 (4H, m, arom), 7.87 (1H, d, *J* = 8.3, arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.3, 112.2, 118.1, 122.2, 125.2, 126.9, 129.0, 129.8 (2C), 130.5 (2C), 131.5, 133.7, 137.2, 156.1; HRMS *m/z* calcd $C_{15}H_{10}N_2SCl$ $[M+H]^+$: 285.0247; found: 285.0248.

3-(4-Methoxyphenyl)[1,3]thiazolo[3,2-*a*]benzimidazole **5n**. Yield: 55% (450 mg); White solid; Mp = 153°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (3H, s, OCH_3), 6.58 (1H, s, H5), 7.06-7.11 (3H, m, arom), 7.24 (1H, d, *J* = 8.2, arom), 7.32-7.37 (1H, m, arom), 7.55-7.60 (2H, m, arom), 7.80 (1H, d, *J* = 8.2, arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 107.1, 111.9, 114.6 (2C), 118.9, 120.9, 121.4, 123.9, 129.9, 130.5 (2C), 134.4, 147.4, 156.9, 161.2; HRMS *m/z* calcd $C_{16}H_{13}N_2OS$ $[M+H]^+$: 281.0743; found: 281.0743.

3-(Naphthalen-2-yl)[1,3]thiazolo[3,2-*a*]benzimidazole **5o**. Yield: 33% (300 mg); White solid; Mp = 164°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (1H, s, H5), 7.03-7.09 (1H, m, arom), 7.24 (1H, d, *J* = 8.2, arom), 7.33-7.38 (1H, m, arom), 7.59-7.67 (2H, m, arom), 7.83 (1H, dd, *J* = 8.4, *J* = 1.8, arom), 7.83 (1H, d, *J* = 8.5, arom), 7.91-8.01 (2H, m, arom), 8.05 (1H, d, *J* = 8.5, arom), 8.16 (1H, s, arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.5, 112.2, 118.8, 121.2, 124.1, 125.7, 126.4, 127.4, 127.7, 128.2, 128.5, 128.9, 129.1, 129.9, 133.1, 134.0, 134.6, 147.0, 156.9; HRMS *m/z* calcd $C_{19}H_{13}N_2S$ $[M+H]^+$: 301.0794; found: 301.0794.

Synthesis of [1,3]thiazolo[3,2-*a*]benzimidazol-9-ium 3

Experimental procedures and characterization data for compounds **3a-f** and **3p-q**: see reference 17.

9-Benzyl-3-*tert*-butyl[1,3]thiazolo[3,2-*a*]benzimidazol-9-ium chloride **3i**. A solution of 3-*tert*-butyl-thiazolo[3,2-*a*]benzimidazole **5i** (349 mg, 1.52 mmol) in benzyl chloride (2 mL) was stirred at 100°C for 24 hours. The crude was purified by column chromatography (eluent: CH_2Cl_2/MeOH 9:1) providing the desired compound (540 mg). Yield: 100%; Pale orange solid; Mp = 177°C; ^{1}H NMR (400 MHz, CD_3OD) δ 1.69 (9H, s, CH_3), 5.86 (2H, s, NCH_2), 7.36 (1H, s, H5), 7.48 (3H, s, arom), 7.61 (2H, s, arom), 7.75-7.87 (2H, m, arom), 8.18 (1H, br d, *J* = 6.1, arom), 8.44 (1H, br d, *J* = 6.2, arom); ^{13}C NMR (100 MHz, CD_3OD) δ 29.0, 34.8, 51.9, 111.7, 114.2, 118.0, 126.3, 128.5, 129.0, 130.5 (2C), 130.8 (3C), 132.5, 137.9, 147.7, 157.8; HRMS *m/z* calcd $C_{20}H_{21}N_2S^+$ $[M]^+$: 321.1420; found: 321.1415.

9-[3,5-Bis(trifluoromethyl)benzyl]-3-*tert*-butyl[1,3]thiazolo[3,2-*a*]benzimidazol-9-ium chloride **3j**. To a solution of 3-*tert*-butyl-thiazolo[3,2-*a*]benzimidazole **5i** (273 mg, 1.19 mmol) in acetonitrile (3 mL), 3,5-bis(trifluoromethyl)benzyl chloride (935 mg, 3.56 mmol)

was added and the mixture was stirred at reflux for 24 hours. The crude was purified by column chromatography (eluent: CH_2Cl_2/MeOH 9:1) providing the desired compound (395 mg). Yield: 68%; White solid; Mp = 161°C; ^{1}H NMR (400 MHz, CD_3OD) δ 1.71 (9H, s, CH_3), 6.04 (2H, s, NCH_2), 7.34 (1H, s, H5), 7.75-7.84 (2H, m, arom), 8.03-8.06 (1H, m, arom), 8.11 (1H, s, arom), 8.23 (2H, s, arom), 8.43-8.47 (1H, m, arom); ^{13}C NMR (150 MHz, CD_3OD) δ 29.0 (3C), 35.0, 50.5, 111.3, 113.9, 118.3, 124.3 (m), 124.5 (2C, q, J = 272), 126.5, 128.6, 129.4, 130.9 (2C, m), 133.7 (2C, q, J = 34), 136.6, 137.9, 148.5, 158.6; HRMS *m/z* calcd $C_{22}H_{19}N_2SF_6^+$ $[M]^+$: 457.1168; found: 457.1165.

General procedure for compounds **3k-o**: To a solution of the corresponding compound **5** (1 mmol) in acetone (3 mL), methyl iodide (10 mmol) was added and the mixture was stirred at reflux (3 hours for **3k** and **3o**; 5 hours for **3l-n**). The desired compound was then isolated by filtration.

9-Methyl-3-phenyl[1,3]thiazolo[3,2-*a*]benzimidazol-9-ium iodide **3k**. Yield: 100% (87 mg); White solid; Mp = 202°C; ^{1}H NMR (400 MHz, CD_3OD) δ 4.24 (3H, s, NCH_3), 7.35 (1H, d, J = 8.4, arom), 7.48 (1H, td, J = 8.4, J = 0.9, arom), 7.65 (1H, s, H5), 7.69-7.87 (6H, m, arom), 8.01 (1H, d, J = 8.5, arom); ^{13}C NMR (100 MHz, CD_3OD) δ 33.7, 113.8, 114.7, 114.8, 125.9, 128.4, 128.7, 130.6 (2C), 130.8, 130.9 (2C), 132.6, 137.7, 138.5, 156.9; HRMS *m/z* calcd $C_{16}H_{13}N_2S^+$ $[M]^+$: 265.0793; found: 265.0793.

3-(4-Fluorophenyl)-9-methyl[1,3]thiazolo[3,2-*a*]benzimidazol-9-ium iodide **3l**. Yield: 97% (159 mg); White solid; Mp = 264°C; ^{1}H NMR (400 MHz, CD_3OD) δ 4.11 (3H, s, NCH_3), 7.20 (1H, d, J = 8.4, arom), 7.31-7.41 (3H, m, arom), 7.53 (1H, s, H5), 7.60-7.65 (1H, m, arom), 7.73-7.79 (2H, m, arom), 7.88 (1H, d, J = 8.4, arom); ^{13}C NMR (75 MHz, CD_3OD) δ

33.6, 113.8, 113.8, 114.6, 115.2, 117.6, 117.9, 124.6, 124.6, 126.0, 128.7, 133.4, 136.7, 138.4, 156.9, 166.0 (d, J = 250.5); HRMS *m/z* calcd $C_{16}H_{12}N_2SF^+$ $[M]^+$: 283.0699; found: 283.0700.

3-(4-Chlorophenyl)-9-methyl[1,3]thiazolo[3,2-*a*]benzimidazol-9-ium iodide **3m**. Yield: 98% (73 mg); White solid; Mp = 276°C; ^{1}H NMR (400 MHz, CD_3OD) δ 4.24 (3H, s, NCH_3), 7.39 (1H, d, J = 8.5, arom), 7.53 (1H, t, J = 7.6, arom), 7.69 (1H, s, H5), 7.73-7.87 (5H, m, arom), 8.02 (1H, d, J = 8.5, arom); ^{13}C NMR (75 MHz, CD_3OD) δ 33.6, 113.8, 114.7, 115.4, 126.1, 127.0, 128.5, 130.9 (2C), 131.7, 132.5 (2C), 136.6, 138.4, 138.9, 157.0; HRMS *m/z* calcd $C_{16}H_{12}N_2SCl^+$ $[M]^+$: 299.0404; found: 299.0404.

3-(4-Methoxyphenyl)-9-methyl[1,3]thiazolo[3,2-*a*]benzimidazol-9-ium iodide **3n**. Yield: 100% (163 mg); Pale brown solid; Mp = 216°C; ^{1}H NMR (400 MHz, CD_3OD) δ 3.97 (3H, s, OCH_3), 4.22 (3H, s, NCH_3), 7.22-7.28 (2H, m, arom), 7.38 (1H, d, J = 8.5, arom), 7.46-7.52 (1H, m, arom), 7.54 (1H, s, H5), 7.71-7.77 (3H, m, arom), 8.01 (1H, d, J = 8.4, arom); ^{13}C NMR (75 MHz, CD_3OD) δ 33.6, 56.2, 113.7, 113.9, 114.7, 115.9 (2C), 120.1, 125.9, 128.4, 128.7, 132.4 (2C), 137.9, 138.4, 156.8, 163.6; HRMS *m/z* calcd $C_{17}H_{15}N_2OS^+$ $[M]^+$: 295.0899; found: 295.0900.

9-Methyl-3-(naphthalen-2-yl)[1,3]thiazolo[3,2-*a*]benzimidazol-9-ium iodide **3o**. Yield: 100% (91 mg); Pale brown solid; Mp = 193°C; ^{1}H NMR (400 MHz, CD_3OD) δ 4.25 (3H, s, NCH_3), 7.30 (1H, d, J = 8.5, arom), 7.42 (1H, t, J = 8.3, arom), 7.65-7.76 (4H, m, arom+H5), 7.85 (1H, dd, J = 8.5, J = 1.7, arom), 8.01 (1H, d, J = 8.4, arom), 8.07 (2H, t, J = 7.3, arom), 8.20 (1H, d, J = 8.5, arom), 8.38 (1H, s, arom); ^{13}C NMR (100 MHz, CD_3OD) δ 33.7, 113.8, 114.8, 115.0, 125.5, 125.9, 126.8, 128.4, 128.7, 128.7, 129.2, 129.3, 129.6, 130.4, 131.2, 134.4, 135.7, 137.8, 138.4, 157.0; HRMS *m/z* calcd $C_{20}H_{15}N_2S^+$ $[M]^+$: 315.0950; found: 315.0950.

Synthesis of benzo[*d*]imidazo-[2,1-*b*]benzothiazoles 4

General procedure for compounds **4a-c** and **4g**: To a solution of the corresponding compound **6** (1 mmol) in pentan-3-one (1-4 mL), alkylating reagent (for **4a** and **4c**: 10 mmol of methyl p-toluenesulfonate; for **4b**: 8 mmol of p-chlorobenzyl chloride; for **4g**: 12 mmol of 1-iodoheptane) was added and the mixture was stirred at reflux (for **4a**: 20 hrs; for **4b**: 24 hrs; for **4c**: overnight; for **4g**: 48 hrs). The desired compound was then isolated by filtration and washed with acetone (for **4b**: before this filtration, excess of p-chlorobenzyl chloride was removed under vacuum).

6-methyl[3,1]benzimidazo[2,1-*b*][1,3]benzothiazol-6-ium 4-methylbenzenesulfonate **4a**. Yield: 58% (2.354 g); White solid; Mp = 245-247°C; ^{1}H NMR (400 MHz, CD_3OD) δ 2.38 (3H, s, CH_3 tos), 4.25 (3H, s, NCH_3), 7.23 (2H, d, *J* = 8.0, arom), 7.70 (2H, d, *J* = 8.1, arom), 7.78 (1H, t, *J* = 7.8, arom), 7.82-7.89 (2H, m, arom), 7.94 (1H, t, *J* = 7.8, arom), 8.05-8.11 (1H, m, arom), 8.31 (1H, d, *J* = 8.2, arom), 8.61-8.68 (2H, m, arom); ^{13}C NMR (100 MHz, CD_3OD) δ 21.3, 34.0, 114.0, 114.7, 116.4, 126.7, 126.9 (2C), 127.3, 128.4, 128.5, 128.9, 129.7, 129.8 (2C), 130.2, 133.9, 137.9, 141.6, 143.6, 156.6; HRMS *m/z* calcd $C_{14}H_{11}N_2S^+$ $[M]^+$: 239.0637; found: 239.0639.

6-(4-chlorobenzyl)[3,1]benzimidazo[2,1-*b*][1,3]benzothiazol-6-ium chloride **4b**. Yield: 70% (457 mg); Pale brown solid; Mp = 240°C (decomposition); ^{1}H NMR (400 MHz, CD_3OD) δ 5.87 (2H, s, NCH_2), 7.54 (2H, d, *J* = 8.5, arom), 7.63 (2H, d, *J* = 8.4, arom), 7.71 (1H, t, *J* = 7.9, arom), 7.82-7.87 (2H, m, arom), 7.89 (1H, t, *J* = 7.9, arom), 8.10-8.16 (1H, m, arom), 8.18 (1H, d, *J* = 8.2, arom), 8.61-8.67 (2H, m, arom); ^{13}C NMR (100 MHz, CD_3OD) δ 51.3, 114.3, 114.9, 116.5, 126.5, 127.6, 128.6 (2C), 129.2, 130.1, 130.2, 130.8 (2C), 131.1, 132.7 (2C), 133.6, 137.3, 137.5, 156.0; HRMS *m/z* calcd $C_{20}H_{14}N_2SCl^+$ $[M]^+$: 349.0561; found: 349.0564.

2-chloro-6-methyl[3,1]benzimidazo[2,1-*b*][1,3]benzothiazol-6-ium 4-methylbenzenesulfonate **4c**. Yield: 87% (785 mg); White solid; Mp = 247°C (decomposition); ^{1}H NMR (400 MHz, CD_3OD) δ 2.32 (3H, s, CH_3), 4.21 (3H, s, NCH_3), 7.14 (2H, d, *J* = 8.0, arom), 7.60 (2H, d, *J* = 8.2, arom), 7.74 (1H, dd, *J* = 8.8, *J* = 1.8, arom), 7.78-7.86 (2H, m, arom), 8.01-8.06 (1H, m, arom), 8.24 (1H, d, *J* = 8.8, arom), 8.59-8.64 (1H, m, arom), 8.67 (1H, d, *J* = 1.8); ^{13}C NMR (100 MHz, CD_3OD) δ 21.3, 33.9, 114.0, 114.8, 116.7, 126.8 (2C), 127.5, 127.8, 128.3, 128.6, 128.7, 128.8, 129.7 (2C), 134.7, 136.3, 137.8, 141.5, 143.6, 157.4; HRMS *m/z* calcd $C_{14}H_{10}N_2SCl^+$ $[M]^+$: 273.0248; found: 273.0251.

2-chloro-6-heptyl[3,1]benzimidazo[2,1-*b*][1,3]benzothiazol-6-ium iodide **4g**. Yield: 65% (583 mg); White solid; Mp = 255°C; ^{1}H NMR (400 MHz, CD_3OD) δ 0.87-0.93 (3H, m, CH_3), 1.28-1.57 (8H, m, $4CH_2$), 2.05-2.16 (2H, m, CH_2), 4.69 (2H, t, *J* = 7.3, NCH_2), 7.77 (1H, dd, *J* = 8.8, *J* = 1.8, arom), 7.80-7.87 (2H, m, arom), 8.09-8.15 (1H, m, arom), 8.30 (1H, d, *J* = 8.8, arom), 8.64-8.69 (1H, m, arom), 8.72 (1H, d, *J* = 1.8, arom); ^{13}C NMR (100 MHz, CD_3OD) δ 14.4, 23.6, 27.7, 29.1, 29.9, 32.8, 49.0, 114.2, 115.1, 116.9, 127.6, 127.9, 128.3, 128.7, 128.8, 129.1, 134.8, 136.4, 137.3, 156.7; HRMS *m/z* calcd $C_{20}H_{22}N_2SCl^+$ $[M+H]^+$: 357.1187; found: 357.1184.

6-benzyl-2-chloro[3,1]benzimidazo[2,1-*b*][1,3]benzothiazol-6-ium bromide **4e**. A solution of 2-chlorobenzo[*d*]benzo[4,5]imidazo[2,1-*b*]thiazole **6c** (128 mg, 0.49 mmol) in benzyl bromide (2 mL, 16.92 mmol) was added and the mixture was stirred at 90°C for 4 hours. After cooling at room temperature, diethylether (10 mL) was added and the desired compound was then isolated by filtration (210 mg).Yield: 100%; White solid; Mp = 246°C (decomposition); ^{1}H NMR (400 MHz, CD_3OD) δ 5.97 (2H, s, NCH_2), 7.52-7.73 (6H, m, arom), 7.82-7.89 (2H, m, arom), 8.07-8.19 (2H, m, arom), 8.65-8.72 (2H, m, arom); ^{13}C NMR

(100 MHz, CD_3OD) δ 52.2, 103.8, 114.3, 115.0, 116.7, 127.5, 127.7, 128.8, 129.1, 130.8 (2C), 131.5 (3C), 131.9, 134.2, 136.3, 137.5, 156.5; HRMS *m/z* calcd $C_{20}H_{14}N_2SCl^+$ $[M]^+$: 349.0561; found: 349.0561.

Synthesis of benzimidazol-2-one 1

Experimental procedures and characterization data for compounds **1a-h** and **1p-q**: see reference 17.

Procedure to access to compound $\mathbf{1g_1}$ as a single isomer (Table 1, entry 6): To a solution of 9-benzyl-3-methyl[1,3]thiazolo[3,2-*a*]benzimidazol-9-ium chloride **3d** (65 mg, 0.21 mmol) in benzyl alcohol (3 mL), 1.5 mL of a freshly prepared solution of sodium benzylate (prepared by addition of sodium [22 mg, 0.96 mmol] in 5 mL of benzyl alcohol) was added at room temperature and the mixture was stirred for 24 hours. The solvent was then evaporated, water was added (25 mL) and the mixture was extracted with dichloromethane (3 × 25 mL). The organic layer was dried on $MgSO_4$ and evaporated under reduced pressure providing the desired compound (45 mg, 56%). Characterization data are consistent with reference 17.

General procedure for compounds **1i-o**: To a solution of the corresponding compound **3** (1 mmol) in methanol (60 mL), purchased sodium methoxide (4 mmol) was added and the mixture was stirred at r.t. for 48 hours. The solvent was then evaporated, water was added (25 mL) and the mixture was extracted with dichloromethane (3 × 25 mL). The organic layer was dried on $MgSO_4$ and evaporated under reduced pressure providing the desired compound.

1-Benzyl-3-[(1*Z*)-3,3-dimethyl-1-(methylsulfanyl)but-1-en-2-yl]-1,3-dihydro-2*H*-benzimidazol-2-one **1i**. Yield: 100% (239 mg); Pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (9H, s, CH_3), 2.21 (3H, s, SCH_3), 5.02 (1H, d, J_{AB} = 15.8, CH_2), 5.15 (1H, d, J_{AB} = 15.9,

CH_2), 6.40 (1H, s, H5), 6.78-6.86 (2H, m, arom), 6.91-7.01 (2H, m, arom), 7.17-7.32 (5H, m, arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 29.5, 38.8, 44.9, 108.5, 109.4 (2C), 121.3, 121.5, 127.4 (2C), 127.6, 128.8 (2C), 129.2, 129.6, 136.5, 137.9, 153.5; HRMS *m/z* calcd $C_{21}H_{24}N_2OS^+$ $[M+H]^+$: 353.1682; found: 353.1684.

1-[3,5-Bis(trifluoromethyl)benzyl]-3-[(1*Z*)-3,3-dimethyl-1-(methylsulfanyl)but-1-en-2-yl]-1,3-dihydro-2*H*-benzimidazol-2-one **1j**. Yield: 100% (313 mg); White solid; Mp = 143°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (9H, s, CH_3), 2.25 (3H, s, SCH_3), 5.05 (1H, d, J_{AB} = 16.3, CH_2), 5.41 (1H, d, J_{AB} = 16.2, CH_2), 6.45 (1H, s, H5), 6.81-6.84 (1H, m, arom), 6.91-6.94 (1H, m, arom), 7.01-7.10 (2H, m, arom), 7.77 (1H, s, arom), 7.80 (2H, s, arom); ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.4, 29.4 (3C), 38.7, 43.9, 107.8, 109.9, 121.8, 121.9, 122.1, 123.3 (2C, q, *J* = 273), 127.6 (2C), 128.9, 129.6, 130.0, 132.2, (2C, q, *J* = 33), 138.0, 139.4, 153.4; HRMS *m/z* calcd $C_{23}H_{22}N_2OSF_6^+$ $[M+H]^+$: 489.1430; found: 489.1432.

1-Methyl-3-[(*Z*)-2-(methylsulfanyl)-1-phenylethenyl]-1,3-dihydro-2*H*-benzimidazol-2-one **1k**. Yield: 100% (43 mg); White crystals; Mp = 168°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (3H, s, SCH_3), 3.51 (3H, s, NCH_3), 6.73 (1H, d, *J* = 7.8, arom), 6.97-7.32 (9H, m, arom+H5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3, 27.6, 107.8, 109.5, 121.6, 122.0, 124.7 (2C), 128.0, 128.1, 128.4, 128.9 (2C), 130.6, 130.7, 135.5, 152.7; HRMS *m/z* calcd $C_{17}H_{17}N_2OS^+$ $[M+H]^+$: 297.1056; found: 297.1056.

1-[(*Z*)-1-(4-Fluorophenyl)-2-(methylsulfanyl)ethenyl]-3-methyl-1,3-dihydro-2*H*-benzimidazol-2-one **1l**. Yield: 100% (51 mg); Colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (3H, s, SCH_3), 3.50 (3H, s, NCH_3), 6.72 (1H, d, *J* = 7.7, arom), 6.91-7.28 (8H, m, arom+H5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3, 27.6, 107.9, 109.4, 115.8, 116.1, 121.6, 122.1,

126.5, 126.6, 127.3, 128.2, 130.3, 130.6, 131.9, 152.6, 162.7 (d, J = 250.6); HRMS *m/z* calcd $C_{17}H_{16}N_2OSF^+$ $[M+H]^+$: 315.0961; found: 315.0962.

1-[(*Z*)-1-(4-Chlorophenyl)-2-(methylsulfanyl)ethenyl]-3-methyl-1,3-dihydro-2*H*-benzimidazol-2-one **1m**. Yield: 100% (49 mg); Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (3H, s, SCH_3), 3.51 (3H, s, NCH_3), 6.71 (1H, d, J = 7.7, arom), 6.98-7.29 (8H, m, arom+H5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3, 27.6, 107.9, 109.4, 121.7, 122.1, 126.0 (2C), 127.0, 128.1, 129.1 (2C), 130.6, 131.5, 133.8, 134.1, 152.5; HRMS *m/z* calcd $C_{17}H_{16}N_2OSCl^+$ $[M+H]^+$: 331.0666; found: 331.0666.

1-[(*Z*)-1-(4-Methoxyphenyl)-2-(methylsulfanyl)ethenyl]-3-methyl-1,3-dihydro-2*H*-benzimidazol-2-one **1n**. Yield: 100% (61 mg); Pale brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (3H, s, SCH_3), 3.50 (3H, s, NCH_3), 3.77 (3H, s, OCH_3), 6.72 (1H, d, J = 7.6, arom), 6.76-7.21 (8H, m, arom+H5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3, 27.5, 55.4, 107.7, 109.5, 114.3 (2C), 121.5, 121.9, 126.1 (2C), 128.0, 128.2, 128.3, 128.5, 130.6, 152.7, 159.6; HRMS *m/z* calcd $C_{18}H_{19}N_2O_2S^+$ $[M+H]^+$: 327.1161; found: 327.1161.

1-Methyl-3-[(*Z*)-2-(methylsulfanyl)-1-(naphthalen-2-yl)ethenyl]-1,3-dihydro-2*H*-benzimidazol-2-one **1o**. Yield: 95% (21 mg); Pale brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (3H, s, SCH_3), 3.55 (3H, s, NCH_3), 6.74 (1H, d, J = 7.7, arom), 6.95-7.82 (11H, m, arom+H5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 27.6, 107.8, 109.5, 121.6, 122.0, 122.7, 123.6, 126.3, 126.6, 127.7, 128.2, 128.4, 128.5, 128.7, 130.7, 131.3, 132.8, 133.1, 133.6, 152.7; HRMS *m/z* calcd $C_{21}H_{19}N_2OS^+$ $[M+H]^+$: 347.1212; found: 347.1212.

Synthesis of benzimidazol-2-one 2

General procedure for compounds **2a** and **2e**: To a solution of the corresponding compound **4** (1 mmol) in methanol (for **2a**: 50 mL; for **2e**: 70 mL), purchased sodium methoxide (for **2a**: 1.1 mmol; for **2e**: 5 mmol) was added and the mixture was stirred (for **2a**: 40°C for 5 hours; for **2e**: reflux for 3 hours). The solvent was then evaporated, water was added (25 mL) and the mixture was extracted with dichloromethane (3 × 25 mL). The organic layer was dried on $MgSO_4$ and evaporated under reduced pressure providing the desired compound.

1-methyl-3-[2-(methylsulfanyl)phenyl]-1,3-dihydro-2*H*-benzimidazol-2-one **2a**. Yield: 77% (50 mg); Pale brown solid; Mp = 127-129°C; ^{1}H NMR (400 MHz, CD_3OD) δ 2.39 (3H, s, SCH_3), 3.50 (3H, s, NCH_3), 6.64 (1H, d, J = 7.9, arom), 7.06 (1H, t, J = 7.7, arom), 7.15-7.25 (2H, m, arom), 7.31-7.39 (2H, m, arom), 7.51-7.58 (2H, m, arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 27.5, 107.7, 108.9, 121.5, 122.0, 126.0, 126.8, 129.6, 129.8, 129.9, 130.4, 132.0, 139.2, 153.5; HRMS *m/z* calcd $C_{15}H_{15}N_2OS^+$ $[M+H]^+$: 271.0900; found: 271.0900.

1-benzyl-3-[5-chloro-2-(methylsulfanyl)phenyl]-1,3-dihydro-2*H*-benzimidazol-2-one **2e**. Yield: 100% (163 mg); White solid; Mp = 159°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (3H, s, SCH_3), 5.11 (1H, d, J_{AB} = 15.8, CH_2), 5.21 (1H, d, J_{AB} = 15.8, CH_2), 6.69-6.72 (1H, m, arom), 6.91-6.94 (1H, m, arom), 6.99-7.07 (2H, m, arom), 7.27-7.42 (7H, m, arom), 7.46 (1H, dd, J = 8.5, J = 2.3, arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.7, 45.2, 108.8, 108.9, 121.7, 122.3, 127.6 (2C), 127.9, 128.0, 128.9 (2C), 129.5, 129.6, 129.9, 130.1, 131.4, 132.9, 136.2, 138.1, 153.2; HRMS *m/z* calcd $C_{21}H_{18}N_2OSCl^+$ $[M+H]^+$: 381.0823; found: 381.0823.

General procedure for compounds **2b-c** and **2g**: To a solution of the corresponding compound **4** (1 mmol) in methanol (for **2b** and **2c**: 40 mL; for **2g**: 146 mL), purchased sodium methoxide (for **2b**: 2.4 mmol; for **2c**: 5 mmol; for **2g**: 2 mmol) was added and the mixture was stirred

(for **2b**: 40°C, overnight; for **2c**: reflux for 4 hours; for **2g**: 40°C for 1 hour). The solvent was then evaporated and the crude was purified by column chromatography (eluent: CH_2Cl_2/AcOEt 10:0 → 9:1) providing the desired compound.

1-(4-chlorobenzyl)-3-[2-(methylsulfanyl)phenyl]-1,3-dihydro-2*H*-benzimidazol-2-one **2b**. Yield: 98% (95 mg); White solid; Mp = 154°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (3H, s, SCH_3), 5.07 (1H, d, J_{AB} = 15.8, NCH_2), 5.99 (1H, d, J_{AB} = 15.9, NCH_2), 6.68-6.71 (1H, m, arom), 6.87-6.91 (1H, m, arom), 6.99-7.07 (2H, m, arom), 7.29-7.43 (7H, m, arom), 7.46-7.51 (1H, m, arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 44.4, 108.4, 109.0, 121.7, 122.0, 126.0, 126.9, 129.0 (2C), 129.1 (2C), 129.2, 129.6, 129.9, 130.0, 131.7, 133.6, 134.9, 139.2, 153.3; HRMS *m/z* calcd $C_{21}H_{18}N_2OSCl^+$ $[M+H]^+$: 381.0823; found: 381.0825.

1-[5-chloro-2-(methylsulfanyl)phenyl]-3-methyl-1,3-dihydro-2*H*-benzimidazol-2-one **2c**. Yield: 72% (110 mg); Pale yellow oil; Mp = 184°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (3H, s, SCH_3), 3.51 (3H, s, NCH_3), 6.70 (1H, br d, *J* = 8.3, arom), 7.03-7.07 (2H, m, arom), 7.14-7.18 (1H, m, arom), 7.31-7.34 (1H, m, arom), 7.35 (1H, d, *J* = 2.0, arom), 7.44 (1H, dd, *J* = 8.6, *J* = 2.2, arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.7, 27.6, 107.9, 108.9, 121.7, 122.3, 127.9, 129.4, 129.8, 130.1, 130.4, 131.3, 132.9, 138.0, 153.2; HRMS *m/z* calcd $C_{15}H_{14}N_2OSCl^+$ $[M+H]^+$: 305.0510; found: 305.0506.

1-[5-chloro-2-(methylsulfanyl)phenyl]-3-heptyl-1,3-dihydro-2*H*-benzimidazol-2-one **2g**. Yield: 50% (80 mg); White solid; Mp = 75°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, br t, *J* = 6.9, CH_3), 1.24-1.46 (8H, m, $4CH_2$), 1.77-1.86 (2H, m, CH_2), 3.89-4.01 (2H, m, NCH_2), 6.70 (1H, d, *J* = 7.7, arom), 7.04 (1H, t, *J* = 7.6, arom), 7.07 (1H, d, *J* = 8.2, arom), 7.14 (1H, t, *J* = 7.6, arom), 7.32 (1H, d, *J* = 8.6, arom), 7.36 (1H, d, *J* = 2.1, arom), 7.44 (1H, dd, *J* = 8.5, *J* = 2.2, arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 15.7, 22.7, 26.9, 28.4, 29.1, 31.9,

41.5, 108.1, 108.9, 121.4, 122.1, 128.0, 129.5, 129.8, 129.9, 130.0, 131.3, 133.0, 138.1, 153.0; HRMS *m/z* calcd $C_{21}H_{26}N_2OSCl^+$ $[M+H]^+$: 389.1449; found: 389.1452.

1-[5-chloro-2-(ethylsulfanyl)phenyl]-3-methyl-1,3-dihydro-2*H*-benzimidazol-2-one **2d**. To a solution of 2-chloro-6-methyl[3,1]benzimidazo[2,1-*b*][1,3]benzothiazol-6-ium 4-methylbenzenesulfonate **4c** (238 mg, 0.54 mmol) in ethanol (5 mL), 5 mL of a freshly prepared solution of sodium ethoxide (prepared by addition of sodium [25.6 mg, 1.11 mmol] in 10 mL of ethanol) was added at 0°C. The mixture was allowed to warm to room temperature overnight. The solvent was then evaporated, water was added (25 mL) and the mixture was extracted with dichloromethane (3 × 25 mL). The organic layer was dried on $MgSO_4$ and evaporated under reduced pressure providing the desired compound (145 mg).Yield: 81%; White solid; Mp = 101°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, t, *J* = 7.4, CH_3), 2.78-2.91 (2H, m, SCH_2), 3.51 (3H, s, NCH_3), 6.67-6.71 (1H, m, arom), 7.02-7.08 (2H, m, arom), 7.13-7.18 (1H, m, arom), 7.34-7.37 (1H, m, arom), 7.40-7.43 (2H, m, arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 27.4, 27.5, 107.8, 108.8, 121.6, 122.2, 129.9 (2C), 130.2, 130.3, 132.0, 134.1, 136.5, 153.3; HRMS *m/z* calcd $C_{16}H_{16}N_2OSCl^+$ $[M+H]^+$: 319.0666; found: 319.0665.

1-benzyl-3-[5-chloro-2-(ethylsulfanyl)phenyl]-1,3-dihydro-2*H*-benzimidazol-2-one **2f**. To a solution of 6-benzyl-2-chloro[3,1]benzimidazo[2,1-*b*][1,3]benzothiazol-6-ium bromide **4e** (100 mg, 0.23 mmol) in ethanol (40 mL), 7 mL of a freshly prepared solution of sodium ethoxide (prepared by addition of sodium [73 mg, 1.11 mmol] in 40 mL of ethanol) was added at 40°C. The mixture was allowed to cool to room temperature overnight. The solvent was then evaporated, water was added (25 mL) and the mixture was extracted with dichloromethane (3 × 25 mL). The organic layer was dried on $MgSO_4$ and evaporated under

reduced pressure providing the desired compound (81 mg).Yield: 89%; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (3H, t, J = 7.3, CH_3), 2.79-2.92 (2H, m, CH_2), 5.11 (1H, d, J_{AB} = 15.6, NCH_2), 5.22 (1H, d, J_{AB} = 15.6, NCH_2), 6.70 (1H, d, J = 7.1, arom), 6.92 (1H, d, J = 7.1, arom), 6.98-7.07 (2H, m, arom), 7.27-7.47 (8H, m, arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 27.6, 45.2, 108.8, 108.9, 121.7, 122.2, 127.7 (2C), 127.9, 128.9 (2C), 129.5, 129.8, 129.9, 130.0, 130.6, 132.1, 134.3, 136.3, 136.6, 153.3; HRMS *m/z* calcd $C_{22}H_{20}N_2OSCl^+$ $[M+H]^+$: 395.0979; found: 395.0975.

Supporting Information Available

Copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds and compounds described in reference 17. X-Ray analysis of **1k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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