# First Example of Lewis Acid Catalyzed 3-Substituted 5-Arylidene-1-methyl-2-thiohydantoin Formation

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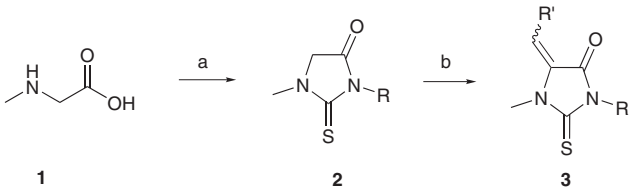
**Abstract:** A survey of Lewis acids was conducted to facilitate the formation of arylidenethiohydantoins. The use of indium(III) triflate shows significant advantages in facilitating this reaction. In most examples, the Lewis acid promoted catalysis gave shorter reaction times, higher conversion, and better purity profiles as compared to the traditional uncatalyzed reactions.

**Key words:** Lewis acids, catalysis, heterocycles, indium, condensation

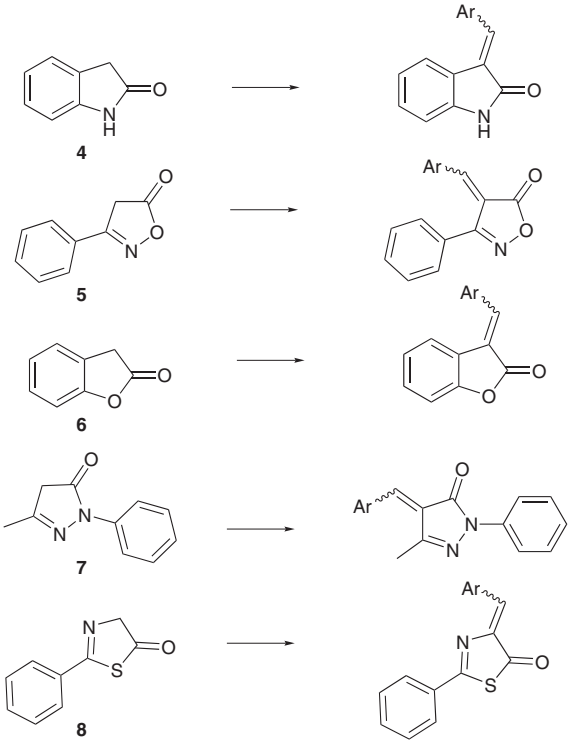
The 3-substituted 5-arylidene-1-methyl-2-thiohydantoin moiety **3** is known to be a biologically active heterocycle in areas of antimycobacterial,[1] antiviral[2] and potentially anticonvulsant indications.[3] As part of our efforts to generate libraries of medicinally relevant compounds, we set out to prepare a focused library of approximately 400 compounds elaborating this interesting core. Most recently Nielsen[4] reported the preparation of a small 28-member library of 3-substituted 5-arylidene-1-methyl-2-thiohydantoins **3** via microwave-mediated and traditional reflux conditions with good results. Our initial approach for the preparation of 3-substituted 5-arylidene-1-methyl-2-thiohydantoins involved the direct condensation of aldehydes with 3-substituted 1-methyl-2-thiohydantoins **2** in the presence of an organic base and a solvent such as toluene or 1,4-dioxane (Scheme 1). Our observations showed that, in general, uncatalyzed reactions give modest to good yields of 40% to 80% with unhindered aldehydes and that sterically hindered aldehydes typically gave very poor results. Similar results (Scheme 2) are found in the literature for other carbonyl compounds including 1,3-dihydroindol-2-one (**4**, oxindole),[5] α,β-unsaturated ketones,[6,7] 3-phenylisoxazol-5-one (**5**),[8] benzofuran-2(3*H*)-one (**6**),[9] pyrazol-5-one (**7**),[10] and 2-phenyl-3-thiazolin-5-one (**8**).[11] The use of catalysts ($AlCl_3$, TsOH and KF/alumina) has been reported for other similar substrates, in particular oxindole, with good results for a limited number of examples. We envisaged using a large diversity of the library ligand sets; however, the microwave-assisted synthesis would not be viable for a two-dimensional library consisting of several hundred compounds. Hence we sought to develop a reaction protocol which generated the target 3-substituted 5-arylidene-1-methyl-2-thiohydantoins **3** in good yield for a wide variety of R and R′ groups. We herein report our findings for the protocol validation phase of our compound library synthesis. A number of potential Lewis acid catalysts were surveyed to efficiently and reproducibly generate a library of previously unreported 3-substituted 5-arylidene-1-methyl-2-thiohydantoins **3**.




1 2 3

a) RNCS, EtOH, reflux, 6 h
b) aldehyde, catalyst, pyrrolidine, 1,4-dioxane, 60 °C, 30 min

**Scheme 1** General synthetic sequence for the preparation of 3-substituted 5-arylidene-1-methyl-2-thiohydantoins.




**Scheme 2** Examples of literature substrates and subsequent aldehyde condensation products.

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After reviewing the literature for Lewis acid catalyzed reactions, we chose to investigate three primary catalysts (10 mol% concentration): aluminum trichloride, boron trifluoride diethyl etherate and indium(III) triflate. Starting thiohydantoin cores **2** were prepared as previously described in the literature[12] by the reaction of *N*-methylglycine (sarcosine, **1**) with isothiocyanates in ethanol at reflux for 6 hours. Figures 1 and 2, respectively, show the four thiohydantoins and five aldehydes that were used in this study for the generation of a validation library of 20 compounds. Also included are our results for the aldehyde condensation reaction with oxindole to demonstrate the versatility of this methodology.

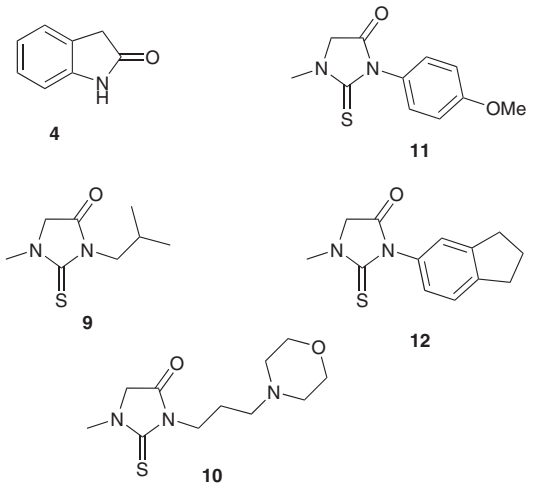


**Figure 1** Core 3-substituted 1-methyl-2-thiohydantoins **9**–**12** and oxindole **4** utilized in this study.

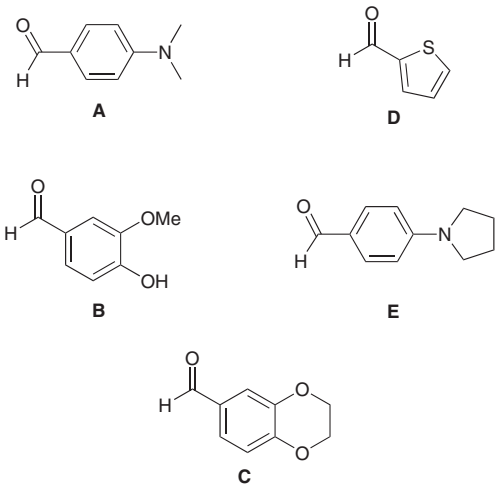


**Figure 2** Aldehydes **A**–**E** used in condensation reaction of 3-substituted 1-methyl-2-thiohydantoins to generate 3-substituted 5-arylidene-1-methyl-2-thiohydantoins.

Figures 3 through 7 show the percentage conversion (RP-HPLC/MS analysis at $t = 30$ min) for the catalyzed and uncatalyzed condensation reaction of aldehydes **A**–**E** with the four thiohydantoin cores **9**–**12** and oxindole **4**.

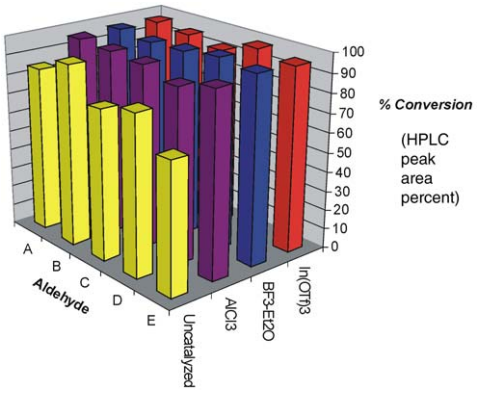


**Figure 3** Extent of product formation for the condensation reaction of aldehydes **A**–**E** with oxindole (**4**, peak area percent from analytical RP-HPLC/MS monitored via UV absorbance at 220 nm and 254 nm) with and without the addition of catalysts.

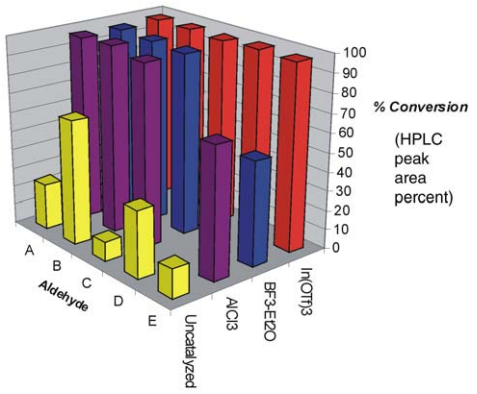


**Figure 4** Extent of product formation for the condensation reaction of aldehydes **A**–**E** with 3-isopropyl-1-methyl-2-thiohydantoin (**9**, peak area percent from analytical RP-HPLC/MS monitored via UV absorbance at 220 nm and 254 nm) with and without the addition of catalysts.

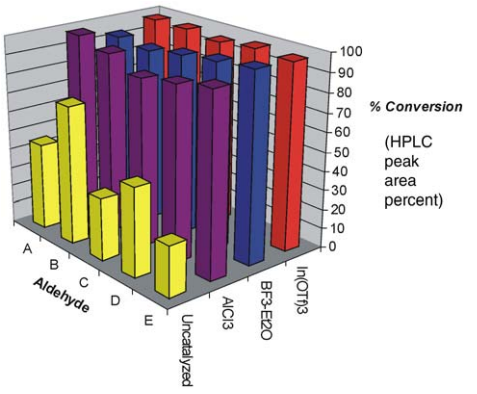


**Figure 5** Extent of product formation for the condensation reaction of aldehydes **A**–**E** with 3-(3-morpholin-4-yl-propyl)-1-methyl-2-thiohydantoin (**10**, peak area percent from analytical RP-HPLC/MS monitored via UV absorbance at 220 nm and 254 nm) with and without the addition of catalysts.

Our observations indicate that reactions which proceed in less than 40% overall yield after 30 minutes typically show little additional conversion to desired product with

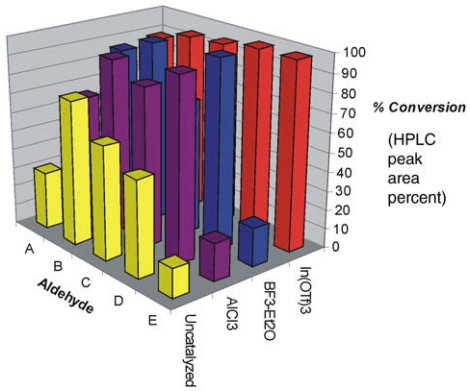


**Figure 6** Extent of product formation for the condensation reaction of aldehydes **A**–**E** with 3-(4-methoxyphenyl)-1-methyl-2-thiohydantoin (**11**, peak area percent from analytical RP-HPLC/MS monitored via UV absorbance at 220 nm and 254 nm) with and without the addition of catalysts.

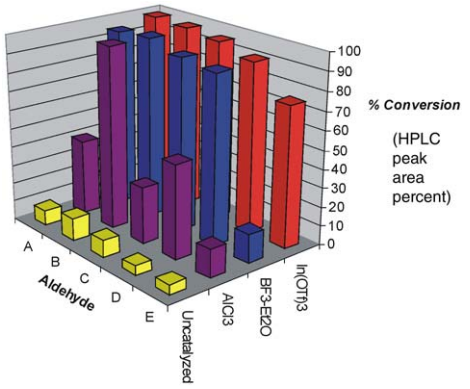


**Figure 7** Extent of product formation for the condensation reaction of aldehydes **A**–**E** with 3-(indan-5-yl)-1-methyl-2-thiohydantoin (**12**, peak area percent from analytical RP-HPLC/MS monitored via UV absorbance at 220 and 254 nm) with and without the addition of catalysts.

increased reaction time, and in some cases additional byproduct formation was observed that would have made the sample intractable to purification in a parallel format.

All three catalysts [$AlCl_3$, $BF_3{\cdot}Et_2O$, $In(OTf)_3$] showed an increase in *% conversion* for the formation of 3-substituted 5-arylidene-1-methyl-2-thiohydantoins compared to the uncatalyzed reactions. Indium(III) triflate was generally superior to the other catalysts both in terms of *% conversion* and ease of experimental and work-up procedures. The most dramatic example of the catalyst effectiveness is illustrated in Figures 4 and 5 where aldehydes **A**, **C** and **E** are nearly unreactive towards the condensation reaction in the absence of a catalyst yet show significant conversion to the desired products with the addition of a catalyst. Specifically, the versatility of indium(III) triflate can be seen in Figure 7 with aldehyde **E**, 4-(1-pyrrolidino)benzaldehyde, and 1-methyl-5-indan-2-thiohydantoin (**12**) where the *% conversion* increased from <30% to 72% while the other catalysts surveyed only resulted in <20% conversion. Similar results are found in Figure 6 whereby the condensation of aldehyde **E** with 3-(4-methoxyphenyl)-1-methyl-2-thiohydantoin (**11**) resulted in >90% conversion to the desired product with indium(III) triflate, yet shows only a modest *% conversion* with the other catalysts.

While it was not within the scope of this work to determine the *E* vs *Z* isomer formation and ratio of the resulting 3-substituted 5-arylidene-1-methyl-2-thiohydantoins, in some cases both isomers were detected by HPLC/MS analysis and were further characterized by $^1H$ and $^{13}C$ NMR analysis that was in agreement with previously reported data for similar compounds.[11]

In conclusion, indium(III) triflate, aluminum chloride and boron trifluoride diethyl etherate were all found to be efficient catalysts for the formation of 3-substituted 5-arylidene-1-methyl-2-thiohydantoins. Indium(III) triflate was chosen as the catalyst for the subsequent library synthesis due to the scope of application, easy of handling, air stability, reproducible results, low toxicity and cost. Isolated yields were in excess of 80% for all catalyzed reactions and reaction times were typically less than 30 minutes.

**Thiohydantoins 9–12; General Procedure**[12]

To a 250 mL single-neck round-bottomed flask fitted with a magnetic stir bar was charged sarcosine (**1**; 1.5 g, 16.8 mmol) and anhyd EtOH (100 mL). To the resulting solution was added the appropriate isothiocyanate (1.0 equiv, 16.8 mmol) and the mixture was refluxed for 6 h after which time the reaction was allowed to cool to r.t. The EtOH was removed under reduced pressure and the resulting crude material was dissolved into a minimum of $CH_2Cl_2$ and purified by silica gel chromatography (50 g) with EtOAc–hexanes (1:4) to give the title compound.

**Catalyst Survey for the Preparation of Arylidene Thiohydantoins 4A–E, 9A–E, 10A–E, 11A–E and 12A–E; General Procedure**

To a 2 dram vial fitted with a magnetic stir bar was added the appropriate thiohydantoin **4**, **9**–**12** (0.75 mmol), aldehyde **A**–**E** (1.2 equiv, 0.90 mmol), pyrrolidine (1.5 equiv, 1.13 mmol) and 1,4-dioxane (1.5 mL). To the mixture was added the desired catalyst (0.1 equiv, 0.075 mmol) and the mixture was heated to 60 °C using a J-Chem heater block. Aliquots were removed and the samples analyzed after 30 min, 90 min, 5 h and 24 h by HPLC at 210 and 254 nm. For all reactions with $In(OTf)_3$ as the catalyst, the reaction mixtures were concentrated to dryness under reduced pressure and the crude residue was chromatographed on silica gel (10 g) with $CH_2Cl_2$–MeOH (95:5) to give the title compound.

**4A**

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 3.08 [6 H, s, $N(CH_3)_2$], 6.72–6.76 (4 H, m, Ar), 6.81–6.92 [2 H, m, C*H*=CHN$(CH_3)_2$], 7.77 (1 H, s, =CH), 7.82 [2 H, d, *J* = 7.73 Hz, CH=C*H*N$(CH_3)_2$], 8.39 (1 H, d, *J* = 8.94 Hz, Ar).

HRMS-EI: *m/z* calcd for $C_{17}H_{16}N_2O$: 265.1341; found: 265.1333.

**4B**

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 3.82 (3 H, s, $OCH_3$), 5.85 (1 H, s, OH), 6.80–6.98 (4 H, m, Ar), 7.11–7.36 (3 H, m, Ar), 7.70 (1 H, s, =CH), 7.74 (1 H, d, *J* = 7.70 Hz, Ar).

HRMS-EI: *m/z* calcd for $C_{16}H_{13}NO_3$: 268.0973; found: 268.0966.

**4C**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 4.32 (4 H, m, $OCH_2$), 6.83–7.02 (4 H, m, Ar), 7.18–7.43 (2 H, m, Ar), 7.78 (1 H, s, =CH), 7.90 (1 H, d, *J* = 7.71 Hz, Ar), 8.10 (1 H, d, *J* = 8.15 Hz, Ar).

HRMS-EI: *m*/*z* calcd for $C_{17}H_{13}NO_3$: 280.0973; found: 280.0966.

**4D**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 6.86–6.95 (1 H, m, Ar), 7.01–7.10 (1 H, m, Ar), 7.15–7.24 (2 H, m, Ar), 7.53 (1 H, m, Ar), 7.65 (1 H, m, Ar), 7.73 (1 H, s, =CH), 7.85 (1 H, d, *J* = 3.68 Hz, Ar).

HRMS-EI: *m*/*z* calcd for $C_{13}H_9NOS$: 228.0483; found: 228.0480.

**4E**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 2.04 (4 H, m, $NCH_2CH_2$), 3.40 (4 H, m, $NCH_2CH_2$), 6.58–6.61 (3 H, m, Ar), 6.80–7.00 (2 H, m, Ar), 7.14–7.49 (1 H, m, Ar), 7.67 (2 H, m, Ar), 7.91 (1 H, s, =CH), 8.41 (1 H, d, *J* = 8.79 Hz, Ar).

HRMS-EI: *m*/*z* calcd for $C_{19}H_{18}N_2O$: 291.1497; found: 291.1487.

**9A**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.94 [6 H, d, *J* = 6.70 Hz, $CH(CH_3)_2$], 2.32 [1 H, sept, *J* = 6.70 Hz, $CH(CH_3)_2$], 3.05 [6 H, s, $N(CH_3)_2$], 3.62 (3 H, s, $NCH_3$), 3.77 [2 H, d, *J* = 7.39 Hz, $CH_2CH(CH_3)_2$], 6.46 (1 H, s, =CH), 6.69 (2 H, d, *J* = 8.96 Hz, Ar), 8.10 (2 H, d, *J* = 8.95 Hz, Ar).

HRMS-EI: *m*/*z* calcd for $C_{17}H_{23}N_3OS$: 318.1640; found: 318.1635.

**9B**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.95 [6 H, d, *J* = 6.73 Hz, $CH(CH_3)_2$], 2.31 [1 H, sept, *J* = 6.73 Hz, $CH(CH_3)_2$], 3.62 (3 H, s, $NCH_3$), 3.77 [2 H, d, *J* = 7.61 Hz, $CH_2CH(CH_3)_2$], 4.00 (3 H, s, $OCH_3$), 5.95 (1 H, s, OH), 6.44 (1 H, s, =CH), 6.92 (1 H, d, *J* = 8.21 Hz, Ar), 7.28 (1 H, d, *J* = 8.21 Hz, Ar), 8.41 (1 H, d, *J* = 1.75 Hz, Ar).

HRMS-EI: *m*/*z* calcd for $C_{16}H_{20}N_2O_3S$: 321.1273; found: 321.1278.

**9C**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.95 [6 H, d, *J* = 6.71 Hz, $CH(CH_3)_2$], 2.30 [1 H, sept, *J* = 6.72 Hz, $CH(CH_3)_2$], 3.60 (3 H, s, $NCH_3$), 3.74 [2 H, d, *J* = 7.59 Hz, $CH_2CH(CH_3)_2$], 4.29 (4 H, m, $OCH_2$), 6.38 (1 H, s, =CH), 6.86 (1 H, d, *J* = 8.56 Hz, Ar), 7.52 (1 H, d, *J* = 8.54 Hz, Ar), 7.81 (1 H, d, *J* = 1.94 Hz, Ar).

HRMS-EI: *m*/*z* calcd for $C_{17}H_{20}N_2O_3S$: 333.1273; found: 333.1286.

**9D**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.94 [6 H, d, *J* = 6.84 Hz, $CH(CH_3)_2$], 2.32 [1 H, sept, *J* = 7.04 Hz, $CH(CH_3)_2$], 3.60 (3 H, s, $NCH_3$), 3.77 [2 H, d, *J* = 7.50 Hz, $CH_2CH(CH_3)_2$], 6.71 (1 H, s, =CH), 7.11 (1 H, m, Ar), 7.52 (1 H, d, *J* = 4.89 Hz, Ar), 7.72 (1 H, d, *J* = 3.67 Hz, Ar).

HRMS-EI: *m*/*z* calcd for $C_{13}H_{16}N_2OS_2$: 281.0782; found: 281.0782.

**9E**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.94 [6 H, d, *J* = 6.74 Hz, $CH(CH_3)_2$], 2.01 (4 H, m, $NCH_2CH_2$), 2.33 [1 H, sept, *J* = 6.71 Hz, $CH(CH_3)_2$], 3.35 (4 H, m, $NCH_2CH_2$), 3.63 (3 H, s, $NCH_3$), 3.77 [2 H, d, *J* = 7.52 Hz, $CH_2CH(CH_3)_2$], 6.47 (1 H, s, =CH), 6.56 (2 H, d, *J* = 8.98 Hz, Ar), 8.12 (2 H, d, *J* = 8.91 Hz, Ar).

HRMS-EI: *m*/*z* calcd for $C_{19}H_{25}N_3OS$: 344.1796, found: 344.1812.

**10A**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.84 (2 H, pent, *J* = 7.17 Hz, $NCH_2CH_2CH_2$), 2.38 (6 H, m), 2.96 [6 H, d, *J* = 5.39 Hz, $N(CH_3)_2$], 3.45 (3 H, s, $NCH_3$), 3.60 (4 H, m, $NCH_2CH_2O$), 3.94 (2 H, m $NCH_2CH_2CH_2$), 6.36 (1 H, s, =CH), 6.60 (2 H, d, *J* = 8.96 Hz, Ar), 7.18 (1 H, d, *J* = 9.38 Hz, Ar), 8.02 (1 H, d, *J* = 8.99 Hz, Ar).

HRMS-EI: *m*/*z* calcd for $C_{20}H_{28}N_4O_2S$: 389.2011; found: 389.2005.

**10B**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.92 (2 H, pent, *J* = 6.95 Hz, $NCH_2CH_2CH_2$), 2.45 (6 H, m), 3.59 (3 H, s, $NCH_3$), 3.67 (4 H, m, $NCH_2CH_2O$), 3.96 (3 H, s, $OCH_3$), 4.02 (2 H, m $NCH_2CH_2CH_2$), 6.40 (1 H, s, =CH), 6.88 (2 H, d, *J* = 8.26 Hz, Ar), 7.27 (1 H, d, *J* = 8.96 Hz, Ar), 8.37 (1 H, d, *J* = 1.88 Hz, Ar).

HRMS-EI: *m*/*z* calcd for $C_{19}H_{25}N_3O_4S$: 392.1644; found: 392.1638.

**10C**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.87 (2 H, pent, *J* = 7.13 Hz, $NCH_2CH_2CH_2$), 2.41 (6 H, m), 3.58 (3 H, s, $NCH_3$), 3.67 (4 H, m, $NCH_2CH_2O$), 4.00 (2 H, m $NCH_2CH_2CH_2$), 4.29 (4 H, m, $OCH_2$), 6.36 (1 H, s, =CH), 6.86 (1 H, d, *J* = 8.53 Hz, Ar), 7.49 (1 H, d, *J* = 8.52 Hz, Ar), 7.82 (1 H, d, *J* = 2.09 Hz, Ar).

HRMS-EI: *m*/*z* calcd for $C_{20}H_{25}N_3O_4S$: 404.1644, found: 404.1643.

**10D**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.92 (2 H, pent, *J* = 7.15 Hz, $NCH_2CH_2CH_2$), 2.44 (6 H, m), 3.60 (3 H, s, $NCH_3$), 3.66 (4 H, m, $NCH_2CH_2O$), 4.03 (2 H, m $NCH_2CH_2CH_2$), 6.71 (1 H, s, =CH), 7.11 (1 H, m, Ar), 7.52 (1 H, d, *J* = 5.15 Hz, Ar), 7.71 (1 H, d, *J* = 3.65 Hz, Ar).

HRMS-EI: *m*/*z* calcd for $C_{16}H_{21}N_3O_2S_2$ requires 352.1153; found: 352.1161.

**10E**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.93 (2 H, m, $NCH_2CH_2CH_2$), 2.01 (4 H, m, $NCH_2CH_2$), 2.46 (6 H, m), 3.38 (4 H, m, $NCH_2CH_2$), 3.62 (3 H, s, $NCH_3$), 3.69 (4 H, m, $NCH_2CH_2O$), 4.04 (2 H, m $NCH_2CH_2CH_2$), 6.46 (1 H, s, =CH), 6.56 (2 H, d, *J* = 8.71 Hz, Ar), 8.12 (2 H, d, *J* = 8.73 Hz, Ar).

HRMS-EI: *m*/*z* calcd for $C_{22}H_{30}N_4O_2S$: 415.2167; found: 415.2171.

**11A**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.03 [6 H, s, $N(CH_3)_2$], 3.66 (3 H, s, $NCH_3$), 3.82 (3 H, s, $OCH_3$), 6.51 (1 H, s, =CH), 6.64 (2 H, d, *J* = 9.10 Hz, Ar), 7.00 (2 H, d, *J* = 8.90 Hz, Ar), 7.28 (2 H, d, *J* = 8.90 Hz, Ar), 8.13 (2 H, d, *J* = 9.04 Hz, Ar).

HRMS-EI: *m*/*z* calcd for $C_{20}H_{21}N_3O_2S$: 368.1432; found: 368.1435.

**11B**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.72 (3 H, s, $NCH_3$), 3.84 (3 H, s, $OCH_3$), 3.97 (3 H, s, $OCH_3$), 5.31 (1 H, s, OH), 6.53 (1 H, s, =CH), 6.87–7.04 (3 H, m, Ar), 7.24–7.29 (3 H, m, Ar), 8.50 (1 H, d, *J* = 1.86 Hz, Ar).

HRMS-EI: *m*/*z* calcd for $C_{19}H_{18}N_2O_4S$: 371.1065; found: 371.1075.

**11C**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.70 (3 H, s, $NCH_3$), 3.84 (3 H, s, $OCH_3$), 4.28 (4 H, m, $OCH_2$), 6.46 (1 H, s, =CH), 6.85 (1 H, d, *J* = 8.55 Hz, Ar), 6.99 (2 H, d, *J* = 8.95 Hz, Ar), 7.26 (2 H, d, *J* = 8.94 Hz, Ar), 7.56 (1 H, d, *J* = 8.62 Hz, Ar), 7.81 (1 H, d, *J* = 2.09 Hz, Ar).

HRMS-EI: *m*/*z* calcd for $C_{20}H_{18}N_2O_4S$: 383.1065; found: 383.1077.

**11D**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.70 (3 H, s, $NCH_3$), 3.84 (3 H, s, $OCH_3$), 6.81 (1 H, s, =CH), 7.01 (2 H, d, *J* = 8.97 Hz, Ar), 7.14 (1 H, m, Ar), 7.26 (2 H, m, Ar), 7.54 (1 H, d, *J* = 4.90 Hz, Ar), 7.75 (1 H, d, *J* = 3.62 Hz, Ar).

HRMS-EI: *m*/*z* calcd for $C_{16}H_{14}N_2O_2S_2$: 331.0575; found: 331.0584.

**11E**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 2.00 (4 H, m, $NCH_2CH_2$), 3.32 (4 H, m, $NCH_2CH_2$), 3.63 (3 H, s, $NCH_3$), 3.82 (3 H, s, $OCH_3$), 6.48 (1 H, s, =CH), 6.52 (2 H, m, Ar), 7.00 (2 H, d, *J* = 8.87 Hz, Ar), 7.27 (2 H, d, *J* = 8.89 Hz, Ar), 8.12 (2 H, d, *J* = 8.87 Hz, Ar).

HRMS-EI: *m*/*z* calcd for $C_{22}H_{23}N_3O_2S$: 394.1589; found: 394.1594.

**12A**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 2.12 (2 H, sept, *J* = 7.45 Hz, $CH_2CH_2CH_2$), 2.94 (4 H, m, $CH_2CH_2CH_2$), 3.03 [6 H, s, $N(CH_3)_2$], 3.67 (3 H, s, $NCH_3$), 6.51 (1 H, s, =CH), 6.64 (2 H, d, *J* = 9.11 Hz, Ar), 7.11 (1 H, d, *J* = 7.89 Hz, Ar), 7.17 (1 H, s, Ar), 7.32 (1 H, d, *J* = 7.87 Hz, Ar), 8.16 (2 H, d, *J* = 9.06 Hz, Ar).

HRMS-EI: *m*/*z* calcd for $C_{22}H_{23}N_3OS$: 378.1640; found: 378.1651.

**12B**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 2.13 (2 H, sept, *J* = 7.40 Hz, $CH_2CH_2CH_2$), 2.95 (4 H, m, $CH_2CH_2CH_2$), 3.70 (3 H, s, $NCH_3$), 3.93 (3 H, s, $OCH_3$), 6.01 (1 H, s, OH), 6.52 (1 H, s, =CH), 6.93 (1 H, d, *J* = 9.11 Hz, Ar), 7.08 (1 H, d, *J* = 7.86 Hz, Ar), 7.16 (1 H, s, Ar), 7.26 (1 H, d, *J* = 8.28 Hz, Ar), 7.34 (1 H, d, *J* = 7.89 Hz, Ar), 8.51 (1 H, d, *J* = 1.94 Hz, Ar).

HRMS-EI: *m*/*z* calcd for $C_{22}H_{23}N_3O_2S$: 381.1273; found: 381.1273.

**12C**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 2.11 (2 H, sept, *J* = 7.48 Hz, $CH_2CH_2CH_2$), 2.93 (4 H, m, $CH_2CH_2CH_2$), 3.66 (3 H, s, $NCH_3$), 4.26 (4 H, m, $OCH_2$), 6.44 (1 H, s, =CH), 6.83 (1 H, d, *J* = 8.54 Hz, Ar), 7.07 (1 H, d, *J* = 7.89 Hz, Ar), 7.15 (1 H, s, Ar), 7.32 (1 H, d, *J* = 7.91 Hz, Ar), 7.56 (1 H, dd, *J* = 8.56, 2.09 Hz, Ar), 7.82 (1 H, d, *J* = 2.12 Hz, Ar).

HRMS-EI: *m*/*z* calcd for $C_{22}H_{23}N_3O_2S$: 393.1273; found: 393.1276.

**12D**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 2.11 (2 H, sept, *J* = 7.32 Hz, $CH_2CH_2CH_2$), 2.95 (4 H, m, $CH_2CH_2CH_2$), 3.68 (3 H, s, $NCH_3$), 6.79 (1 H, s, =CH), 7.10 (1 H, m, Ar), 7.17 (1 H, s, Ar), 7.33 (1 H, d, *J* = 7.90 Hz, Ar), 7.52 (1 H, d, *J* = 4.98 Hz, Ar), 7.73–7.76 (2 H, m, Ar).

HRMS-EI: *m*/*z* calcd for $C_{22}H_{23}N_3O_2S$: 341.0782; found: 341.0791.

**12E**

$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.98 (4 H, m, $NCH_2CH_2$), 2.10 (2 H, sept, *J* = 7.44 Hz, $CH_2CH_2CH_2$), 2.94 (4 H, m, $CH_2CH_2CH_2$), 3.35 (4 H, m, $NCH_2CH_2$), 3.67 (3 H, s, $NCH_3$), 6.49 (1 H, s, = *CH*), 6.58 (2 H, m, Ar), 7.12 (1 H, d, *J* = 7.89 Hz, Ar), 7.18 (1 H, s, Ar), 7.32 (1 H, d, *J* = 7.92 Hz, Ar), 8.15 (2 H, d, *J* = 8.92 Hz, Ar).

HRMS-EI: *m*/*z* calcd for $C_{22}H_{23}N_3O_2S$: 404.1796; found: 404.1796.

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