Supporting Information

2,3-Diaryl-substituted Indole based COX-2 Inhibitors as Leads for Imaging Tracer Development

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Crystal structure of compound 5c

Compound **5c** crystallized in the triclinic space group *P1* with one molecule in the asymmetric unit and two molecules in the unit cell (table S1). The crystal structure of **5c** is in accordance with the spectroscopic data (figure S1).

Table S1. Crystal data and parameters for structure refinement of 5c.

Empirical formula	$C_{15} H_{13} F O_3 S$	
Formula weight	292.31	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	$P\ \bar{1}$	
Unit cell dimensions	a = 5.5241(2) Å	α= 82.578(1)°
	b = 8.5534(2) Å	β= 88.938(1)°
	c = 14.6136(4) Å	γ = 72.577(1)°
Volume	653.14(3) $Å^3$	
Z	2	
Density (calculated)	1.486 g/cm^3	
Absorption coefficient	0.264 mm^{-1}	
F(000)	304	
Crystal size	0.35 x 0.15 x 0.10 mm^3	
Theta range for data collection	1.41 to 38.33°.	
Index ranges	$-9 \leq h \leq 9, -14 \leq k \leq 14, -25 \leq l \leq 23$	
Reflections collected	33122	
Independent reflections	7225, R_{int} = 0.0483	
Absorption correction	Multiscan (SADABS)	
Max. and min. transmission	0.9741 and 0.9133	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7225 / 0 / 182	
Goodness-of-fit on F^2	1.042	
Final R indices [I>2sigma(I)]	R1 = 0.0419, wR2 = 0.1100	
R indices (all data)	R1 = 0.0601, wR2 = 0.1216	
Largest diff. peak and hole	0.487 and -0.419 e·$Å^{-3}$	

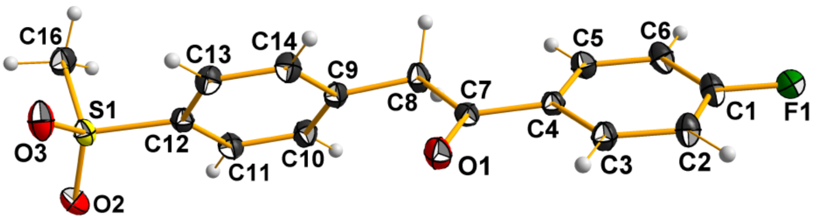


Figure S1. Molecular structure of compound 5c **in the crystal (ORTEP plot: displacement thermal ellipsoids are drawn at 50% probability level)**

The bond lengths of the C-C single bonds [d = 1.494-1.519 Å] and of the C=O double bond (d = 1.217(1) Å) as well as the bond lengths in the two phenyl rings [d = 1.380-1.397 Å] are comparable to those described by Rieker[1] for 2-phenylacetophenone. In difference to this molecule, the bond angles in the fluoro-substituted phenyl ring of **5c** [θ = 117.74-123.26°] deviate from the ideal 120° of benzene. However, the bond lengths and angles of the phenyl ring as well as the bond lengths of C1-F1 (d = 1.348(1) Å) are still in the expected range and a similar binding situation was observed for 4-fluoroacetophenone.[2] The bond lengths of the C-S single bonds (d(C16-S1) = 1.760(1) and d(C12-S1) = 1.7654(9) Å) as well as the S-O double bonds (d(S1-O2) = 1.43282(8) and d(S1-O3) = 1.4423(9) Å) are also in the expected range and are comparable to those in 4-(Methylsulfonyl)toluene.[3] Interestingly, the molecular geometry is also very similar to that of 2-phenylacetophenone. The plane of the fluoro-substituted phenyl ring and the plane of the ethanone subunit (C8-C7-O1) are only very little twisted to each other and enclose an angle of 2.41°. In contrast, the plane of the methylsulfonyl substituted phenyl ring is twisted to the plane of the ethanone subunit with an angle of 62.84°. In 2-phenylacetophenone, the respective angles are -8.2° and 72.3°.[1]

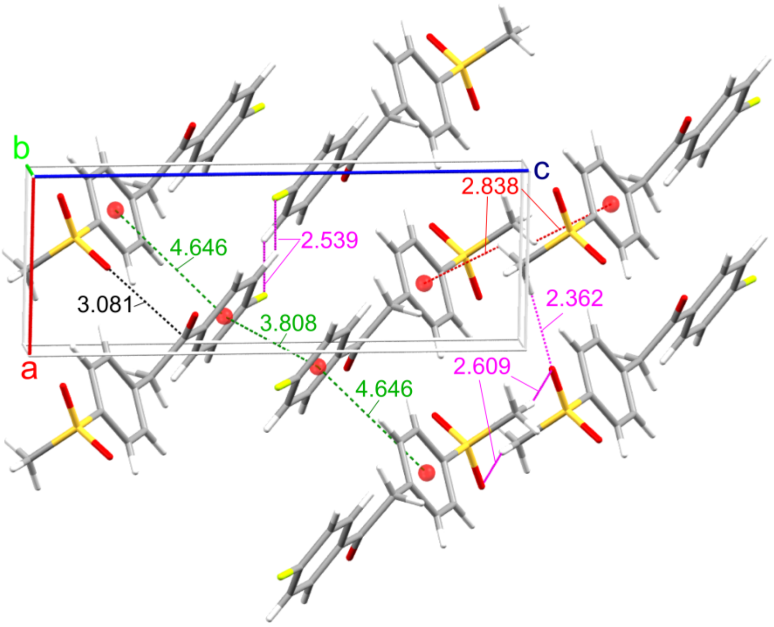


Figure S2. **Intermolecular interactions between molecules of 5c in the crystal (view along the crystallographic b-axis, distances given in Å).**

Table S2. Interatomic distances and geometries for intermolecular contacts of compound 5c **in the crystal**

Atoms	r / Å	d / Å	D / Å	$D_{lateral\ offset}$ / Å	Dihedral angle / °	θ / °	Symmetry operation
C2-H2···F1	0.95	2.54	3.163(1)	-	-	123	-1-x,3-y,1-z
C16-H16A···O3	0.98	2.61	3.563(1)	-	-	165	1-x,-y,-z
C16-H16B···O3	0.98	2.36	3.279(1)	-	-	155	1+x,y,z
$Z_{F\text{-}Phenyl}\cdots Z_{F\text{-}Phenyl}$	-	3.8075(6)	-	1.603	0	-	-X,2-Y,1-Z
$Z_{F\text{-}Phenyl}\cdots Z_{SO_2\text{-}Phenyl}$	-	4.6456(6)	-	-	60.62(4)	-	-1+X,1+Y,Z
$Z_{F\text{-}Phenyl}\cdots Z_{SO_2\text{-}Phenyl}$	-	5.0763(6)	-	-	60.62(4)	-	X,-1+Y,Z
C16-H16C···$Z_{SO_2\text{-}Phenyl}$	-	2.84	3.466(1)	-	-	132	1-X,1-Y,-Z
	$Z_{F\text{-}Phenyl}$... Centroid of C1-C6; $Z_{SO_2\text{-}Phenyl}$... Centroid of C9-C14						

The two molecules of the unit cell do not interact with each other. On the one hand, π···π-interactions determine the packing in the plane (1,0,0). So, anti-parallel positioned fluoro-substituted phenyl rings can be found that interact with a distance between the centroids (Z) of d($Z_{F\text{-Phenyl}}$···$Z_{F\text{-Phenyl}}$) = 3.808 Å. Also, interactions between edge-to-face positioned fluoro and methylsulfonyl substituted phenyl rings (d($Z_{SO2\text{-Phenyl}}$···$Z_{F\text{-Phenyl}}$) = 4.646 Å, dihedral angle 60.62 °) stabilize the packing in this plane (figure S2). On the other hand, weak hydrogen bonds and dipolar interactions are involved in the intermolecular interactions in this plane. Weak hydrogen bonds are formed between the fluoro substituted phenyl rings (d(C2-H2···F1) = 2.539 Å) and a stabilizing dipolar S=O···C=O-interactions (d(S1-O2···C7-O1) = 3.081(1) Å and θ(O-S-O) = 87.39(6)°) is present. Along the c-axis, the molecules of neighboring unit cells interact by further weak hydrogen bonds between the methylsulfonyl-moieties (d(C16-H16B···O3) = 2.3624(8) Å and d(C16-H16A···O3) = 2.6085(8) Å) as well as C-H···π-interactions with a distance of d(C16-H16C···$Z_{SO2\text{-Phenyl}}$) = 2,838 Å.

Crystal structure of compound 3j

Compound **3j** crystallized in the monoclinic space group $P2_1/c$ with one molecule in the asymmetric unit and four molecules in the unit cell (table S3). The crystal structure of **3j** is in accordance with the spectroscopic data (figure S3).

Table S3. Crystal data and parameters for structure refinement of 3j.

Empirical formula	$C_{22}H_{19}NO_3S$	
Formula weight	377.44	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 11.6987(6) Å	α= 90°
	b = 18.059(1) Å	β= 110.647(2)°
	c = 9.5364(5) Å	γ = 90°
Volume	1885.3(2) $Å^3$	
Z	4	
Density (calculated)	1.330 g/cm^3	
Absorption coefficient	0.194 mm^{-1}	
F(000)	792	
Crystal size	0.35 x 0.26 x 0.15 mm^3	
Theta range for data collection	2.92 to 39.46°.	
Index ranges	-20 ≤ h ≤ 20, -32 ≤ k ≤ 32, -17 ≤ l ≤ 17	
Reflections collected	54915	
Independent reflections	11261, R_{int} = 0.0239	
Absorption correction	multi-scan (SADABS)	

Table S3 continued. Crystal data and parameters for structure refinement of 3j.

Max. and min. transmission	0.9715 and 0.9352
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	11261 / 0 / 246
Goodness-of-fit on F^2	1.043
Final R indices [I>2sigma(I)]	R1 = 0.0396, wR2 = 0.1091
R indices (all data)	R1 = 0.0558, wR2 = 0.1204
Largest diff. peak and hole	0.628 and -0.296 e·Å^{-3}

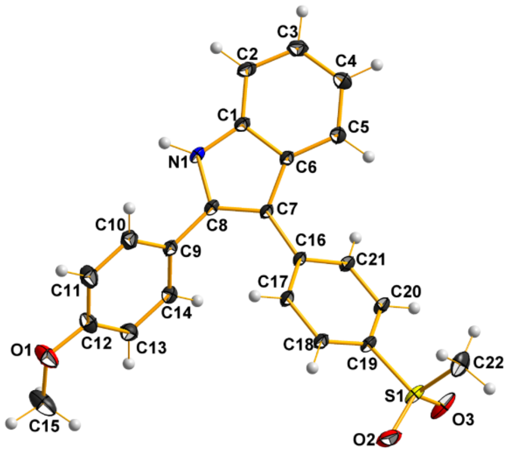
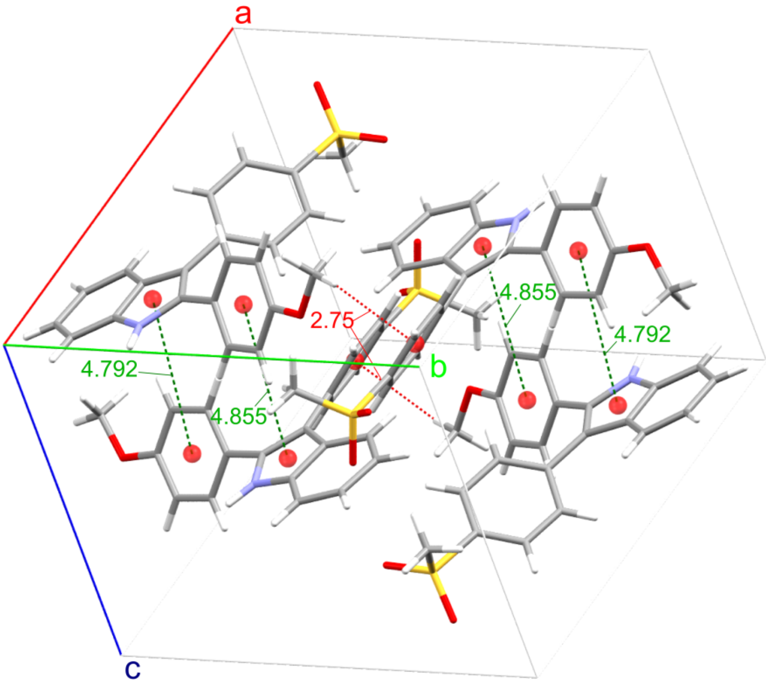


Figure S3. **Molecular structure of compound** 3j **in the crystal (ORTEP plot: displacement thermal ellipsoids are drawn at 50% probability level)**

The bond lengths and bond angles in both phenyl rings [d = 1.384-1.403 Å, θ = 119.04-121.30°], in the five-membered ring of the indole [d = 1.371-1.444 Å, θ = 106.61-109.76°], in the six-membered ring of the indole [d = 1.385-1.413 Å, θ = 117.32-121.64°] as well as the bond lengths of the C-C single bonds (d(C7-C16) = 1.4635(9) Å, d(C8-C9) = 1.470(1) Å) are in the expected range. They are furthermore comparable to those observed for 2,3-diphenyl-1*H*-indole as presented by Schmelter *et al.*[4]. Also, the geometry of the methoxy group (d(C12-O1) = 1.3641(9) Å, d(C15-O1) = 1.423(1) Å, θ(C-O-C) = 117.81(8)°) and the methylsulfonyl group [d = 1,438-1,759 Å] is as expected. Interestingly, the molecular geometry of **7b** significantly differs in comparison to its unsubstituted chemical lead 2,3-diphenyl-1*H*-indole. The plane of the methoxy-substituted phenyl ring is twisted with a dihedral angle of 52.89° in relative to the plane of the indole core. The methylsulfonyl substituted phenyl ring is less twisted. The dihedral angle between the two planes is 39.62°. In 2,3-diphenyl-1*H*-indole the orientation of the phenyl rings is opposite. The phenyl ring in 2-position is less twisted than its neighboring phenyl ring in 3-position. The dihedral angles are 44.0° and 54.2°, respectively.[4] This indicates a preferred interaction of the electron-deficient methylsulfonyl substituted phenyl ring with the electron-rich indole system.

a)



b)

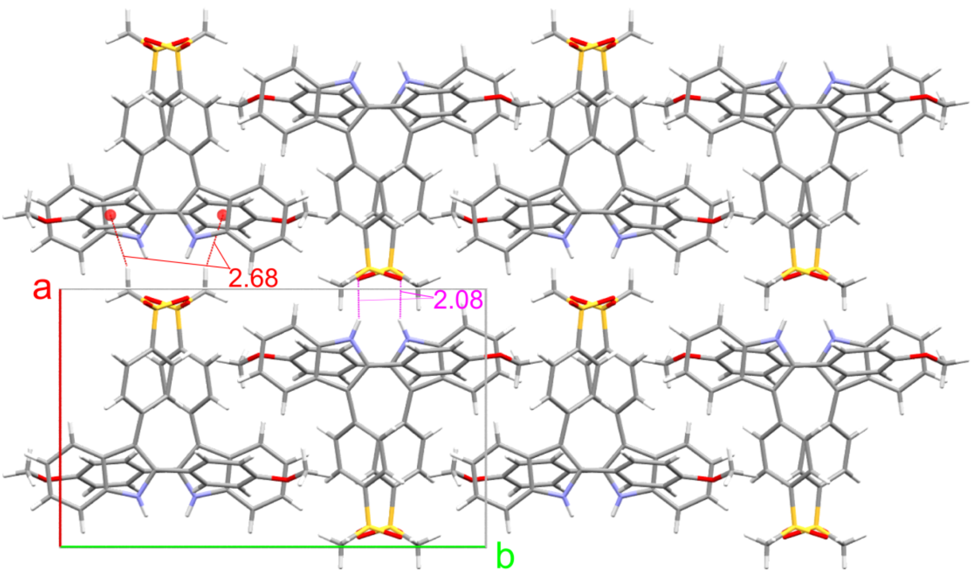


Figure S4. **a) intermolecular interactions in the unit cell of the crystal of 3j (distances given in Å), b) packing in the crystal of 3j with selected intermolecular interactions. The intermolecular distances given in a) and b) are given in Å.**

Within one unit cell, two molecules in each case are positioned by π···π-interactions along the crystallographic c-axis. So, each methoxy substituted phenyl-ring is positioned edge-to-face to the neighboring phenyl ring ($d(Z_{MeO\text{-}Phenyl}\cdots Z_{N1\text{-}C8})$ = 4.855 Å and $d(Z_{MeO\text{-}Phenyl}\cdots Z_{N1\text{-}C8})$ = 4.792 Å, respectively; dihedral angle is in both cases 51.66°) (table S4). C-H···π-contacts between the methoxy group of one molecule with the methylsulfonyl substituted phenyl ring of the neighboring molecule ($d(C15\text{-}H15A\cdots Z_{SO2\text{-}Phenyl})$ = 2.75 Å) cause the binding of the molecules within the unit cell (figure S4a) . These interactions continue with molecules of neighboring unit cells and lead to the orientation of the molecules in the plane (0,0,1) (figure S4b). The packing along the crystallographic a-axis is finally caused by moderate hydrogen bonds between the methylsulfonyl moiety and NH-groups of the indole moieties sticking out of these planes (d(N1-H1···O3) = 2.085 Å) as well as C-H···π-contacts (d(C22-H22C···$Z_{MeO\text{-}Phenyl}$) = 2,08 Å).

Table S4. Interatomic distances and geometries for intermolecular contacts of compound 3j in the crystal

Atoms	r / Å	d / Å	D / Å	Dihedral angle / °	θ / °	Symmetry operation
C15-H15A ···$Z_{SO_2\text{-}Phenyl}$	-	2.75	3.420(1)	-	126	1-X,-1/2+Y,3/2-Z
C22-H22C ···$Z_{MeO\text{-}Phenyl}$	-	2.68	3.485(1)	-	140	1+X,1/2-Y,1/2+Z
N1-H1···$O3_I$	0.88	2.08	2.9102(9)	-	156	-1+x,y,z
$Z_{MeO\text{-}Phenyl}$···$Z_{N1\text{-}C8}$	-	4.8550(5)	-	51.66(4)	-	X,1/2-Y,-1/2+Z
$Z_{MeO\text{-}Phenyl}$··· $Z_{N1\text{-}C8}$	-	4.7924(5)	-	51.66(4)	-	X,1/2-Y,1/2+Z
	$Z_{N1\text{-}C8}$... Centroid of N1-C1-C6-C7-C8; $Z_{MeO\text{-}Phenyl}$... Centroid of C9-C10-C11-C12-C13-C14; $Z_{SO_2\text{-}Phenyl}$ ... Centroid of C16-C17-C18-C19-C20-C21					

Crystal structure of compound 2c

Compound **2c** crystallized in the monoclinic space group $P2_1/c$ with one molecule in the asymmetric unit and four molecules in the unit cell (table S5).The crystal structure of **2c** is in accordance with the spectroscopic data (figure S5).

Table S5. Crystal data and parameters for structure refinement of 2c.

Empirical formula	$C_{22} H_{18} F N O_4 S$	
Formula weight	411.43	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 13.4778(7) Å	α= 90°
	b = 5.3885(3) Å	β= 94.875(3)°
	c = 26.674(1) Å	γ = 90°
Volume	1930.2(2) Å^3	
Z	4	
Density (calculated)	1.416 g/cm^3	
Absorption coefficient	0.207 mm^{-1}	
F(000)	856	
Crystal size	0.45 x 0.27 x 0.19 mm^3	

Table S5 continued. Crystal data and parameters for structure refinement of 2c.

Theta range for data collection	2.25 to 32.64°
Index ranges	$-20 \le h \le 20$, $-8 \le k \le 7$, $-40 \le l \le 37$
Reflections collected	25185
Independent reflections	6986, R_{int} = 0.0349
Absorption correction	multi-scan (SADABS)
Max. and min. transmission	0.9618 and 0.9127
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6986 / 0 / 262
Goodness-of-fit on F^2	1.067
Final R indices [I>2sigma(I)]	R1 = 0.0437, wR2 = 0.1173
R indices (all data)	R1 = 0.0704, wR2 = 0.1324
Largest diff. peak and hole	0.301 and -0.467 e·Å^{-3}

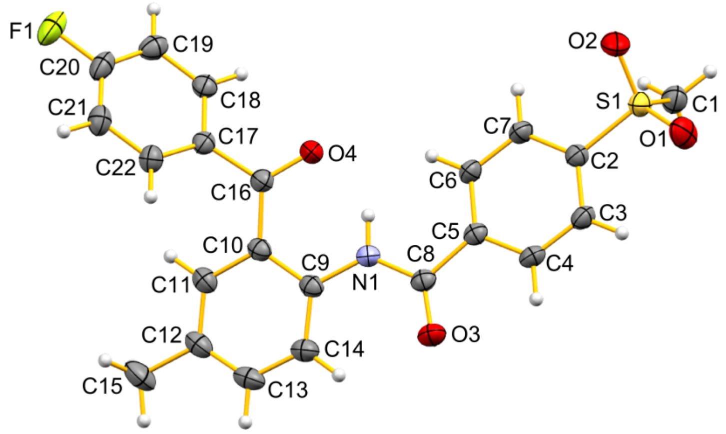
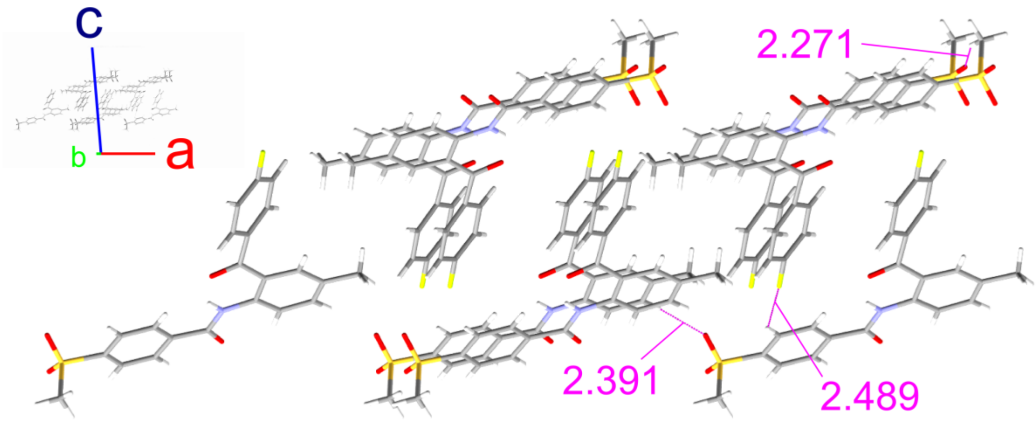


Figure S5. **Molecular structure of compound** 2c **in the crystal (ORTEP plot: displacement thermal ellipsoids are drawn at 50% probability level)**

The bond lengths and bond angles in both phenyl rings [d = 1.373-1.415 Å, θ = 117.55-123.31°] as well as the bond lengths of the C-C single bonds (d(C10-C16) = 1.481(2) Å, d(C16-C17) = 1.496(2) Å, d(C5-C8) = 1.503(2) Å) and of the C-N-single bonds (d(C8-N1) = 1.362(2) Å, d(C9-N1) = 1.401(2)) are in the expected range and comparable to those of *N*-(2-benzoylphenyl)benzamide described by Alberti *et al.*[5]. Also, the bond lengths of the C-F bond (d(C20-F1) = 1.352(2) Å), of the C-C single bond between methyl group and pheny ring (d(C12-C15) = 1.504(2) Å) and bonds within the methylsulfonyl group [d = 1.436-1.765 Å] are as expected. The molecular geometry of **2c** is similar to that of its unsubstituted chemical lead. So, also in compound **2c** an intramolecular moderate hydrogen bond (d(N1-H1D···O4) = 1.899 Å) causes the orientation of the C16-O4 double bond in one plane with the methyl substituted phenyl ring. The planes formed by C59-N1-C8-C5 and by C17-C16-O4-C10 are twisted by a dihedral angle of 7.11° and 18.79° in relative to the central phenyl ring what is a little more than found for *N*-(2-Benzoylphenyl)benzamid (4.60° and 10.55°)[5]. Interestingly, this in turn causes a smaller dihedral angle between central phenyl ring and the planes of the fluoro as well as methylsulfonyl substituted phenyl ring, namely, 46.43° and 9.11°, compared to that in *N*-(2-Benzoylphenyl)benzamid (64.63° and 15.31°)[5].

a)



b)

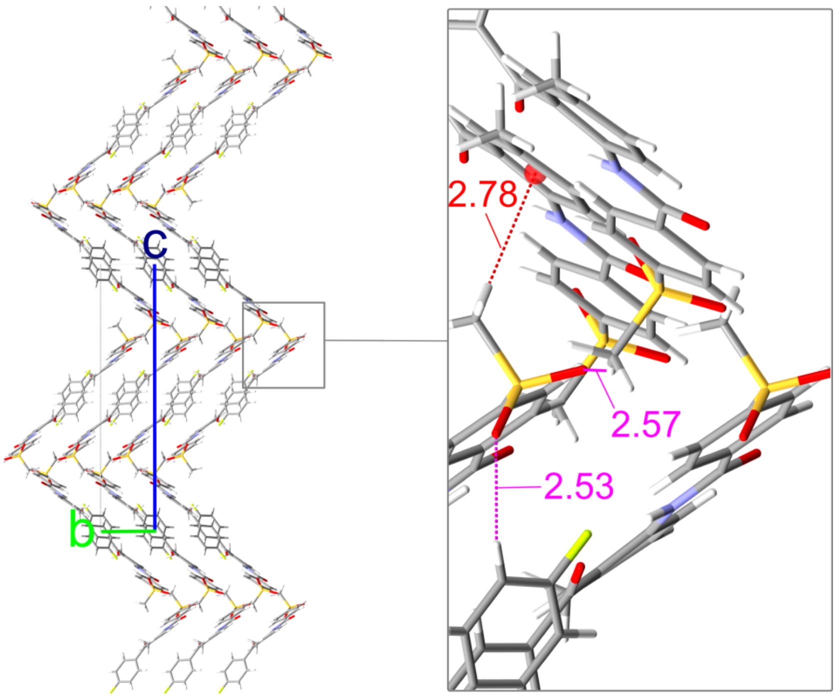


Figure S6. **a) packing of 2c in layers along (0,0,1) in the crystal, b) sawtooth-shaped orientation of 2c in the crystal (left) and selected intermolecular interaction between the layers. The intermolecular distances given in a) and b) are given in Å.**

The molecules in the unit cell do not interact with each other. In the crystal, weak hydrogen bonds (d(C7-H7A···F1) = 2.489 Å, d(C1-H1B···O1) = 2.271 Å and d(C13-H13A···O2) = 2.391 Å) cause the binding within layers in the plane (0,0,1) (figure S6a). With view along the crystallographic a-axis, a sawtooth-shaped orientation of the molecules is present (figure S6b left). This orientation is determined by weak hydrogen bonds (d(C21-H21A···O2) = 2.53 Å and d(C1-H1A···O1) = 2.57 Å) as well as C-H···π-interactions (d(C1-H1C···$Z_{Me\text{-}Phenyl}$) = 2.78 Å). (table S6, figure S6b right). Interestingly, in the direction [0,1,0] the molecules are stacked with a constant distance of d = 5.389 Å in the whole crystal.

Table S6. Interatomic distances and geometries for intermolecular contacts of compound 2c in the crystal

Atoms	r / Å	d / Å	D / Å	Dihedral angle / °	θ / °	Symmetry operation
C1-H1A···O1	0.98	2.57	3.493(2)	-	157	1-x,-1/2+y,1/2-z
C1-H1B···O1	0.98	2.27	3.205(2)	-	159	x,-1+y,z
C7-H7A···F1	0.95	2.49	3.217(2)	-	133	-x,-2-y,-z
C13-H13A···O2	0.95	2.39	3.306(2)	-	162	-1+x,y,z
C21-H21A···O2	0.95	2.53	3.448(2)	-	162	-x,-1-y,-z
C1-H1C···$Z_{Me\text{-}Phenyl}$	-	2.78	3.681(2)	154	-	-X,1/2+Y,1/2-Z
	$Z_{Me\text{-}Phenyl}$… Centroid of C9-C14; **$Z_{F\text{-}Phenyl}$**… Centroid of C17-C22; **$Z_{SO_2\text{-}Phenyl}$**… Centroid of C2-C7					

Crystal structure of compound 3a

Compound **3a** crystallized in the monoclinic space group *P*2$_1$/c with one molecule in the asymmetric unit and four molecules in the unit cell (table S7). The crystal structure of **3a** is in accordance with the spectroscopic data (figure S7).

Table S7. Crystal data and parameters for structure refinement of 3a.

Empirical formula	C_{21} H_{16} F N O_2 S	
Formula weight	365.41	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*P*2$_1$/*c*	
Unit cell dimensions	a = 17.9195(8) Å	α= 90°
	b = 5.9807(3) Å	β= 99.089(2)°
	c = 16.6142(8) Å	γ = 90°
Volume	1758.2(2) Å^3	
Z	4	
Density (calculated)	1.380 g/cm^3	
Absorption coefficient	0.209 mm^{-1}	
F(000)	760	
Crystal size	0.57 x 0.14 x 0.11 mm^3	
Theta range for data collection	3.92 to 28.34°	
Index ranges	-23 ≤ h ≤ 23, -7 ≤ k ≤ 7, -21 ≤l ≤ 22	
Reflections collected	26355	
Independent reflections	4340, R_{int} = 0.0321	
Absorption correction	multi-scan (SADABS)	
Max. and min. transmission	0.9774 and 0.8389	
Refinement method	Full-matrix least-squares on F^2	

Table S7 continued. Crystal data and parameters for structure refinement of 3a.

Data / restraints / parameters	4340 / 0 / 236
Goodness-of-fit on F^2	1.051
Final R indices [I>2sigma(I)]	R1 = 0.0397, wR2 = 0.1007
R indices (all data)	R1 = 0.0489, wR2 = 0.1075
Largest diff. peak and hole	0.356 and -0.429 e·Å^{-3}

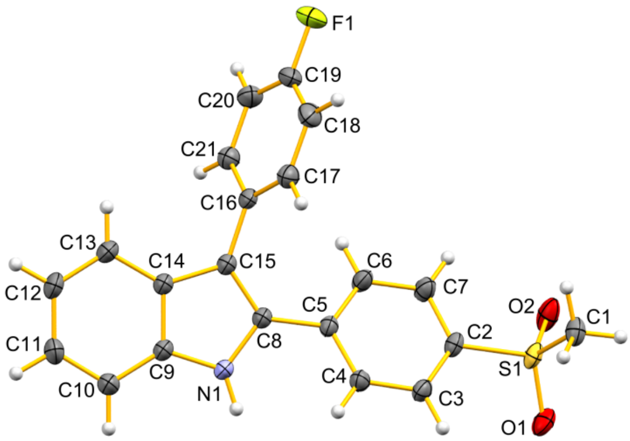
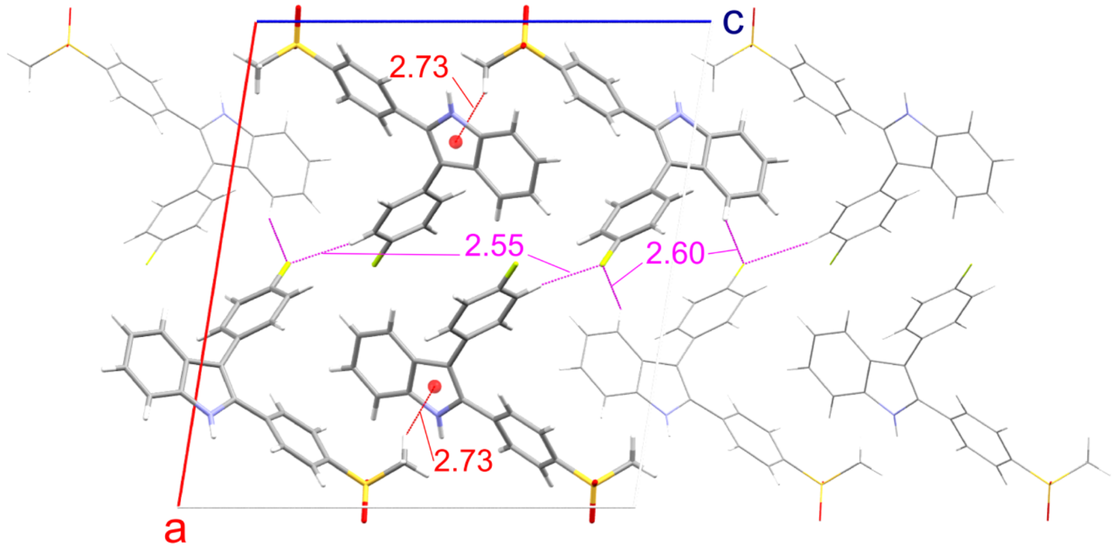


Figure S7. **Molecular structure of compound** 3a **in the crystal (ORTEP plot: displacement thermal ellipsoids are drawn at 50% probability level)**

The bond lengths and bond angles in both phenyl rings [d = 1,375-1,411 Å, θ = 117,62-121,66°], in the five-membered ring of the indole [d = 1,374-1,443 Å, θ = 106,81-109,19°], in the six-membered ring of the indole [d = 1,370-1,388 Å, θ = 118,06-123,31°] as well as the bond lengths of the C-C single bonds (d(C5-C8) = 1,464(2) Å, d(C15-C16) = 1,477(2) Å), of the C-F single bond (d(C19-F1) = 1,364(2) Å) and of the methylsulfonyl group [d = 1,439-1,756 Å] are in the expected range. The intramolecular atomic distances are comparable to those in 2,3-diphenyl-1*H*-indole considering the deviations caused by the fluoro substitution onto the geometry of the phenyl ring as seen e.g. for the phenyl ring in **5c** or 4-fluoroacetophenone[2, 4]. In comparison to its unsubstituted chemical lead, the molecular geometry is similar with respect to the general orientation of the phenyl rings in the molecule. The phenyl ring in 2-position of the indole is less twisted than the neighboring phenyl ring in 3-position. However, in compound **3a** the dihedral angle between planes of the methyl sulfonyl substituted phenyl ring and the indole core is 26.74° and thus significantly less twisted than in 2,3-diphenyl-1*H*-indole where this angle is 44.0°. In turn, the fluoro substituted phenyl ring is more twisted. The dihedral angles are 66,36° in **3a** and 54.2° in its unsubstituted counterpart[4]. This indicates the favored interaction of the electron-deficient methylsulfonyl substituted phenyl ring with the electron-rich indole system.

a)



b)

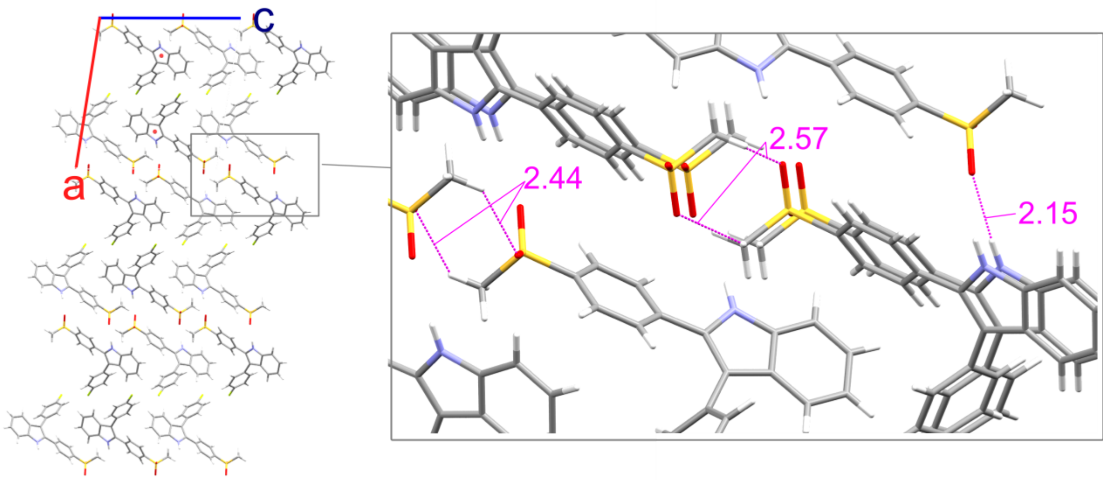


Figure S8. a) **Orientation of 3a in layers along (1,0,0) in the crystal (view along the crystallographic b-axis, molecules of the unit cell are shown as capped sticks), b) schematic presentation of the crystal packing of 3a (left) and intermolecular interactions leading to binding between the layers. The intermolecular distances given in a) and b) are given in Å.**

In the unit cell, weak hydrogen bonds (d(C18-H18A···F) = 2.547 Å) as well as C-H···π-interactions (D(C1···$Z_{N1\text{-}C9}$) = 3.606(2) Å) cause binding of the molecules (table S8). The continuation of these interactions in the crystal causes the orientation of the molecules in layers in the plane (1,0,0) wherein the fluoro substituents are facing to each other (figure S8a). In the direction [1,0,0], these layers are connected at the boundary area of the unit cells with neighboring molecules by moderate (d(N1-H1D···O1) = 2.145 Å) as well as weak (d(C1-H1A···O2) = 2.440 Å, d(C1-H1B···O1) = 2.574 Å) hydrogen bonds. Thereby, the molecules are orientated in planes (0,0,1) that are sawtooth-shaped in the direction of the crystallographic a-axis (figure S8b).

Table S8. Interatomic distances and geometries for intermolecular contacts of compound 3a in the crystal

Atoms	r / Å	d / Å	D / Å	θ / °	Symmetry operation
C18-H18A···F1	0.95	2.55	3.490(2)	172	x,-1+y,z
C13-H13A···F1	0.95	2.60	3.468(2)	152	1-x,2-y,1-z
N1-H1D···O1	0.88	2.15	3.005(1)	165	-x,1/2+y,1/2-z
C1-H1B···O1	0.98	2.57	3.237(2)	125	-x,1-y,-z
C1-H1A···O2	0.98	2.44	3.253(2)	140	-x,2-y,-z
C1-H1C···Z_{N1-C9}	-	2.73	3.6057(18)	149	X,3/2-Y,-1/2+Z
	Z_{pyrrol} ... Centroid of N1-C8-C15-C14-C9				

NMR spectra of new compounds

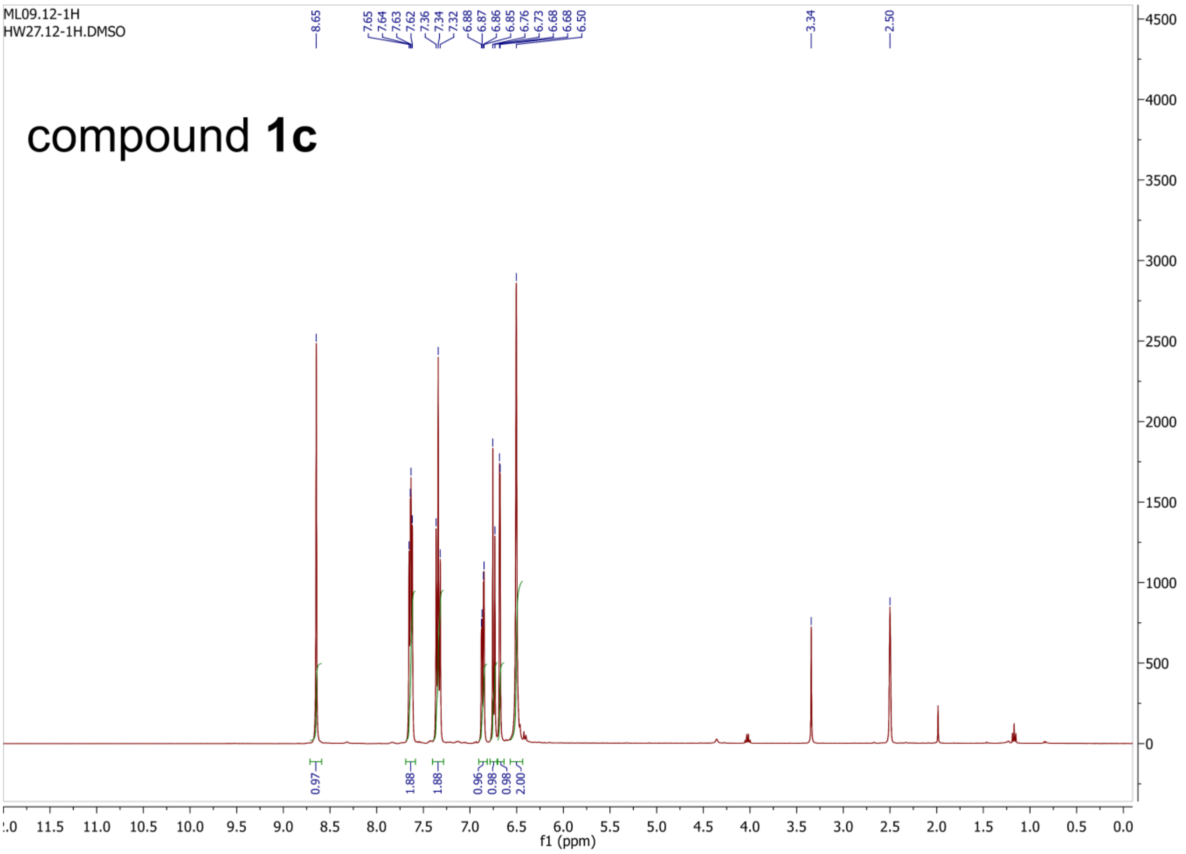


Figure S9. ^{1}H-NMR of compound 1c in DMSO-d_6.

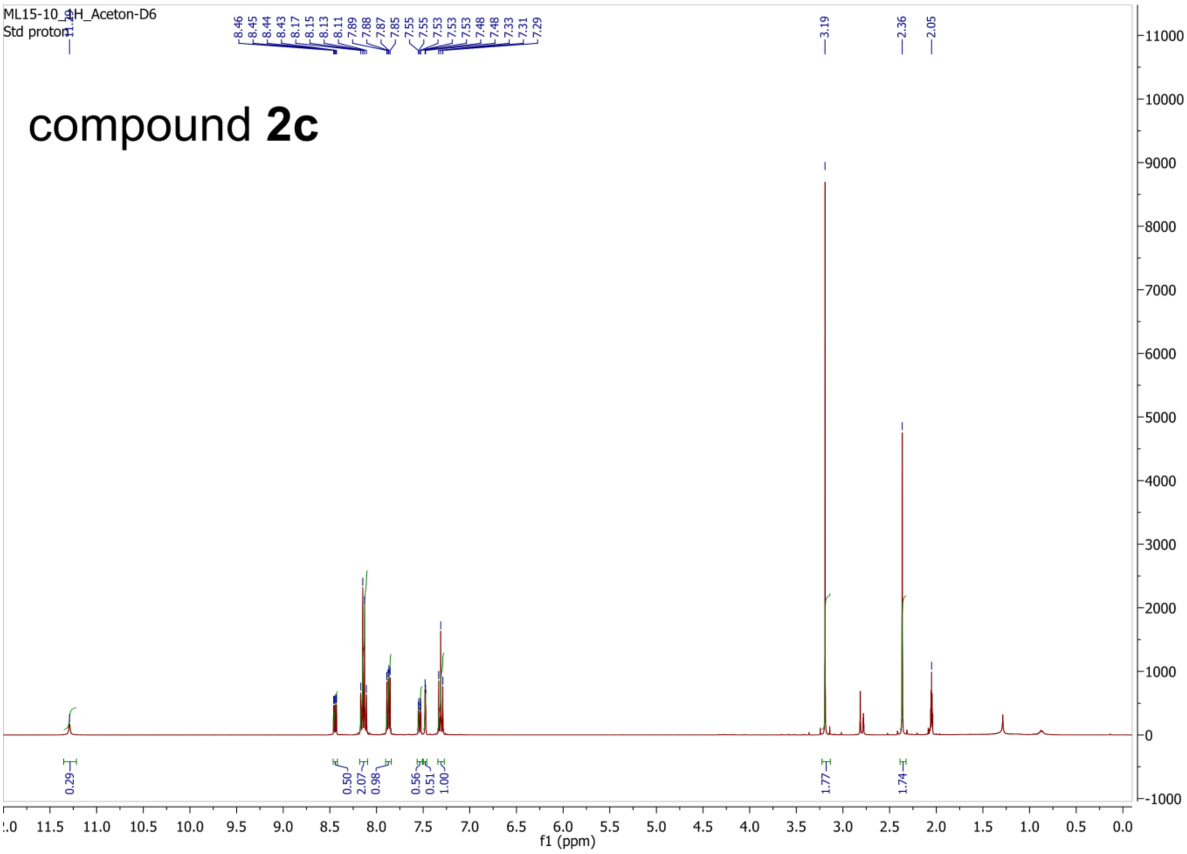


Figure S10. ^{1}H-NMR of compound 2c in acetone-d_6.

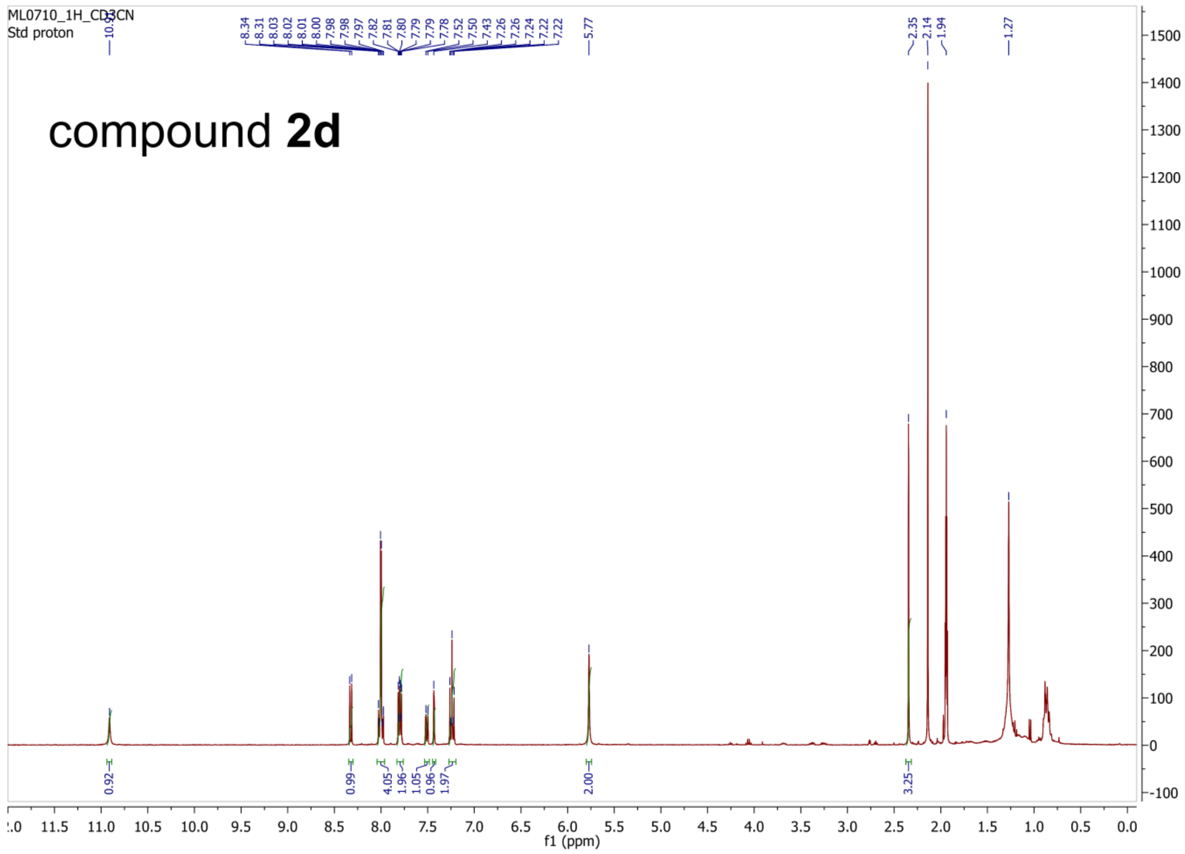


Figure S11. **^{1}H-NMR of compound 2d in CD_3CN.**

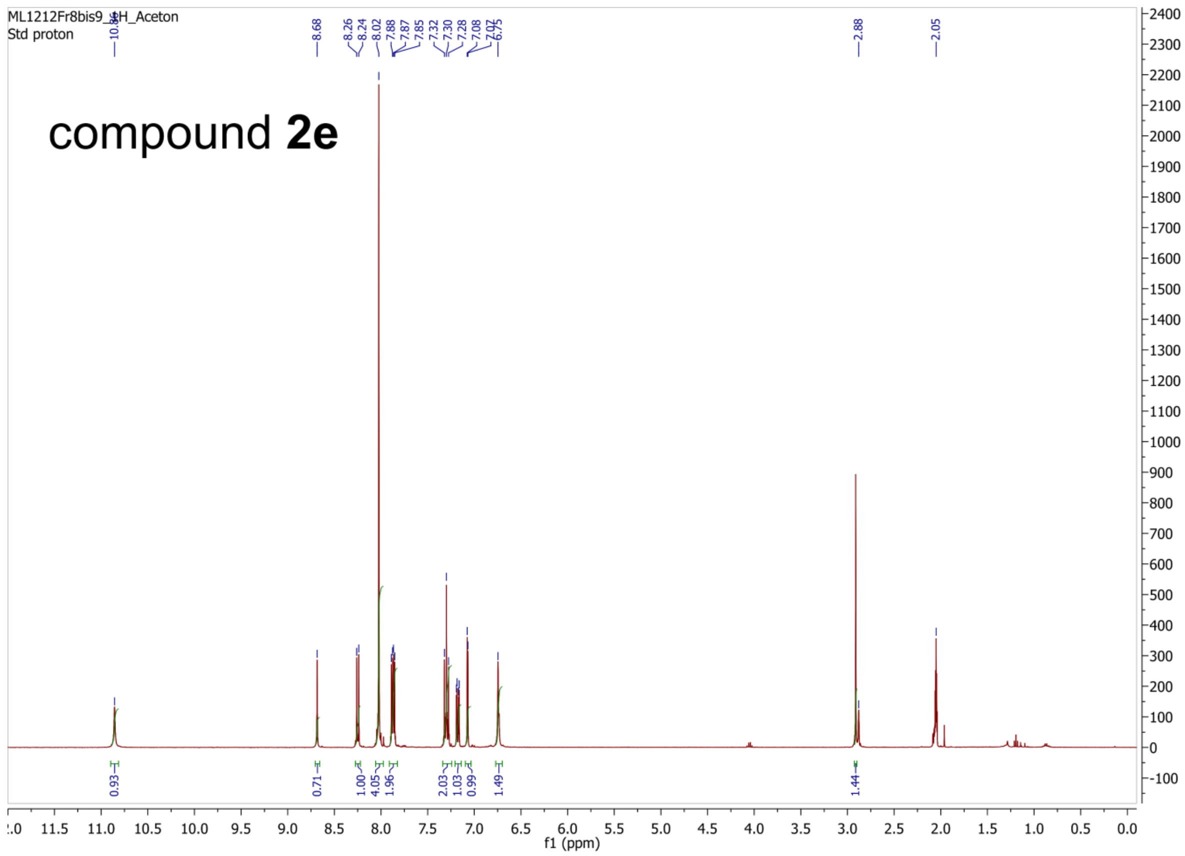


Figure S12. **^{1}H-NMR of compound 2e in acetone-d_6.**

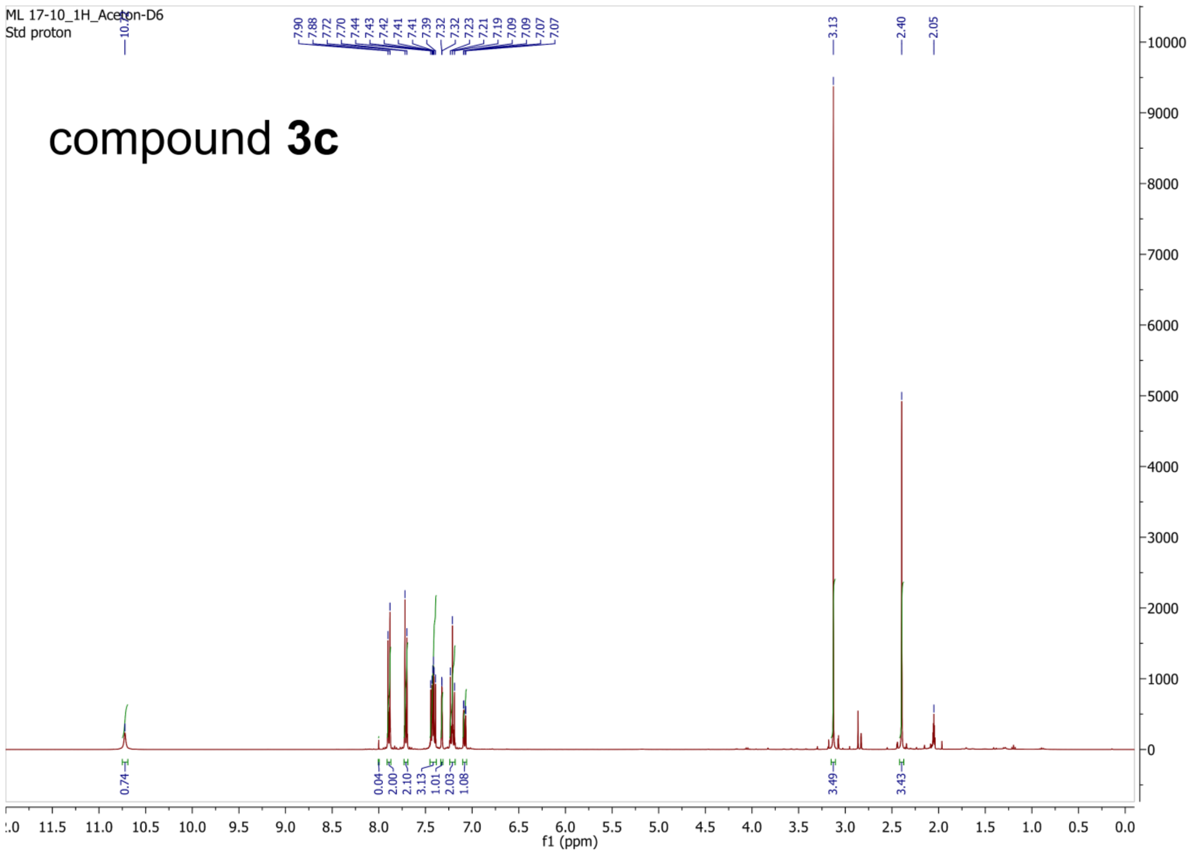


Figure S13. **^{1}H-NMR of compound 3c in acetone-*d_6*.**

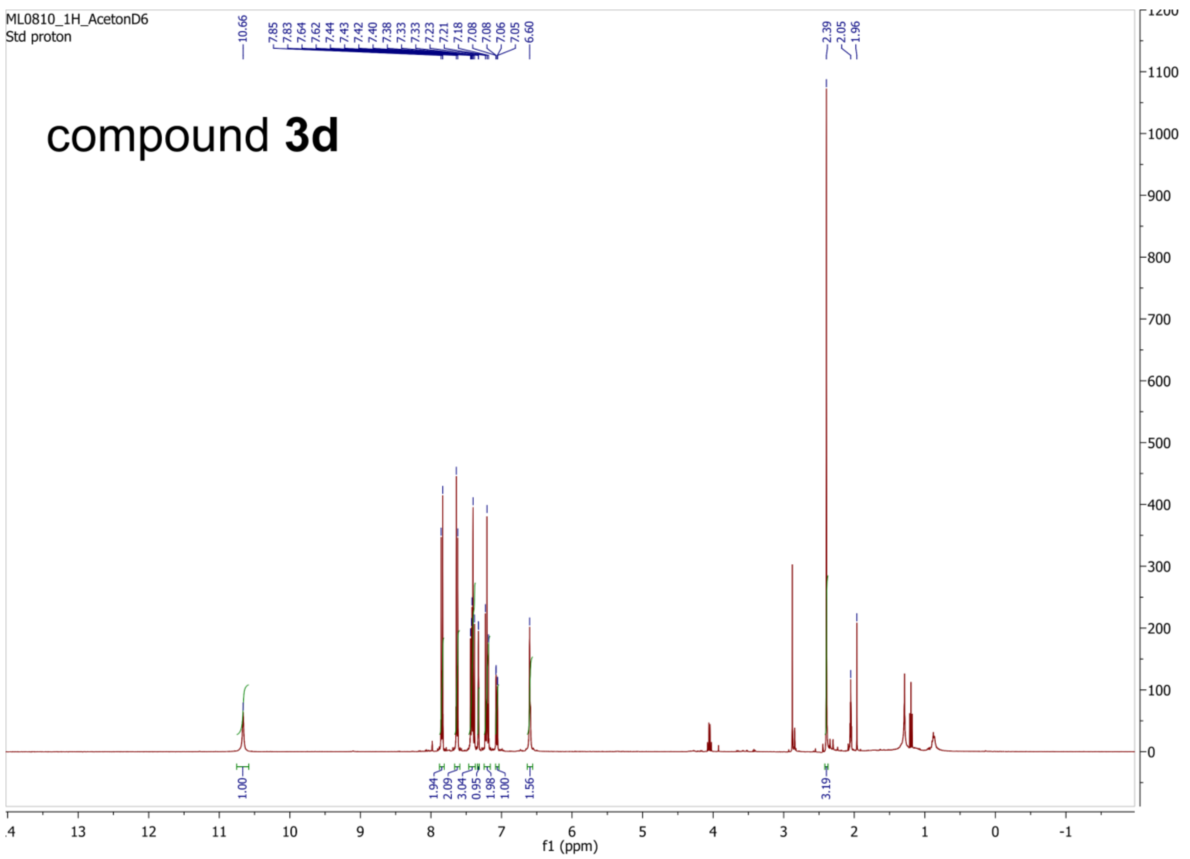


Figure S14. **^{1}H-NMR of compound 3d in acetone-*d_6*.**

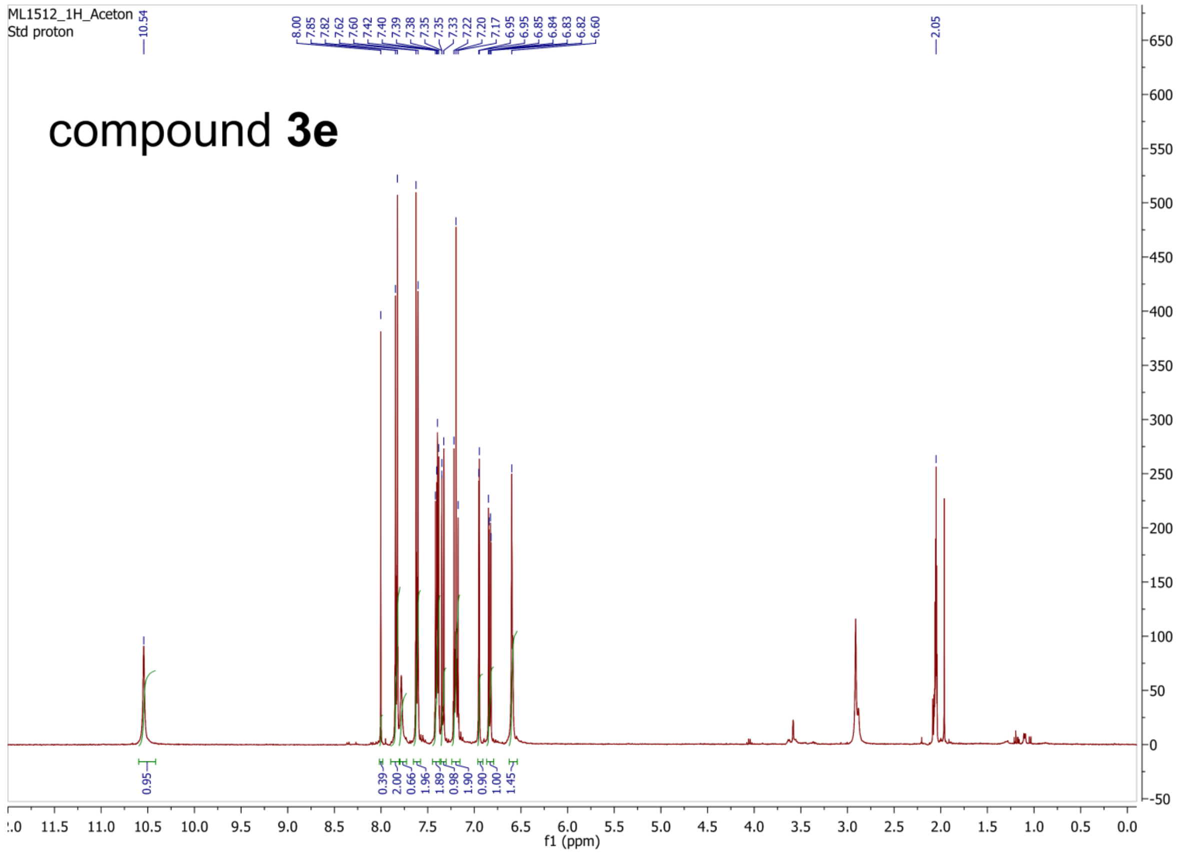


Figure S15. **[1]H-NMR of compound 3e in acetone-*d*$_6$.**

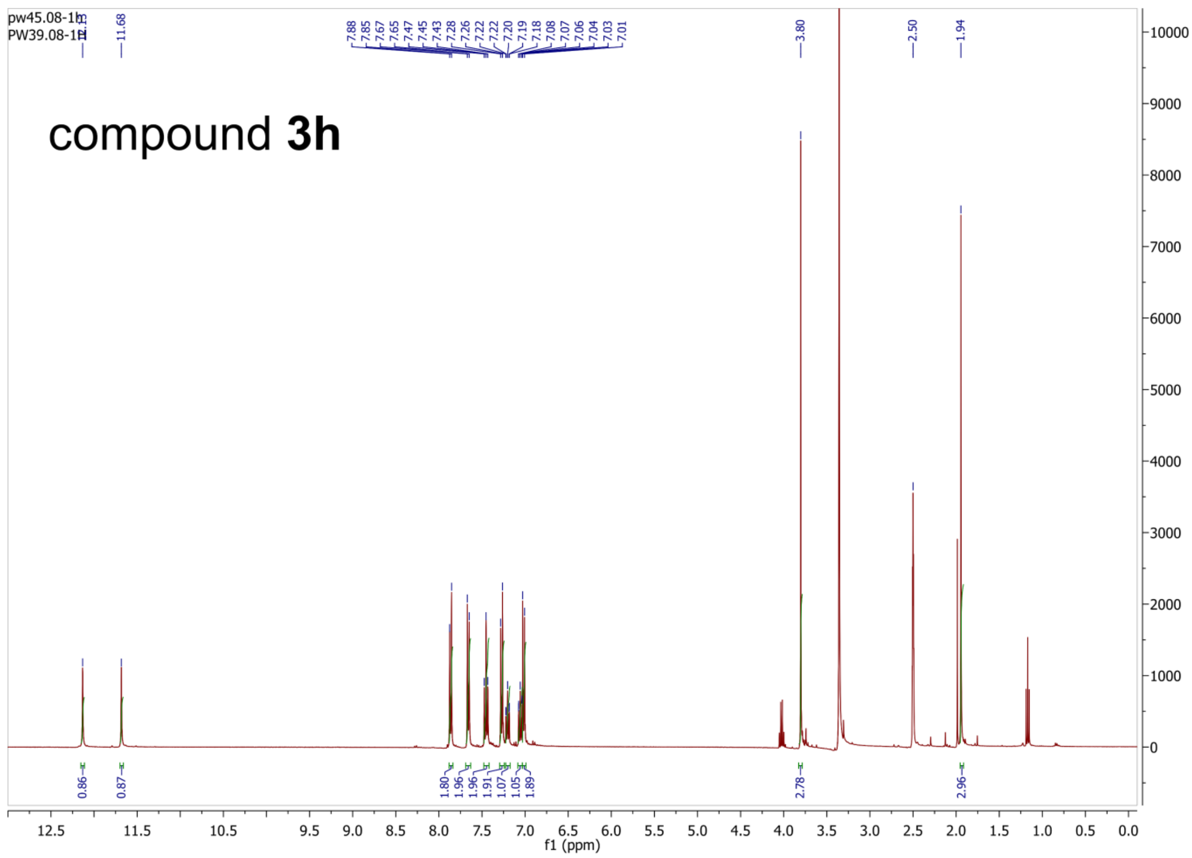


Figure S16. **[1]H-NMR of compound 3h in DMSO-*d*$_6$.**

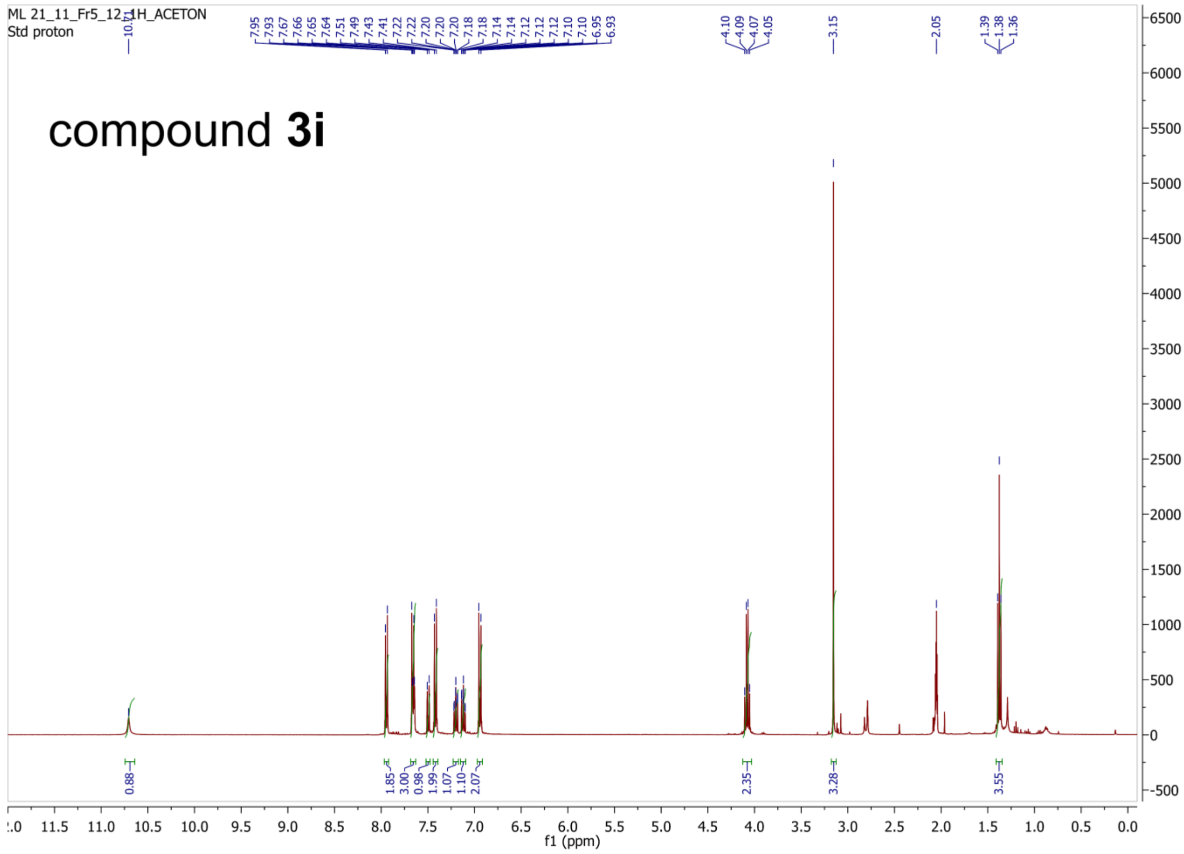


Figure S17. **^{1}H-NMR of compound 3i in acetone-d_6.**

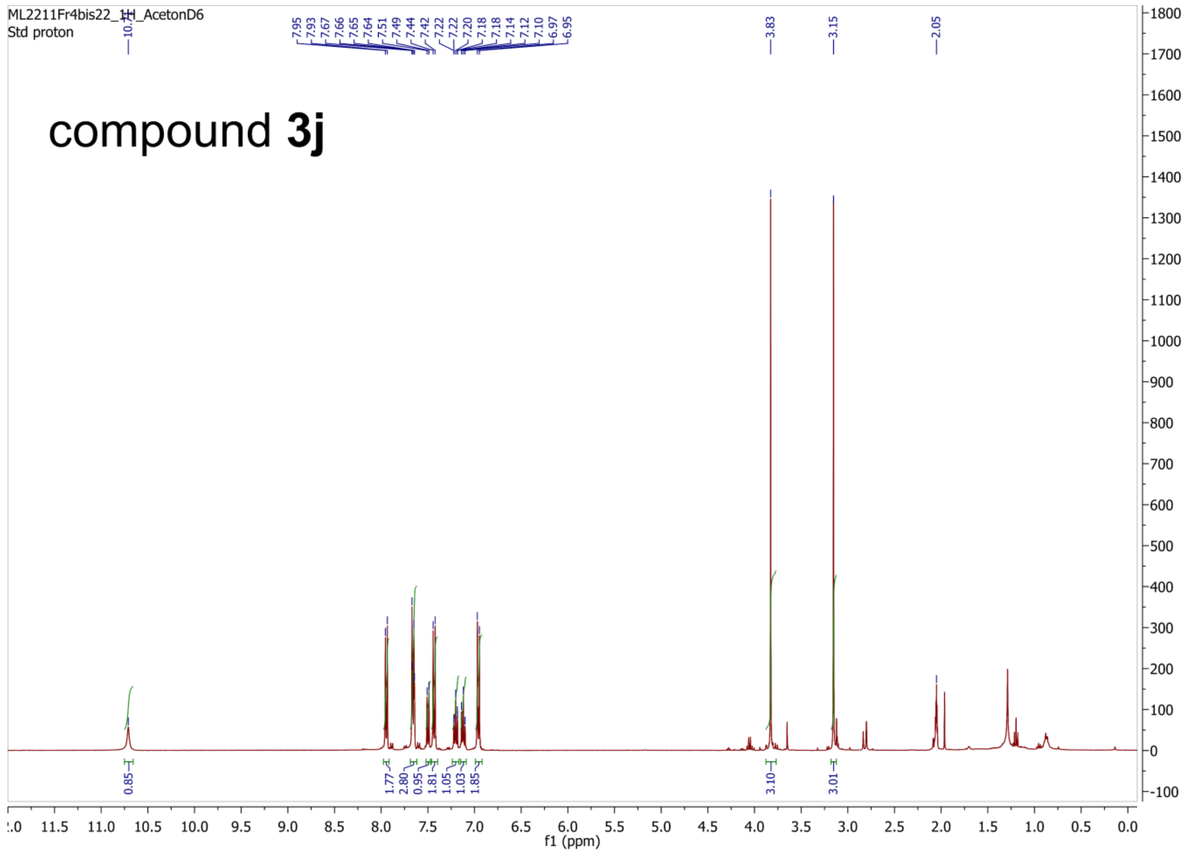


Figure S18. **^{1}H-NMR of compound 3j in acetone-d_6.**

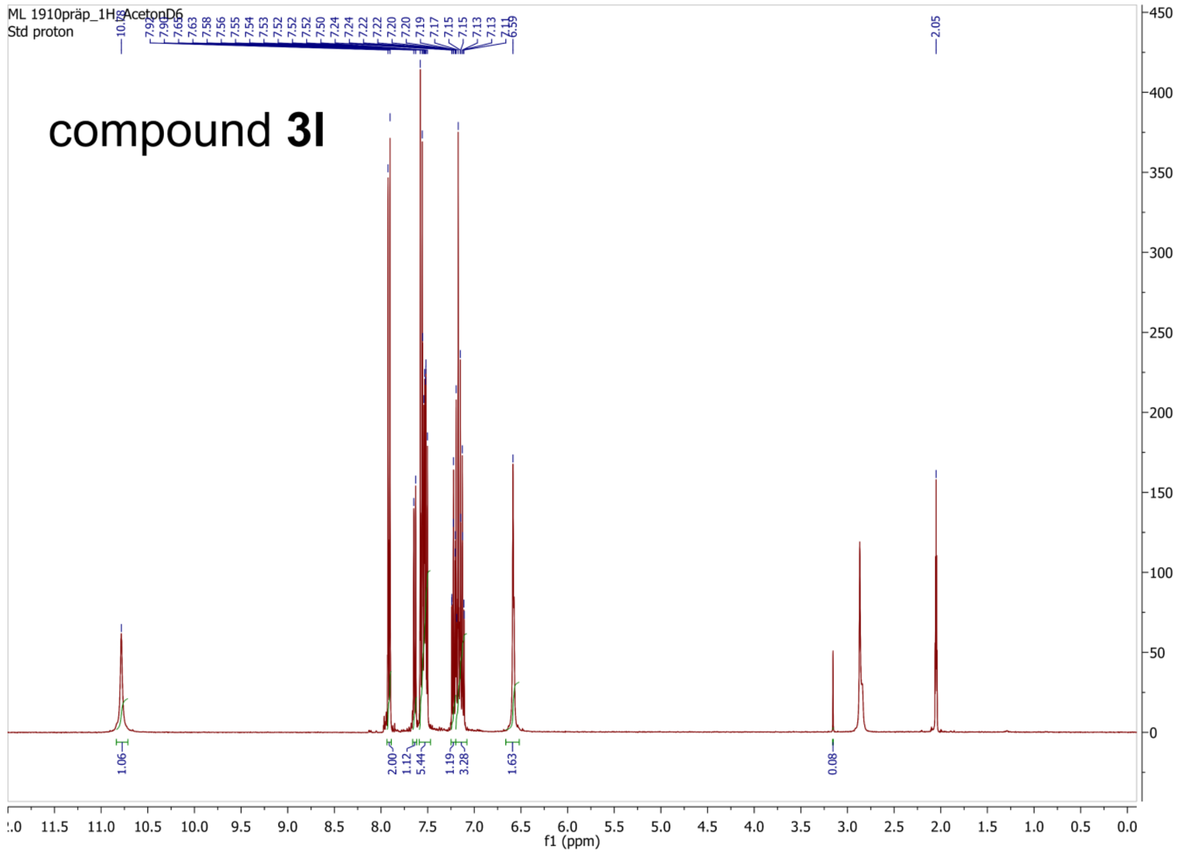


Figure S19. [1]H-NMR of compound 3l in acetone-d_6.

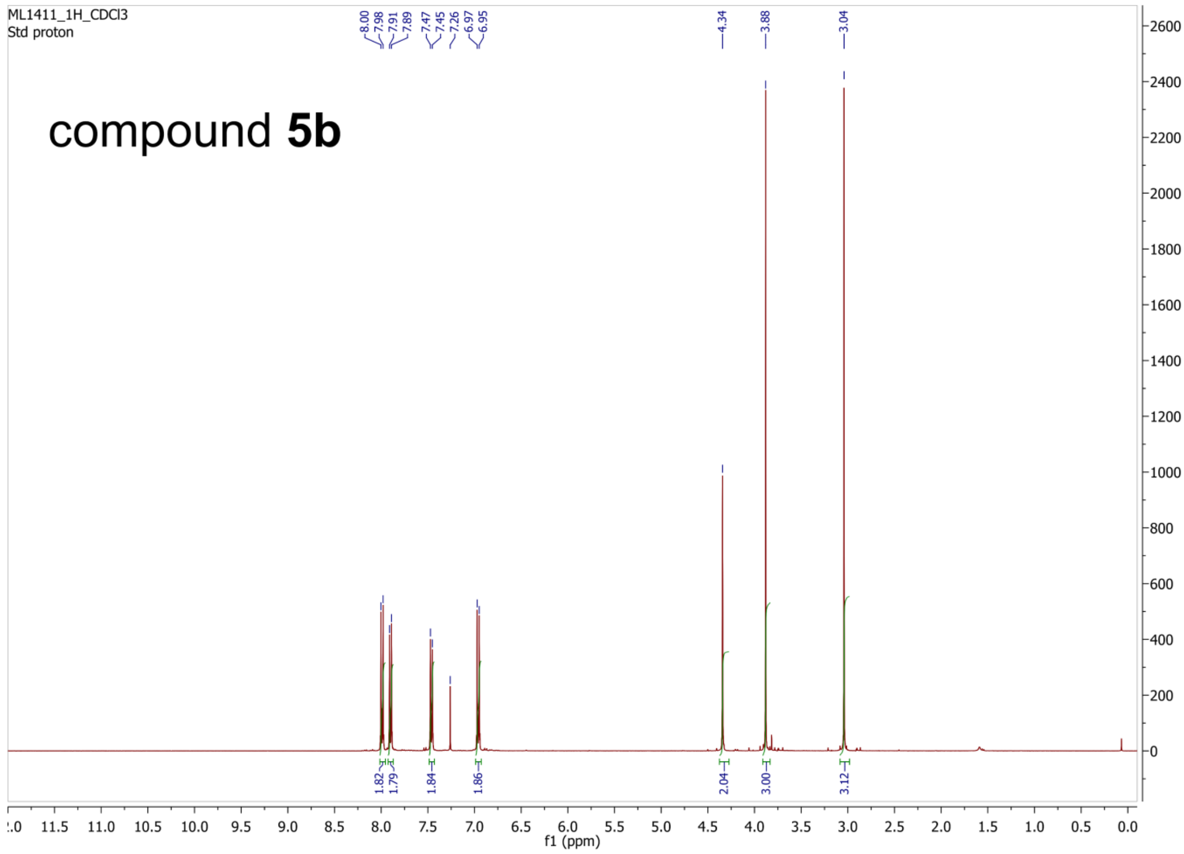


Figure S20. [1]H-NMR of compound 5b in $CDCl_3$.

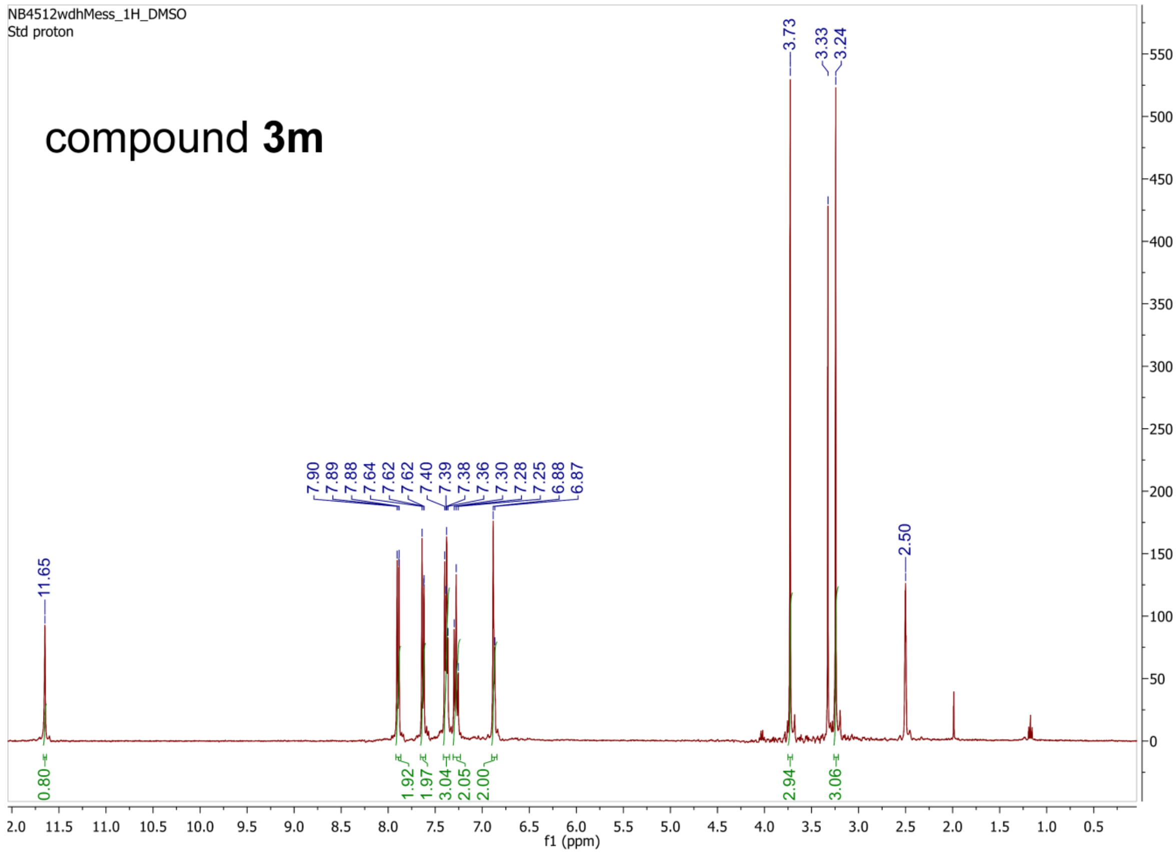


Figure S21. ¹H-NMR of compound 3m in DMSO-*d*₆.

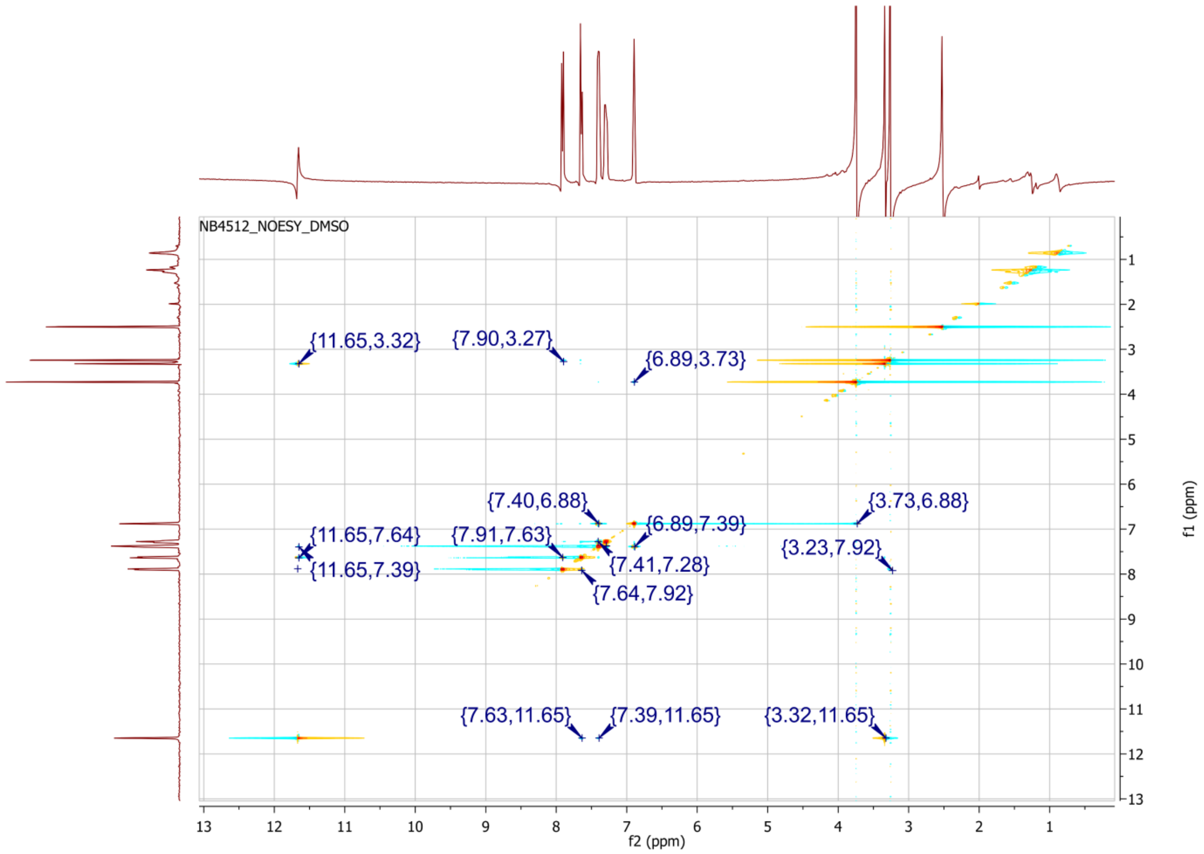


Figure S22. NOESY spectrum of compound 3m in DMSO-*d*₆.

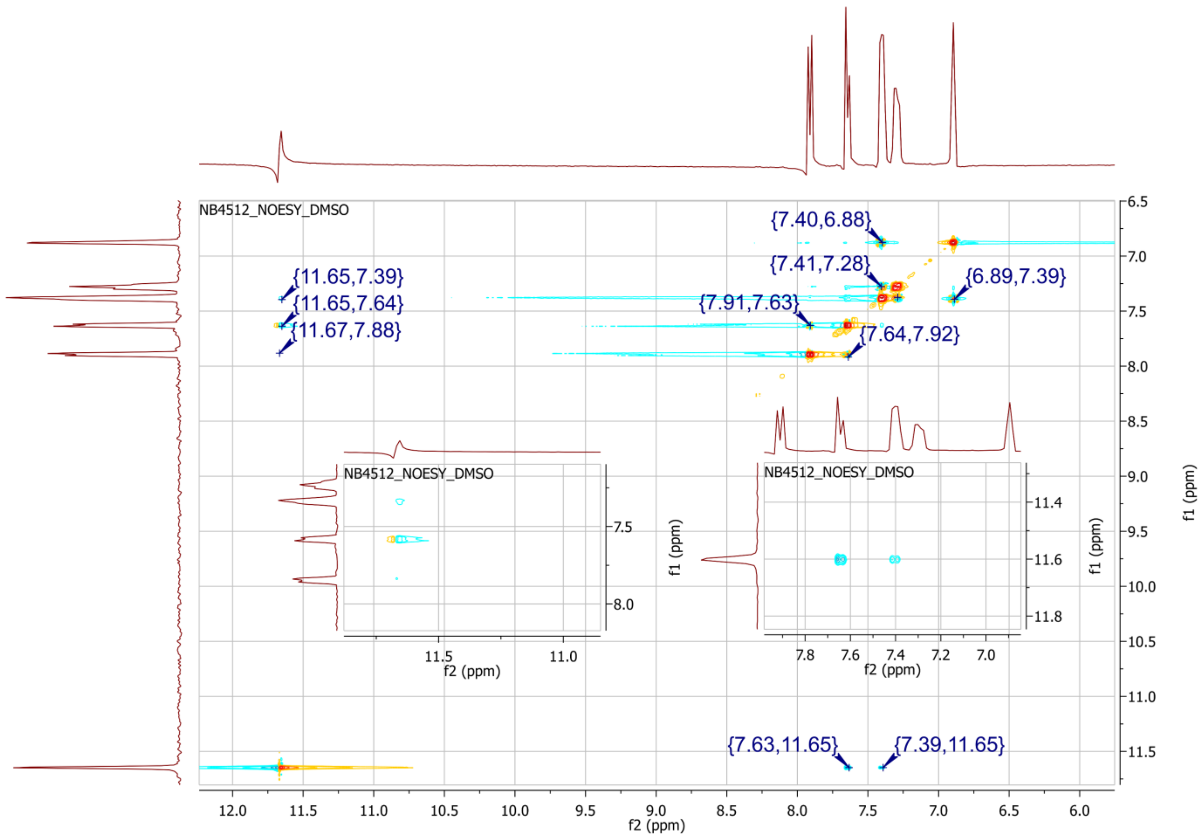


Figure S23. NOESY spectrum of compound 3m in DMSO-d_6 within in the range of 6.5-12 ppm.

The two expansions in the range of {f1 = 7.25-8.0, f2 = 11.0-11.75} (left) and {f1 = 11.3-11.8, f2 = 6.9-7.9} (right) show the cross peaks that assure the structural assignment of **3m**. A strong cross peak {7.63, 11.65} is present for the interaction of the indole-NH at 11.65 ppm with the dublett at 7.63 ppm which can be assigned by ^{1}H-NMR to two protons of the methylsulfonyl-substituted phenyl ring and with NOESY to the protons at position 2 and 6 of the phenyl ring. This interaction can only be found for **3m** and not its regioisomer 2-(4-fluorophenyl)-5-methoxy-3-[4-(methylsulfonyl)phenyl]-1*H*-indole thus assuring the structural assignment of **3m**. A second strong cross peak {7.39, 11.65} between the singulett at 11.65 ppm and the multiplett at 7.33-7.44 ppm ($2H_{F\text{-phenyl } 2/6}/H_{indole}$) can be assigned to the interactions of the indole-NH with one proton of the indole moiety (C7-H). A third weak cross peak {7.88, 11.65} better visible at increased intensity indicates a further weak interaction of the indole-NH with the dublett at 7.88 ppm, which can in turn be assigned to the protons in position 3 and 5 of the methylsulfonyl-substituted phenyl ring.

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