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PAPER

Sequential coupling/desilylation–coupling/cyclization in a single pot under Pd/C–Cu catalysis: Synthesis of 2-(hetero)aryl indoles†‡

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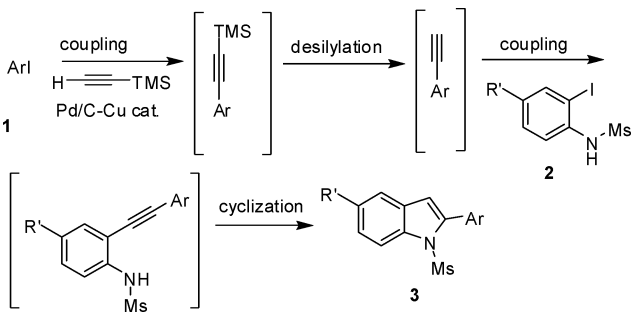
A new one-pot synthesis of 2-(hetero)aryl indoles *via* sequential C–C coupling followed by C–Si bond cleavage and a subsequent tandem C–C/C–N bond forming reaction is described. A variety of functionalized indole derivatives were prepared by conducting this four step reaction under Pd/C–Cu catalysis. The methodology involved coupling of (trimethylsilyl)acetylene with iodoarenes in the presence of 10% Pd/C–CuI–PPh_3 and triethylamine in MeOH, followed by treating the reaction mixture with K_2CO_3 in aqueous MeOH, and finally coupling with *o*-iodoanilides. The single crystal X-ray data of a synthesized indole derivative is presented. Application of the methodology, *in vitro* pharmacological properties of the synthesized compound, along with a docking study is described.

Introduction

2-substituted indole is one of the key structural frameworks found in many naturally occurring alkaloids, bioactive compounds and drugs.[1–4] Many synthetic methods including transition metal catalyzed reactions have been reported for the construction of an indole ring.[5] One of the commonly used methods for the synthesis of 2-substituted indoles involves two steps *e.g.* Sonogashira coupling of 2-aminoaryl halide with a terminal alkyne followed by cyclization of the resulting 2-alkynylanilines. The cyclization step can be carried out in the presence of a range of catalysts or promoters such as Cu(I)salt,[6] metal alkoxide,[7] fluorides,[8] Lewis acids,[9] gold(III),[10] and iodine.[11] Alternatively, 2-substituted indoles can be prepared directly *via* a single step method using Pd/C–Cu mediated coupling-cyclization of *o*-iodoanilides with terminal alkynes.[12] However, to obtain an indole derivative possessing a specific aryl group at the C-2 position, the use of an appropriate terminal alkyne containing the corresponding aryl moiety was necessary in all of these cases. Moreover, many arylalkynes are either expensive or commercially not available, or their preparation requires cumbersome methods.[13–14] Their isolation in the pure form is also sometimes problematic as these compounds are prone to undergo rapid dimerization. Thus a more effective method was necessary to prepare 2-aryl substituted indoles of our interest. Herein we report Pd/C–Cu mediated synthesis of 2-aryl substituted indoles (Scheme 1) *via* sequential (i) C–C coupling followed by (ii) C–Si bond cleavage and subsequent (iii) C–C and (iv) C–N bond forming reactions in a single pot. To the best of our knowledge there is no precedence of preparing 2-aryl indole derivatives using four steps in a single pot under Pd/C–Cu catalysis.



Scheme 1 Strategy to synthesize 2-aryl indoles in a single pot.

Results and discussions

Synthesis

Based on the idea that desilylation of 2-aryl substituted trimethylsilyl alkynes could be achieved easily by using K_2CO_3 in MeOH–H_2O we planned to generate a range of terminal alkynes of our choice *in situ*. We anticipated that once generated these alkynes could undergo a further Pd-mediated coupling reaction with an appropriate *o*-substituted arylhalide in the same pot. To this end, we assessed the reaction sequence involving the use of 1-iodo-4-methyl benzene **1a**, (trimethylsilyl)acetylene (TMSA) and *o*-iodoanilide **2a** under various reaction conditions (Table 1).

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† Dedicated to Prof. Nitya G. Kundu on the occassion of his 75th birthday.

‡ Electronic supplementary information (ESI) available: Crystallographic data (CIF) for compound **3a** and copies of spectra of selected compounds. CCDC reference number 784742. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob01161d

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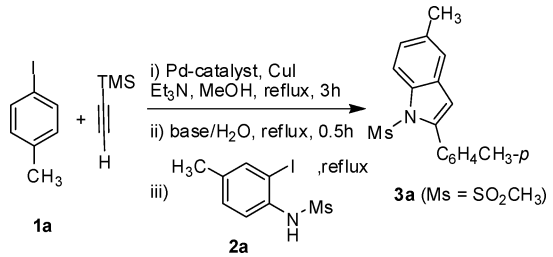
Table 1 The reaction of **1a**, TMSA and **2a** under various reaction conditions[a]



Entry	Catalysts	Base	Time[b] (h)	% Yield[c]
1	$Pd(PPh_3)_2Cl_2$	K_2CO_3	4	78
2	10% Pd/C–PPh_3	K_2CO_3	6	80
3	10% Pd/C–PPh_3	KOH	6	75
4	10% Pd/C	K_2CO_3	6	12
5	PPh_3	K_2CO_3	8	55
6	10% Pd/C–PPh_3[d]	K_2CO_3	8	43

[a] All of the reactions were carried out using iodide **1a** (2.137 mmol), TMSA (4.274 mmol), Pd catalyst (0.02137 mmol), CuI (0.02137 mmol), [PPh_3 (0.04274 mmol)] and Et_3N (0.5 mL) in MeOH (5.0 mL), then a base (4.274 mmol) in water (0.5 mL) and MeOH (1.5 mL) and finally *o*-iodoanilides (**2a**). [b] After adding **2a**. [c] Isolated yield. [d] The reaction was carried out without CuI.

We performed Sonogashira coupling[15] of **1a** with TMSA using a Pd catalyst, CuI and Et_3N in methanol at refluxing temperature. The resulting crude reaction mixture was then directly treated with a solution of an inorganic base in MeOH/H_2O (3 : 1). After stirring this mixture at the refluxing temperature for 0.5 h, *o*-iodoanilides, **2a**, were added and the mixture was stirred at the refluxing temperature. Initially, we used $(PPh_3)_2PdCl_2$ as a catalyst and K_2CO_3 as a base (for the desilylation step) when the desired product, **3a**, was isolated in a good yield (entry 1, Table 1). However, due to our long term interest in the Pd/C-mediated alkynylation reaction[16] we conducted the present reaction using 10% Pd/C–PPh_3 as the catalyst system. Additionally, Pd/C is cheaper, more stable, easier to handle, separable from the product and has the potential to be recycled. To our satisfaction the reaction proceeded well, affording **3a** in a good yield (entry 2, Table 1). Though the use of KOH was found to be equally effective for the desilylation step (entry 3, Table 1) we however preferred milder base K_2CO_3. Omission of any component of the catalyst 10% Pd/C–PPh_3–CuI decreased the product yield (entries 4, 5 and 6, Table 1). The indole, **3a**, was characterized by spectral data and this was supported by the molecular structure, being confirmed by X-ray analysis (Fig. 1).[17]

With the optimized reaction condition in hand we then decided to expand the generality and scope of this methodology *via* employing other iodoarenes and the results of this study are summarized in Table 2. The present four-step reaction in a single pot proceeded well with a number of iodoarenes affording a variety of indoles in good yields. Both electron donating groups such as Me (**1a**), OMe (**1b**), OH (**1d**), NH_2 (**1e** and **1f**) or electron withdrawing groups such as CF_3 (**1c**) and CO_2Et (**1g**) present on the iodoarene ring were well tolerated. A further application of this methodology was demonstrated in the preparation of 2-heteroaryl indoles **5a–c** from 2-iodothiophene derivative **4** (Scheme 2). The iodo compound **4** was prepared

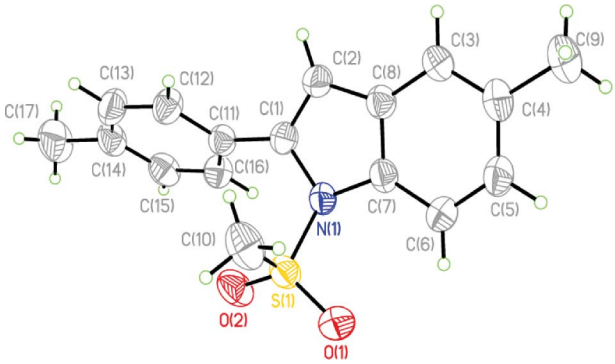
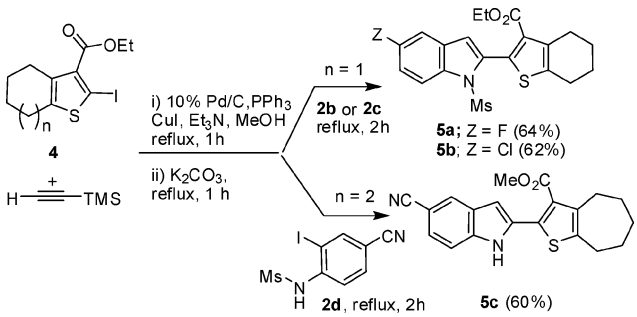
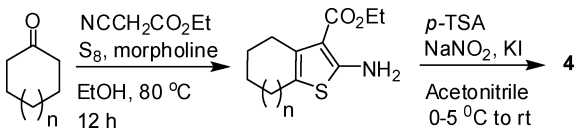


Fig. 1 X-ray crystal structure of **3a** (ORTEP diagram). Displacement ellipsoids are drawn at 50% probability level for non-hydrogen atoms.



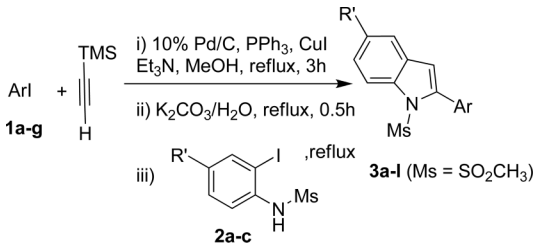
Scheme 2 One pot synthesis of 2-heteroaryl indoles.

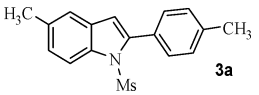
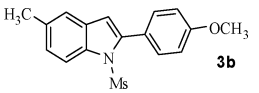
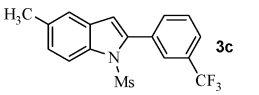
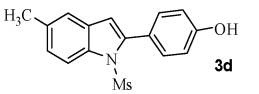
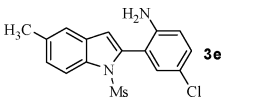
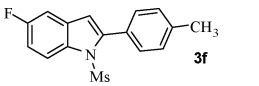
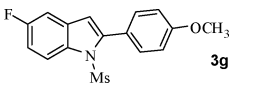
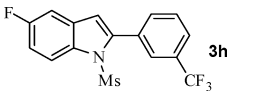
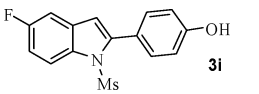
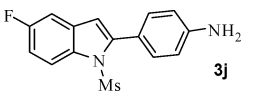
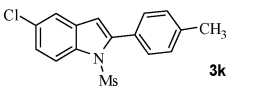
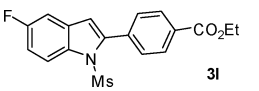


Scheme 3 Preparation of iodo compound **4**.

from an appropriate cyclic ketone according to Scheme 3.[18] Thus condensation of the cyclic ketone with an α-cyanoester in the presence of elemental sulfur, under Gewald reaction conditions, provided a 2-aminothiophene derivative which was converted to the 2-iodo derivative, **4**, under Sandmeyer conditions. The reaction of **4** with TMSA and subsequently with *o*-iodoanilide (**2b**, **2c** or **2d**) under the optimized conditions (entry 2, Table 1) provided the desired 2-heteroaryl indoles (**5a–c**) in 60–64% yield. Notably, *N*-demesylation, as well as trans-esterification, was observed during the preparation of indole **5c** in the same pot. Overall, the present four-step method does not require the addition of any additional amounts of the Pd/Cu-catalyst to facilitate the final coupling–cyclization step. Due to our continued interest in bioactive molecules[19] some of the indoles synthesized were converted to compounds of potential pharmacological interest (Scheme 3 and 4). For example, indole **3b** was converted to a 2-aryl-3-benzoylindole derivative (**7**) *via* TFAA-H_3PO_4 mediated benzoylation,[20a,b] followed by deprotection of the resulting *N*-mesyl product (**6**) (Scheme 4). Compound **3e** was converted to an indole-based quinaxoline derivative (**8**) (Scheme 5) *via* the reaction with quinoxaline-2-carboxylic acid in the presence of coupling reagents *e.g.* 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI.HCl) and 1-hydroxy-benzotriazole (HOBt) under mild conditions. Notably, a quinaxoline derivative, SIRT 1720, has been reported as a potent activator of human SIRT 1.[21]

Table 2 One pot synthesis of 2-aryl indoles[a]



Entry	ArI (**1**; Ar =)	**2**; R′ =	Product (**3**)	Time[b] (h)	% Yield[c]
1	**1a**; $C_6H_4CH_3$-*p*	**2a**; CH_3	 **3a**	6	80
2	**1b**; $C_6H_4OCH_3$-*p*	**2a**	 **3b**	5	85
3	**1c**; $C_6H_4CF_3$-*m*	**2a**	 **3c**	5	78
4	**1d**; C_6H_4OH-*p*	**2a**	 **3d**	8	65
5	**1e**; $C_6H_3NH_2$(o)Cl(m)	**2a**	 **3e**	4	69
6	**1a**	**2b**; F	 **3f**	4	60[d]
7	**1c**	**2b**	 **3g**	5	83
8	**1c**	**2b**	 **3h**	8	68
9	**1d**	**2b**	 **3i**	8	68
10	**1f**	**2b**	 **3j**	11	63
11	**1a**	**2c**; Cl	 **3k**	6	84[d]
12	**1g**;$C_6H_4CO_2Et$-*p*	**2b**	 **3l**	5	70

[a] All the reactions were carried out using iodide **1** (2.137 mmol), TMSA (4.274 mmol), 10% Pd/C (0.02137 mmol), CuI (0.02137 mmol), PPh_3 (0.04274 mmol) and Et_3N (0.5 mL) in MeOH (5.0 mL), then K_2CO_3 (4.274 mmol) in water (0.5 mL) and MeOH (1.5 mL), and finally *o*-iodoanilides (**2**). [b] After adding **2**. [c] Isolated yield. [d] Known compound (see ref. 12*a*).

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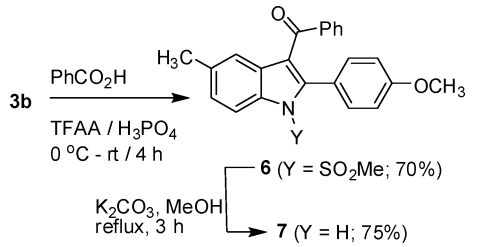
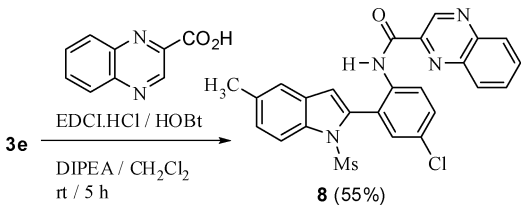
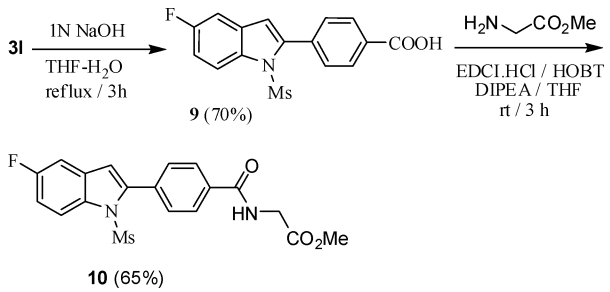


Scheme 4 Synthesis of 2-aryl-3-aroylindole.



Scheme 5 Synthesis of quinaxoline derivative.

Indole **3l** was converted to an α-amino acid derivative, **10**, *via* the corresponding acid, **9** (Scheme 6). Thus, hydrolysis of **3l**, followed by the reaction of the resultant acid **9** with the methyl ester of glycine in the presence of coupling reagents, afforded the desired compound, **10**.



Scheme 6 Synthesis of an α-amino acid analogue of indole **3l**.

Pharmacology

As part of our ongoing program on the identification of activators of SIRT 1 (Silent information regulator 1),[22] we screened some of the compounds synthesized for their SIRT 1 activation properties *in vitro*. SIRT 1 activators have been reported to be beneficial for the potential treatment of type 2 diabetes *via* their anti-aging effect.[23] The *in vitro* activity was determined by using a SIRT 1 fluorescence activity assay kit from Cyclex Inc according to a known method.[21] Thus bacterially purified human SIRT 1 enzyme was incubated with the fluorophore-labelled substrate peptide (25 μM) and cofactor, NAD^+ (25 μM), in the presence or absence of compounds. Suramin, a known inhibitor of SIRT 1 was also used in this assay. Among all the compounds tested, 2-aryl-3-benzoylindole derivative, **7**, was found to be an activator of human SIRT 1 when tested at 10 μM *in vitro* whereas suramin showed significant inhibition (Fig. 2). No significant activation of SIRT 1 was observed when 2-arylindole derivatives (**3**) were used at the same concentration. In order to understand its interaction with SIRT 1, the indole, **7**, was docked into the active site of SIRT 1 (Fig. 2). Indeed, the binding energy (*i.e.* −5.81 Kcal mol^{-1}) of the interaction of compound **7** with the activator domain of hSIRT 1 indicates that it binds well with this NAD^+-dependent protein deacytylase. The key interacting amino acids were found to be Pro2, Leu3, Glu20, Asp5 and ILE27.

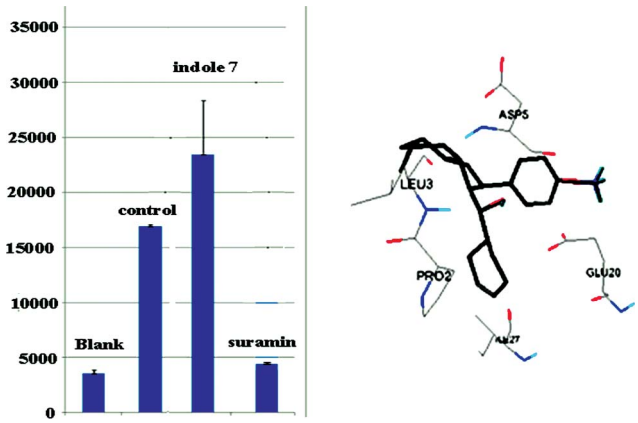


Fig. 2 SIRT 1 activation and docking study of indole **7**.

Conclusions

In conclusion, we have demonstrated a new Pd/C-mediated one-pot synthesis of 2-(hetero)aryl indoles *via* sequential C–C coupling, followed by C–Si bond cleavage and subsequent tandem C–C/C–N bond forming reactions. A variety of indole derivatives were prepared using this methodology. Its application has been demonstrated in preparing compounds of potential pharmacological interest, preparation of which may be tedious *via* other methods. The methodology does not involve the use of any expensive reagents, catalysts or solvents. As far as we know, in spite of a number of reports on efficient palladium-mediated syntheses of 2-(hetero)aryl indoles, no successful examples of indole synthesis using four steps in a single pot under Pd/C–Cu catalysis have been reported. Due to the operational simplicity and potential for introducing complexity into an indole framework the present methodology could become a useful alternative to the previously reported methods. The methodology therefore would find wide application in generating a diversity based library of indoles of potential medicinal value.

Experimental

Chemistry

General methods. Unless stated otherwise, reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F_{254}), visualizing with ultraviolet light or iodine spray. Column chromatography was performed on silica gel (60–120 mesh) using distilled petroleum ether and ethyl acetate. ^1H and ^{13}C NMR spectra were determined in $CDCl_3$ solution using 400 and 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.0$) as the internal standard and expressed in parts per million. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), and m (multiplet) as well as b (broad). Coupling constants (J) are given in hertz. Infrared spectra were recorded on a FT-IR spectrometer. Melting points were determined by using a Buchi melting point B-540 apparatus and are uncorrected. MS spectra were obtained on a

mass spectrometer. HR-MS was determined using waters LCT premier XETOF ARE-047 apparatus. Elemental analyses were performed using a Perkin Elmer 240 C analyzer.

General procedure for the preparation of 2-aryl indoles (3a–l). To a solution of aryl iodide (**1**, 2.137 mmol), 10% Pd/C (0.003 g, 0.0214 mmol), CuI (0.004 g, 0.02137 mmol), and PPh_3 (0.012 g, 0.04274 mmol) in methanol (5.0 mL), were added triethylamine (0.5 mL, 1.26 mmol) and (trimethylsilyl)acetylene (0.42 g, 4.274 mmol) at room temperature with stirring. The mixture was stirred at the refluxing temperature for 3 h (the reaction was monitored by TLC) and a solution of K_2CO_3 (0.59 g, 4.274 mmol), dissolved in water (0.5 mL) and methanol (1.5 mL), was added at the same temperature. The mixture was stirred at the refluxing temperature for an additional 0.5 h and *o*-iodoanilide (**2**, 2.137 mmol) was added. The stirring continued for an additional 4–11 h (the reaction was monitored by TLC) at the same temperature. After completion the reaction mixture was quenched with saturated NH_4Cl solution (60 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were collected, combined, washed with 2.0 N HCl (50 mL) followed by water (50 mL) and saturated NaCl solution (50 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (EtOAc/*n*-Hexane) to give the desired product.

Spectral data of 2-aryl indoles (3a–k)

5-methyl-1-(methylsulfonyl)-2-*p*-tolyl-1*H*-indole (3a). yield 0.51 g (80%); off white solid; mp 178–180 °C; R_f = 0.71 (20% EtOAc-*n*-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.40 (s, 3H), 2.45 (s, 3H), 2.66 (s, 3H), 6.6 (s, 1H), 7.17 (d, J = 8.8 Hz, 1H), 7.21 (d, J = 7.6 Hz, 2H), 7.36 (s, 1H), 7.44 (d, J = 8 Hz, 2H), 7.97 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.2, 21.4, 38.9, 112.6 (2C), 115.6, 120.8 (2C), 126.2, 128.4, 129.1, 129.91, 130.6, 134.2, 136.2, 138.7, 142.2; MS (ES mass): m/z 300.3 (M + 1, 40%); HR-MS: calcd for $C_{17}H_{18}NO_2S$ (M + H): 300.1058, found 300.1056; Elemental Analysis found C, 68.43; H, 5.70; N, 4.44; $C_{17}H_{17}NO_2S$ requires C, 68.20; H, 5.72; N, 4.68

2-(4-methoxyphenyl)-5-methyl-1-(methylsulfonyl)-1*H*-indole (3b). yield 0.57 g (85%); pale yellow solid; mp 184–186 °C; R_f = 0.57 (20% EtOAc-*n*-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.45 (s, 3H), 2.67 (s, 3H), 3.85 (s, 3H), 6.58 (s, 1H), 6.94 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.8 Hz, 1H), 7.35 (s, 1H), 7.49 (d, J = 8.8 Hz, 2H), 7.97 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.4, 39.1, 55.4, 112.4 (2C), 113.3, 115.8, 120.8, 124.4, 126.3, 130.8, 131.5, 134.3, 136.3 (2C), 142.2, 160.2; MS (ES mass): m/z 316.4 (M + 1, 70%); HR-MS: calcd, for $C_{17}H_{18}NO_3S$ (M + H): 316.1007, found: 316.0995; Elemental Analysis found: C, 64.97; H, 5.42; N, 4.32; $C_{17}H_{17}NO_3S$ requires C, 64.74; H, 5.43; N, 4.44

5-methyl-1-(methylsulfonyl)-2-(3-(trifluoromethyl)phenyl) -1*H*-indole (3c). yield 0.59 g (78%); white solid; mp > 150 °C; R_f = 0.37 (10% EtOAc-*n*-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.47 (s, 3H), 2.68 (s, 3H), 6.72 (s, 1H), 7.22 (dd, J_1 = 1.2 Hz, J_2 = 1.2 Hz, 1H), 7.40 (s, 1H), 7.51–7.81 (m, 4H), 7.98 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.2, 39.8, 114.2, 115.5, 121.2, 125.3, 125.3, 126.1, 126.6, 128.0, 129.9, 130.4, 132.8, 133.9, 134.6, 136.4, 140.4; MS (ES mass): m/z 354.1 (M + 1, 50%); HR-MS: calcd for $C_{17}H_{15}F_3NO_2S$ (M + H): 354.0776, found 354.0746; Elemental Analysis found C, 57.54; H, 3.97; N, 4.19; $C_{17}H_{14}F_3NO_2S$ requires C, 57.78; H, 3.99; N, 3.96.

4-(5-methyl-1-(methylsulfonyl)-1*H*-indol-2-yl)phenol (3d). white solid; yield 0.42 g (65%); mp 190–192 °C; R_f = 0.4 (10% EtOAc-*n*-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.30 (s, 3H), 2.56 (s, 3H), 6.8 (s, 1H), 6.90 (d, J = 8.8 Hz, 2H), 7.12–7.20 (m, 2H), 7.5 (d, J = 8.0 Hz, 1H) 7.90 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.2, 39.8, 114.1, 115.5, 121.9, 125.8 (2C), 125.3, 126.6, 130.4, 132.8, 133.5, 134.6, 136.4 (2C), 162.5; MS (ES mass): m/z 302.3 (M + 1, 50%). HR-MS: calcd for $C_{16}H_{16}NO_3S$ (M + H): 302.0851, found: 302.0875; Elemental Analysis found: C, 63.56; H, 5.05; N, 4.79; $C_{16}H_{15}NO_3S$ requires C, 63.77; H, 5.02; N, 4.65.

4-chloro-2-(5-methyl-1-(methylsulfonyl)-1*H*-indol-2-yl)aniline (3e). yield 0.49 g (69%); light brown solid; mp 171–173 °C; R_f = 0.4 (20% EtOAc-*n*-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 2.88 (s, 3H), 3.90 (bs, 2H), 6.63 (s, 1H), 6.68 (d, J = 8.0, 1H), 7.16–7.25 (m, 3H), 7.4 (s, 1H), 7.96 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 39.8, 113.1, 114.9, 116.6, 119.5, 121.1, 122.4, 126.7, 130.2, 130.3, 133, 134.1, 135.6, 136.9, 144.9; MS (ES mass): m/z 335.3 (M + 1, 100%); HR-MS: calcd for $C_{16}H_{16}N_2O_2SCl$ (M + H): 335.0621, found 335.0639; Elemental Analysis found: C, 57.57; H, 4.50; N, 8.29; $C_{16}H_{15}ClN_2O_2S$ requires C, 57.40; H, 4.52; N, 8.37.

5-fluoro-1-(methylsulfonyl)-2-*p*-tolyl-1*H*-indole[12a] (3f). yield 0.39 g (60%); white solid; mp 203–205 °C (209–210 °C[12a]); R_f = 0.47 (10% EtOAc-*n*-Hexane); White solid, mp 190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.41 (s, 3H), 2.74 (s, 3H), 6.6 (s, 1H), 7.16 (s, 1H), 7.30 (d, J = 2 Hz, 2H), 7.32 (d, J = 1.6 Hz, 1H), 7.44 (d, J = 7.6 Hz, 2H), 7.55 (d, J = 2 Hz, 1H), 8.07–8.09 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.4, 39.9, 111.7, 116.9 (2C), 120.4, 125.0, 128.5, 129.1 (2C), 130.1, 131.5, 134.2, 136.2, 139.3, 143.5; IR (cm^{-1}): 3139,1272, 1360; MS (ES mass): m/z 304.6 (M + 1, 100%); HR-MS: calcd for $C_{16}H_{15}FNO_2S$: 304.2546, found 304.2462.

5-fluoro-2-(4-methoxyphenyl)-1-(methylsulfonyl)-1*H*-indole (3g). yield 0.56 g (83%); off white solid; mp 198–200 °C; R_f = 0.55 (10% EtOAc-*n*-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.72 (s, 3H), 3.86 (s, 3H), 6.59 (s, 1H), 6.95 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 2 Hz, 1H), 7.48 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 1.6 Hz, 1H), 8.04 (d, J = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 39.8, 55.3, 111.5, 113.3, 116.9 (2C), 120.3, 123.5, 124.9, 130.2 (2C), 131.5, 131.6, 136.2, 143.3, 160.4; MS (ES mass): m/z 320.3 (M + 1, 10%); HR-MS: calcd for $C_{16}H_{15}FNO_3S$: 320.0757, found 320.0746; Elemental Analysis found C, 60.04; H, 4.40; N, 4.47; $C_{16}H_{14}FNO_3S$ requires C, 60.18; H, 4.42; N, 4.39.

5-fluoro-1-(methylsulfonyl)-2-(3-(trifluoromethyl)phenyl)-1*H*-indole (3h). yield 0.52 g (68%); off white solid; mp 121–123 °C; R_f = 0.35 (10% EtOAc-*n*-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.72 (s, 3H), 6.83 (s, 1H), 7.17 (dd, J_1 = 1.6 Hz, J_2 = 2.0 Hz, 2H), 7.51–7.87 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 39.1, 112.1, 121.8, 122.6, 123.3, 124.5, 125.3, 126.2, 128.3, 129.6, 130.1, 131.4, 132.7, 135.4, 137.6, 142.2; MS (ES mass): m/z 358.9 (M + 1, 10%); HR-MS: calcd for $C_{16}H_{12}F_4NO_2S$: 358.0525, found 358.0536; Elemental Analysis found C, 53.55; H, 3.08; N, 4.05; $C_{16}H_{11}F_4NO_2S$ requires C, 53.78; H, 3.10; N, 3.92.

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4-(5-fluoro-1-(methylsulfonyl)-1*H*-indol-2-yl)phenol (3i). yield 0.44 g (68%); white solid; mp >150 °C; R_f = 0.42 (20% EtOAc-*n*-Hexane) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.57 (s, 3H), 6.79 (s, 1H), 6.93 (d, J = 8.4 Hz, 2H), 7.20–7.79 (m, 3H), 7.88 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 40.3, 112.4, 113.3, 114.9 (2C), 120.8, 123.5, 128.7, 129.8 (2C), 131.9, 132.6, 136.3, 138.5, 161.8; MS (ES mass): m/z 306.3 (M + 1, 10%); HR-MS: calcd for $C_{15}H_{13}FNO_3S$ (M + H): 306.0600, found 306.0623; Elemental Analysis found: C, 59.19; H, 3.95; N, 4.45; $C_{15}H_{12}FNO_3S$ requires C, 59.01; H, 3.96; N, 4.59.

4-(5-fluoro-1-(methylsulfonyl)-1*H*-indol-2-yl)aniline (3j). yield 0.41 g (63%); light brown solid; mp 133–135 °C; R_f = 0.45 (20% EtOAc-*n*-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.72 (s, 3H), 4.10 (bs, 2H), 6.55 (s, 1H), 6.71 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 2.4 Hz, 1H), 7.34 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 1.6 Hz, 1H), 8.03 (d, J = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 40.3, 112.4, 113.3, 115.7 (2C), 120.8, 123.5, 128.7, 129.8 (2C), 131.9, 132.6, 136.3, 138.5, 146.8; MS (ES mass): m/z 305.6 (M + 1, 10%); HR-MS: calcd for $C_{15}H_{14}FN_2O_2S$ (M + H): 305.0760, found 305.0778; Elemental Analysis found: C, 59.43; H, 4.30; N, 9.02; $C_{15}H_{13}FN_2O_2S$ requires C, 59.20; H, 4.31; N, 9.20.

5-chloro-1-(methylsulfonyl)-2-*p*-tolyl-1*H*-indole[12a] (3k). yield 0.57 g (84%); white solid, mp 206–208 °C (207–209 °C[12a]); R_f = 0.65 (20% EtOAc-*n*-Hexane); Brown solid, mp 145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.41 (s, 3H), 2.73 (s, 3H), 6.61 (s, 1H), 7.24 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 1.6 Hz, 1H), 7.43 (d, J = 8 Hz, 2H), 7.55 (d, J = 1.6 Hz, 1H), 8.04 (d, J = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.4, 39.8, 111.7, 115.7 (2C), 120.4, 125.0, 128.5, 128.9 (2C), 130.1, 131.5, 134.2, 136.2, 139.3, 143.5; IR (cm^{-1}): 3258, 1434, 1634; MS (ES mass): m/z 320.1 (M + 1, 10%); HR-MS: calcd for $C_{16}H_{15}ClNO_2S$: 320.0210, found 320.0064.

Ethyl 4-(5-fluoro-1-(methylsulfonyl)-1*H*-indol-2-yl)benzoate(3l). yield 0.54 g (70%); white solid, mp 155 °C; R_f = 0.65 (20% EtOAc-*n*-Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.37–1.49 (t, J = 6.9 Hz, 3H), 2.72 (s, 3H), 4.41–4.44 (q, J = 6.9 Hz, 2H), 6.76 (s, 1H), 7.13 (t, J = 9.7 Hz, 1H), 7.27 (d, J = 7.9 Hz, 2H), 7.63–7.64 (d, J = 7.9 Hz, 2H), 8.16–8.04 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3, 39.3, 61.1, 107.0, 113.2 (2C), 113.7, 117.2, 129.4 (2C), 130.9, 131.2, 134.5, 135.8, 142.7, 159.2, 161.6, 166.1; IR (cm^{-1}): 3016, 1719, 1609, 1481; MS (ES mass): m/z 362.1 (M + 1)$^+$, (100%); HR-MS: calcd for $C_{18}H_{17}FNO_4S$: 362.1019, found 362.1012.

Preparation of 2-heteroaryl indoles (5)

Ethyl-2-(5-fluoro-1-(methylsulfonyl)-1*H*-indol-2-yl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (5a). A mixture of ethyl 2-iodo-4,5,6,7-tetrahydrobenzothiophene-3-carboxylate (**4a**, 0.2 g, 0.593 mmol), 10% Pd/C (0.003 g, 0.023 mmol), PPh_3 (0.01 g, 0.041 mmol), CuI (0.008 g, 0.041 mmol) and triethylamine (0.09 g, 0.13 mL, 0.890 mmol) was stirred in MeOH (3 mL) at room temperature for 15 min. Then trimethylsilylacetylene (0.058 g, 0.084 mL, 0.593 mmol) was added and refluxed for 1 h. After the starting material was consumed, K_2CO_3 (0.082 g, 0.593 mmol) dissolved in 2 : 1 MeOH–H_2O (3 mL) was added and the mixture was refluxed for another 1 h. Then *N*-(4-fluoro-2-iodophenyl)methane sulfonamide (**2b**, 0.187 g, 0.593 mmol), was added and the mixture was allowed to reflux for 2 h. Upon completion of the reaction, the mixture was diluted with saturated aqueous NH_4Cl and extracted with ethyl acetate (3 × 25 mL). The organic layers were collected, combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography using *n*-Hexane/EtOAc (7 : 3) to give the desired product as a white solid (yield: 0.16 g, 64%); R_f = 0.4 (20% EtOAc-*n*-Hexane); mp >200 °C; IR (KBr, cm^{-1}) 2930, 1718, 1274; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.09 (t, J = 7.3 Hz, 3H), 1.87–1.89 (m, 4H), 2.78–2.79 (m, 2H), 2.88–2.89 (m, 2H), 3.09 (s, 3H), 4.12–4.17 (m, 2H), 6.63 (s, 1H), 7.36 (d, J = 2.4 Hz, 1H), 7.61 (s, 1H), 8.02 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.4, 22.8, 25.2, 26.3, 29.6, 40.9, 60.5, 113.3, 116.5, 126.7, 129.7, 133.2, 134.6, 135.7, 136.5, 137.0, 138.2, 148.7, 168.5; MS (ES mass): m/z 420.1 (M–1, 100%); HR-MS: calcd for $C_{20}H_{21}FNO_4S_2$ (M + H): 422.0896, found 422.0892; Elemental analysis found C, 56.78; H, 4.77; N, 3.41; $C_{20}H_{20}FNO_4S_2$ requires C, 56.99; H, 4.78; N, 3.32.

Ethyl-2-(5-chloro-1-(methylsulfonyl)-1*H*-indol-2-yl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (5b). A mixture of ethyl 2-iodo-4,5,6,7-tetrahydrobenzothiophene-3-carboxylate (**4a**, 0.2 g, 0.593 mmol), 10% Pd/C (0.003 g, 0.023 mmol), PPh_3, (0.01 g, 0.041 mmol), CuI (0.008 g, 0.041 mmol) and triethylamine (0.09 g, 0.13 mL, 0.890 mmol) was stirred in MeOH (3 mL) at room temperature for 15 min. Then (trimethylsilyl)acetylene (0.058 g, 0.084 mL, 0.593 mmol) was added and the mixture was refluxed for 1 h. After the starting material was consumed, K_2CO_3 (0.082 g, 0.593 mmol) dissolved in 2 : 1 MeOH–H_2O (3 mL) was added and the mixture was refluxed for another 1 h. Then *N*-(4-chloro-2-iodophenyl)methanesulfonamide (**2c**, 0.203 g, 0.593 mmol), was added and the mixture was heated to reflux for 2 h. Upon completion of the reaction, the reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with ethyl acetate (3 × 25 mL). The organic layers were collected, combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography using *n*-Hexane/EtOAc (7 : 3) to give the desired product as an off white solid (yield 0.16 g, 62%); mp >200 °C; R_f = 0.3 (20% EtOAc-*n*-hexane); IR (KBr, cm^{-1}): 2926, 1714, 1333; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.07 (t, J = 7.3 Hz, 3H), 1.84–1.85 (m, 4H), 2.77–2.79 (m, 2H), 2.86–2.87 (m, 2H), 3.07 (s, 3H), 4.10–4.16 (m, 2H), 6.60 (s, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.56 (s, 1H), 7.97 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 22.4, 22.8, 25.2, 26.2, 29.7, 40.6, 60.4, 112.2, 115.5, 120.6, 125.3, 129.6, 130.3, 132.4, 133.9, 135.1, 136.1, 138.7, 163.4; MS (ES mass): m/z 438.1 (M + 1, 100%); HR-MS: calcd for $C_{20}H_{21}NO_4S_2Cl$ (M + H): 438.0601, found 438.0596; Elemental analysis found C, 54.99; H, 4.58; N, 3.02; $C_{20}H_{20}NO_4S_2Cl$ requires C, 54.85; H, 4.60; N, 3.20.

Methyl 2-(5-cyano-1*H*-indol-2-yl)-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]thiophene-3-carboxylate (5c). A mixture of ethyl 2-iodo-5,6,7,8-tetrahydr-4*H*-cyclohepta[*b*] thiophene-3-carboxylate (**4b**, 0.1 g, 0.2857 mmol), 10% Pd/C (0.002 g, 0.011 mmol), PPh_3 (0.005 g, 0.019 mmol), CuI (0.004 g, 0.019 mmol), triethylamine (0.044 g, 0.07 mL, 0.428 mmol), were stirred in MeOH (3 mL) at room temperature for 15 min. Then trimethylsilylacetylene (0.027 g, 0.04 mL, 0.2857 mmol) was added and the mixture was heated to reflux for 1 h. After the starting material was consumed, K_2CO_3 (0.02 g, 0.2857 mmol) dissolved in 2 : 1 MeOH–H_2O (3 mL) was added and the mixture was stirred at refluxing temperature for another 1 h. Then *N*-(4-cyano-2-iodophenyl)

methanesulfonamide (**2d**, 0.092 g, 0.2857 mmol), was added and stirring continued for 2 h at refluxing temperature. Upon completion of the reaction, the mixture was diluted with saturated aqueous NH_4Cl and the product was extracted with ethyl acetate (3 × 15 mL). The organic layers were collected, combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography using 7 : 3 *n*-hexane: EtOAc to give the desired product as an off white solid (yield 0.06 g, 60%); mp 150–152 °C; R_f = 0.3 (20% EtOAc-*n*-hexane); IR (KBr, cm^{-1}): 3316, 2921, 2847, 1694, 1439; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.68–1.66 (m, 4H), 1.89–1.88 (m, 2H), 2.82–2.80 (m, 4H), 3.9 (s, 3H), 6.78 (s, 1H), 7.44 (d, J = 3.5 Hz, 2H), 7.91 (d, J = 3.5 Hz, 1H), 10.6 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.1, 27.6, 29.2, 29.5, 32.2, 52.6, 102.9, 103.1, 112.2, 120.8, 125.2, 125.8, 127.8, 129.1, 133.4, 133.6, 137.7, 141.3, 141.6, 167.7; MS (ES mass): m/z 348.9 (M–1, 100%); HR-MS: calcd for $C_{20}H_{19}N_2O_2S$ (M + H): 351.1146, found 351.1154; Elemental analysis found C, 68.39; H, 5.20; N, 7.78; $C_{20}H_{18}N_2O_2S$ requires C, 68.55; H, 5.18; N, 7.99.

Preparation of (2-(4-methoxyphenyl)-5-methyl-1-(methylsulfonyl)-1*H*-indol-3-yl) (phenyl) methanone (6). A mixture of TFAA (270 mg, 12.83 mmol) and benzoic acid (360 mg, 3.2 mmol) was stirred for 20 min until all the solids were dissolved. After being stirred for additional 20 min, the indole, **3b** (1.10 g, 3.52 mmol), was added in one portion. To this mixture was added 85% H_3PO_4 (58 mg, 0.59 mmol) drop wise for a duration of 20 min. The mixture was then stirred for 4 h (monitored by TLC) and the excess of TFA/TFAA was distilled out at atmospheric pressure. The remaining liquid was partitioned between $CHCl_3$ (40 mL) and H_2O (20 mL). The organic layer was separated and washed with 5% NaOH (10 mL) and then brine (10 mL). The mixture was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography using EtOAc-*n*-hexane to give the desired product as pale yellow solid (yield 1.03 g, 70%); mp 90–92 °C; R_f = 0.69 (20% EtOAc-*n*-hexane); IR (KBr, cm^{-1}): 2923, 1727, 1377, 1253, 1177; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.44 (s, 3H), 2.78 (s, 3H), 3.71 (s, 3H), 6.68 (d, J = 8.8 Hz, 2H), 7.19–7.37 (m, 6H), 7.52 (s, 1H), 7.56 (d, J = 8.4 Hz, 2H), 8.06 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.3, 40.4, 55.2, 112.9, 115.3 (2C), 120.8, 121.8, 122.6, 127.3 (2C), 128.0 (2C), 129.4 (2C), 130.5, 132.6, 133.1, 134.9, 135.1, 137.5, 142.4, 160.5, 193.4; MS (ES mass): m/z 420.2 (M + 1, 100%); HR-MS: calcd for $C_{24}H_{22}NO_4S$ (M + H): 420.1270, found 420.1291; Elemental analysis found C, 68.69; H, 5.12; N, 3.51; $C_{24}H_{21}NO_4S$ requires C, 68.72; H, 5.05; N, 3.34.

Preparation of (2-(4-methoxyphenyl)-5-methyl-1*H*-indol-3-yl) (phenyl) methanone (7). A mixture of compound **6** (0.993 g, 2.37 mmol) and K_2CO_3 (166 mg, 1.2 eq) in MeOH (5 mL) was refluxed for 3 h. After completion, the reaction mixture was filtered and the residue was washed with MeOH (5 mL). The methanol filtrates were collected, combined and concentrated under reduced pressure. The residue was purified by column chromatography using EtOAc/*n*-hexane to give the desired product as an off white solid (yield 0.61 g, 75%); mp 160–162 °C; R_f = 0.5 (20% EtOAc-*n*-hexane); IR (KBr, cm^{-1}) 2917, 1729, 1248, 1174; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.44 (s, 3H), 3.74 (s, 3H), 6.71 (d, J = 8.4 Hz, 2H), 7.04–7.20 (m, 3H), 7.22–7.27 (m, 4H), 7.63 (d, J = 7.6 Hz, 2H), 7.77 (s, 1H), 8.39 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.3, 55.2, 112.9, 114.2 (2C), 120.8, 121.8, 122.6, 127.1 (2C), 127.4 (2C), 128.9 (2C), 130.5, 132.6, 133.1, 134.9, 135.1, 137.5, 142.4, 160.5, 193.4; MS (ES mass): m/z 342.1 (M + 1, 100%); HR-MS: calcd for $C_{23}H_{20}NO_2$ (M + H) 342.1494 found 342.1479; Elemental analysis found C, 80.78; H, 5.60; N, 4.24; $C_{23}H_{19}NO_2$ requires C, 80.92; H, 5.61; N, 4.10.

Preparation of *N*-(4-chloro-2-(5-methyl-1-(methylsulfonyl)-1*H*-indol-2-yl)phenyl) quinoxaline-2-carboxamide (8). To a mixture of 2-quinoxaline carboxylic acid (11 mg, 0.06 mmol) and compound **3e** (20 mg, 0.06 mmol) in CH_2Cl_2 (5 mL) was added EDCI.HCl (13.5 mg, 0.071 mmol), HOBT (10 mg, 0.071 mmol) and DIPEA (16 mg, 0.119 mmol) under a nitrogen atmosphere. The mixture was stirred at room temperature for 5 h. After completion of the reaction (monitored by TLC), the mixture was poured into cold water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were collected, combined, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography using EtOAc/*n*-hexane to give the desired product as a gummy mass (yield 0.016 g, 55%); R_f = 0.22 (20% EtOAc/*n*-hexane); IR (KBr, cm^{-1}): 3327, 2924, 1690, 1677, 1367, 1173; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.48 (s, 3H), 2.83 (s, 3H), 6.69 (s, 1H), 7.25 (s, 1H), 7.26 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.8 Hz, 1H), 7.31 (bs, 1H), 7.38–7.41 (m, 2H), 7.43–7.45 (m, 2H), 7.98 (d, J = 8.8 Hz, 2H), 8.11 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.6, 40.3, 113.9, 114.4, 114.4, 115.4, 117.4, 118.2, 121.7, 122.1, 122.7, 123.4, 125.4, 128.5, 129.0, 131.9, 132.0, 132.1, 132.4, 134.1, 137.8, 138.3, 138.5, 140.9, 161.6; MS (ES mass): m/z 491.1 (M + 1, 100%); HR-MS: calcd for $C_{25}H_{20}N_4ClO_3S$ (M + H): 491.0945 found 491.0952; Elemental analysis found C, 61.27; H, 3.88; N, 11.24; $C_{25}H_{19}N_4ClO_3S$ requires C, 61.16; H, 3.90; N, 11.41.

Preparation of 4-(5-fluoro-1-(methylsulfonyl)-1*H*-indol-2-yl)benzoic acid (9). To the solution of **3l** (0.16 g, 0.44 mmol) in THF and water (5 ml) (3 : 1), NaOH (0.04 g, 0.968 mmol) was added and refluxed for 3 h. The progress of the reaction was checked by TLC. After completion of the reaction the reaction mixture was neutralized by 1 N HCl, extracted with ethyl acetate, washed with water and brine solution, and dried over anhydrous sodium sulfate. The reaction mixture was concentrated under reduced pressure. Crude was purified by washing with hexane to get the product white solid (yield: 0.01 g, 70%); mp 266 °C; ^1H NMR (400 MHz, acetone-d_6) δ: 2.91 (s, 3H), 6.98–6.85 (m, 1H), 7.25–7.16 (m, 1H), 7.49–7.36 (m, 1H), 7.77–7.62 (m, 2H), 8.20–8.01 (m, 3H), 10.95 (s, 1H). ^{13}C NMR (100 MHz, acetone-d_6) δ: 40.9, 107.0, 107.3, 113.1,113.3, 117.1 (2C), 125.2, 129.0, 130.2, 131.2 (2C), 134.2, 142.8, 158.6, 161.0; IR (cm^{-1}): 3430, 3014, 1691, 1608. MS (ES mass): m/z 331.9 $(M - 1)^+$, 100%); HR-MS: calcd for $C_{16}H_{13}FNO_4S$ is 334.1100 found 334.1102.

Preparation of methyl 2-(4-(5-fluoro-1-(methylsulfonyl)-1*H*-indol-2-yl)benzamido)acetate (10). To a mixture of compound **9** (0.1 g, 0.3 mmol) and methyl glycine ester (0.038 g, 0.3 mmol) in THF (5 mL) was added EDCI.HCl (0.07 g, 0.36 mmol), HOBT (0.05 g, 0.36 mmol) and DIPEA (0.78 g, 0.6 mmol) under a nitrogen atmosphere. The mixture was stirred at room temperature for 3 h. The progress of the reaction was checked by TLC. After completion of reaction the mixture was poured in cold water (10 mL) and extracted with EtOAc (3 × 20 mL). The

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organic layers were collected, combined, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography using EtOAc-*n*-hexane (6 : 4) to give the desired product as a white solid (yield: 0.08 g, 65%); mp: 230 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ: ppm 3.02 (s, 3H), 3.71 (s, 3H), 4.17 (t, J = 5.69 Hz, 2H), 6.92 (s, 1H), 7.23 (dd, J = 13.09, 5.35 Hz, 1H), 7.45 (d, J = 7.82 Hz, 1H), 7.71 (d, J = 7.96 Hz, 2H), 7.92 –8.03 (m, 3H), 8.07 (dd, J = 9.07, 4.37 Hz, 1H), 8.25 (s, 1H). ^{13}C NMR (100 MHz, acetone-d_6) δ: 39.5, 41.1, 51.3, 106.5, 106.7, 112.9, 113.0, 116.8, 116.9, 126.5 (2C), 130.2 (2C), 134.3, 135.1, 142.8, 161.2, 166.5, 170.2; IR (cm^{-1}): 3072, 2951, 1739, 1341. MS (ES mass): m/z 404.7 $(M + 1)^+$, (100%); HR-MS: calcd for $C_{19}H_{18}FN_2O_5S$ is 405.1221 found 405.1209.

Single crystal x-ray diffraction (SXRD). X-ray data for the single crystal of **3a** has been collected at room temperature on a Rigaku AFC-7S diffractometer equipped with a mercury CCD detector using graphite monochromated Mo-K$_\alpha$ (λ = 0.7107 Å) radiation. Data collection, indexing, initial cell refinements, frame integration and final cell refinements were carried out using *CrystalClear* SM 1.3.6 software. The crystal structure was solved with direct methods (SIR2004)[24] and refined using least squares procedure (CRYSTALS)[25] using the *CrystalStructure* 3.8.1 software. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms bonded to carbons were positioned geometrically and refined in the riding model approximation with C–H = 0.95 Å, and with U(H) set to $1.2U_{eq}$I.

Crystal data of 3a. Molecular formula = $C_{17}H_{17}NO_2S$, Formula weight = 299.39, Triclinic, $P\bar{1}$, a = 5.805(4) Å, b = 10.234(6) Å, c = 13.495(8) Å, V = 750.8(8) Å^3, T = 298 K, Z = 2, D_c = 1.324 Mg m^{-3}, μ(Mo-K$_\alpha$) = 0.219 mm^{-1}, 8318 reflections measured, 2988 unique reflections, 2515 observed reflections [$I > 2.0\sigma(I)$], R_1_obs = 0.057, Goodness of fit = 1.089. Crystallographic data (excluding structure factors) for **3a** have been deposited with the Cambridge Crystallographic Data Centre as CCDC 784742.‡

Pharmacology

***In vitro* assay for measuring SIRT 1 activation.** [21]The activity of the small molecules on SIRT 1 was determined by using a SIRT 1 fluorescence activity assay kit from Cyclex Inc. according to the manufacturer's protocol. Briefly, bacterially purified hSIRT 1 enzyme was incubated with the fluorophore-labeled substrate peptide (25 μM) and co-factor, NAD$^+$ (25 μM) in the presence or absence of 10 μM compounds (suramin, an inhibitor of SIRT 1 along with compound **7**) for 15 min at 37 °C. Then 50 μl of stock solution was added and incubated for 45 min at room temperature. Fluorescence was read at E_x = 360 nm and E_m = 450 nm. The blank consists of all components of the reaction mixture except the enzyme. The difference between the blank and control reading gives the enzyme activity. The blank value is subtracted from all the sample readings. The compound control contains all the components of the reaction mixture including the compound but no enzyme. So the reading obtained in the compound control indicates the auto-fluorescence of the compound and this is also subtracted from the reading. Finally a graph is plotted against the samples on the X-axis and the absorbance value after subtracting the blank and auto-fluorescence values from the sample. Absorbance/fluorescence is directly proportional to the enzyme activity (Fig. 2).

Docking studies

Homology Model of hSIRT 1 (144–217). The three dimensional model of hSIRT 1 (uniprot code: Q96EB6, 144–217 amino acid residues) was developed by threading method using PRIME homology modelling program (Schrödinger L.L.C., USA). The multi step Schrödinger's Protein preparation tool (PPrep) has been used for final preparation of the receptor model. Hydrogen's were added to the model automatically *via* the Maestro interface.[26] PPrep neutralizes side chains and residues which are not involved in salt bridges.[27] This step is then followed by restrained minimization using the OPLS 2005 force field to RMSD of 0.3 A^0.

Docking Procedure. The compound **7** was sketched using ChemDraw and then converted to their 3D representation. The compound **7** and protein (homology model of hSIRT 1) were prepared for docking (*i.e.* adding hydrogen's, gasteiger charge addition, and energy minimization) by using Chimera program. Autodock 4.0 program was used for docking.

The best model of activator domain of hSIRT 1 was developed and validated. The receptor grid was generated with co-ordinates X: 43.804; Y: 47.333; Z: 29.948. The best 5 poses and corresponding scores have been evaluated by the Autodock 4.0 program.

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