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[1,3]-Dipolar cycloaddition of *N*-aryl sydnones to benzothiophene 1,1-dioxide, 1-cyclopropylprop-2-yn-1-ol and 1-(prop-2-ynyl)-1*H*-indole

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Graphical Abstract

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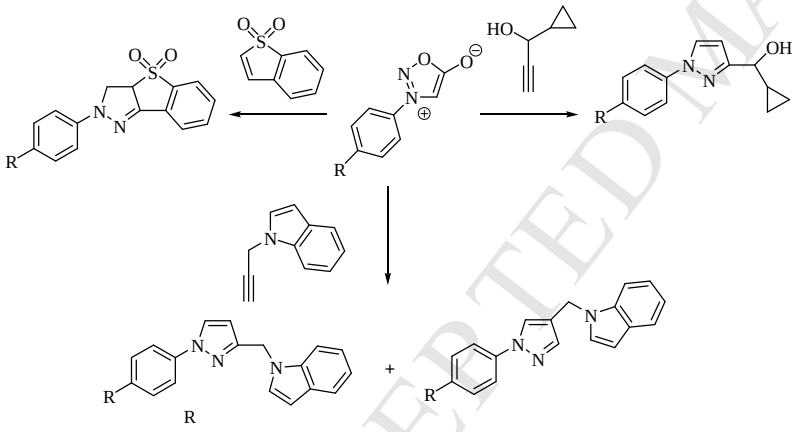

	R
a	H
b	4-Me
c	4-I
d	4-Cl
e	4-OMe
f	4-F
g	3,4-OCH_2O

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[1,3]-Dipolar cycloaddition of *N*-aryl sydnones to benzothiophene 1,1-dioxide, 1-cyclopropylprop-2-yn-1-ol and 1-(prop-2-ynyl)-1*H*-indole

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ABSTRACT

[1,3]-Dipolar cycloadditions of *N*-aryl sydnones to benzothiophene1,1-dioxide, 1-cyclopropylprop-2-yn-1-ol and 1-(prop-2-ynyl)indole gave fused pyrazole derivatives when carried out in refluxing toluene. While the first two dipolarophiles gave single regioisoimers, this indolic derivative gave mixtures, the ratios of which appeared to be controlled by the phenyl substituents. Their structures were identified in the usual manner, supported by single crystal X-ray diffraction measurements.

Keywords: cycloaddition, pyrazole, sydnone, alkyne, benzothiophene, propynyl alcohol

1.Introduction

Sydnones constitute a well-defined class of mesoionic compounds obtained by cyclodehydration, induced by either acetic anhydride or 1,3-dibromo-5,5-dimethylhydantoin, of *N*-nitroso derivatives of *N*-substituted α-amino acids.[1-3] These compounds are of interest because of the varied types of biological activity displayed by some of them, particularly sydnone-4-heterocycles, and especially because they can provide ready access to a variety of heterocyclic systems.[4–6] For example, pyrazole derivatives, which are both important building blocks in organic synthesis and which have numerous applications as pharmaceuticals and agrochemicals, can be sourced from sydnones following [1,3]-dipolar cycloadditions with a variety of dipolarophiles.[7] Amongst the latter group of compounds, poly(hetero)aromatic-substituted pyrazoles are particularly important showing a broad spectrum of useful biological effects, including kinase inhibition,[8] estrogen receptor binding,[9] anti-inflammatory[10] and herbicidal activities[11] as illustrated in Scheme 1.

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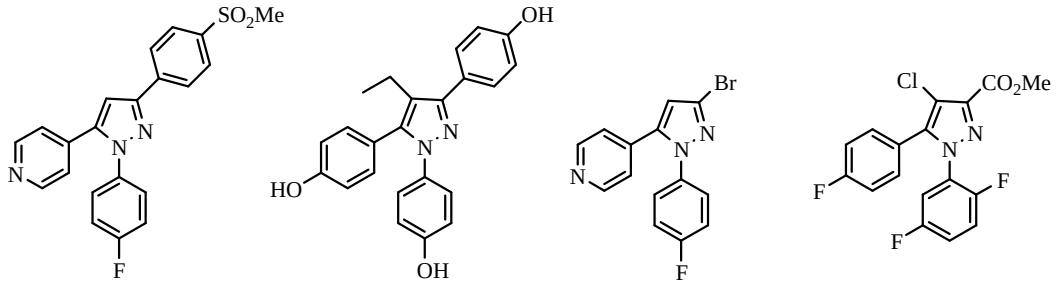

MAP Kinase inhibitor | Estrogen receptor ligand | Anti-inflammatory activity | Herbicidal activity

Scheme 1. Some biologically active pyrazole derivatives.

In general, it is a considerable advantage in drug discovery to work with structures, which contain one or more benzene rings as this facilitates alterations to the initial molecule in a rational and fairly quantifiable manner, in terms of both electronic and steric properties. This implies that a particular synthetic approach to such targets should be successful with many types of different substituent, for example ones placed around a phenyl substituent. A potential problem in the synthesis of pyrazoles from *N*-aryl sydnones, by cycloadditions to unsymmetrical alkenes and alkynes, is one of regioselectivity, as formation of two regioisomers is always possible. Taking account of these considerations, together with our continuing interest in the [1,3]-dipolar cycloaddition chemistry of various ylides leading to pyrazoles, triazoles and spiropyrroles,[12-15] we focus herein on the synthesis of various pyrazole derivatives starting from *N*-aryl sydnone dipoles **1**, which differ by the nature of the 4-substituent on an *N*-phenyl group, in order to probe what influence these might have on both reactivity and regioselectivity. This series of sydnones was reacted with three representative dipolarophiles: an alkene, benzothiophene 1,1-dioxide (**2**) and two 1-alkynes, 1-cyclopropylprop-2-yn-1-ol (**4**) and 1-(prop-2-ynyl)-1*H*-indole (**8**).

Heterocyclic compounds with a benzothiophene dioxide structural feature have been used for the synthesis of pharmaceutically important molecules showing bioactivities including hepatitis C virus NS5B polymerase inhibition and various cytotoxic properties.[16-19]

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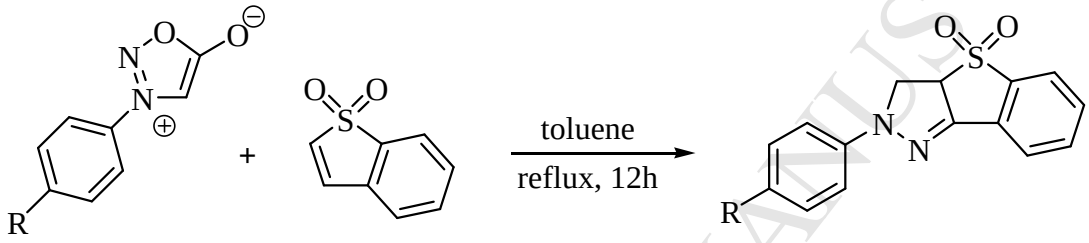
2.Results and Discussion

The key starting compounds, the N-arylsydnones **1a-g**, were prepared according to the procedures previously reported.[1-3] As the only examples of similar [1,3]-dipolar cycloadditions of benzothiophene dioxide which have been reported are with nitrilimines,[20] we first carried out a brief optimization study which showed that relatively prolonged thermolysis in toluene gave the best yields. Thus, the dipolarophile **2** underwent cycloadditions with sydnones **1a-g** and gave only the regioisomers **3a-g** in moderate yields as the only isolable products (Scheme 2).



1 **2** **3**

	R	Yield (%)		R	Yield (%)
3a	H	35	**3e**	4-OMe	35
3b	4-Me	33	**3f**	4-F	45
3c	4-I	38	**3g**	3,4-OCH_2O	30
3d	4-Cl	40			

Scheme 2. Cycloadditions of sydnones **1** to benzothiophene 1,1-dioxide **2** affording **3.**

Typical characteristics of these cycloadducts in their IR spectra are the symmetric and asymmetric stretching vibrations of SO_2 moiety at around 1150 and 1300 cm^{-1}, respectively. Aliphatic ring protons of these compounds resonate in the range of 4-5 ppm as two double doublets and one triplet which correspond to the three hydrogens of the pyrazoline portion in the cycloadduct; the chemical shifts observed strongly support the structural assignment as being the regioisomers **3**. The proton at the bridge position was split into a doublet of doublets (which usually appeared as an apparent triplet) and usually

appeared between the AB double doublet resonances due to the methylene group adjacent to nitrogen. ^{13}C NMR data showed the methylene carbons of the pyrazole ring resonating at around 51 ppm while the bridge methine adjacent to the sulfone resonates at around 63 ppm, again supporting the structural assignment. This outcome also corresponds to a previous observation that nitrile oxides add to benzothiophene-*S*-oxide with the same regioselectivity, consistent with the addition of the electron-rich end of the dipole to the more electron deficient end of the dipolarophiles, the 3-position of the benzothiophene.[21]

The second dipolarophile used in this work was the acetylenic alcohol 1-cyclopropylprop-2-yn-1-ol **4** which is obtained from ethynylmagnesium bromide and cyclopropanecarboxaldehyde.[22] [1,3]-Dipolar cycloadditions of sydnones **1a-g** to alkynol **4** in toluene, under reflux, proceeded slowly but smoothly and were also highly regioselective, yielding the regioisomers **5a-g** as the only isolable products (Scheme 3). That single regioisomers had been formed was clear from the ^{1}H NMR data, which showed a pair of doublets resonating at 6.42 and 7.81 ppm (J = 2.4 Hz) in adduct **5a**, assigned to the vicinal methines of the pyrazole ring; similar resonances were evident in the remaining adducts **5b-g**. This structural assignment is in agreement with with earlier reports[4,23] on the structural elucidation of isomeric 3-methyl-1-phenyl-1*H*-pyrazole and 5-methyl-1-phenyl-1*H*-pyrazoles, both in terms of chemical shifts and coupling constant values, the latter being in the range J = 2.3-2.5 Hz. The structural assignments in general were also supported by the ^{13}C NMR spectroscopic data. As for carbon chemical shifts of the cycloadducts, the carbon attached to the hydroxyl group resonated at around 72.0 ppm, the pyrazole iminic carbon (C3-pyrazole ring numbering) at around 158-160 ppm and the most shielded aliphatic carbons were the cyclopropyl ring carbons[24-27] In the mass spectra, while significant molecular ions were observed, the base peaks were due to loss of a molecule of water.

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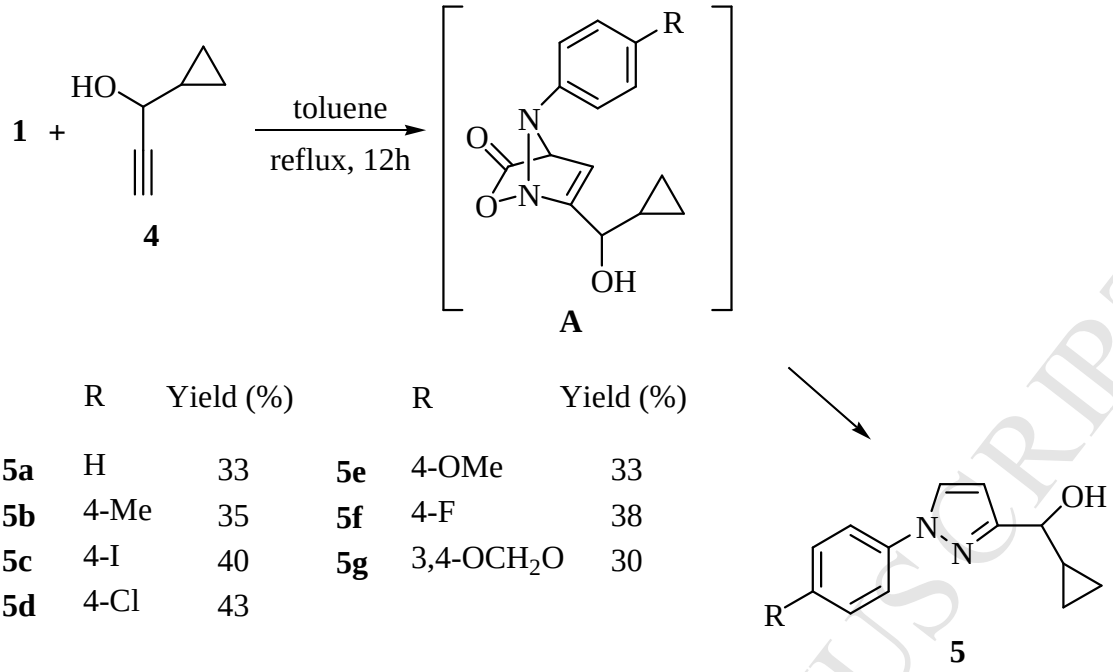

Scheme 3. The formation of single regioisomers **5** from sydnones **1** and 1-alkynol **4.**

This regiochemical outcome is also consistent with previous reports, wherein single isomers are formed from many types of 1-alkyne and strongly suggests the specific formation of intermediate **A** (Scheme 3).[4,23] The present work also shows that there is a lack of an obvious sensitivity to the nature of the 4-substituent on the *N*-phenyl ring in these cycloadditions as, in all cases, single isomers were obtained in similar yields (see also below).

A final example of a dipolarophile, 1-(prop-2-ynyl)-1*H*-indole **8** which was easily obtained from indole **6** and propargyl bromide **7** as shown, underwent [1,3]-dipolar cycloadditions to sydnones **1a-g**, but afforded regioisomeric products **9a-g** and **10a-g** in the ratios shown below (Scheme 4). Fortunately, these proved to be reasonably easy to separate by routine column chromatography, although structural proof of which isomer was which was not immediately forthcoming.

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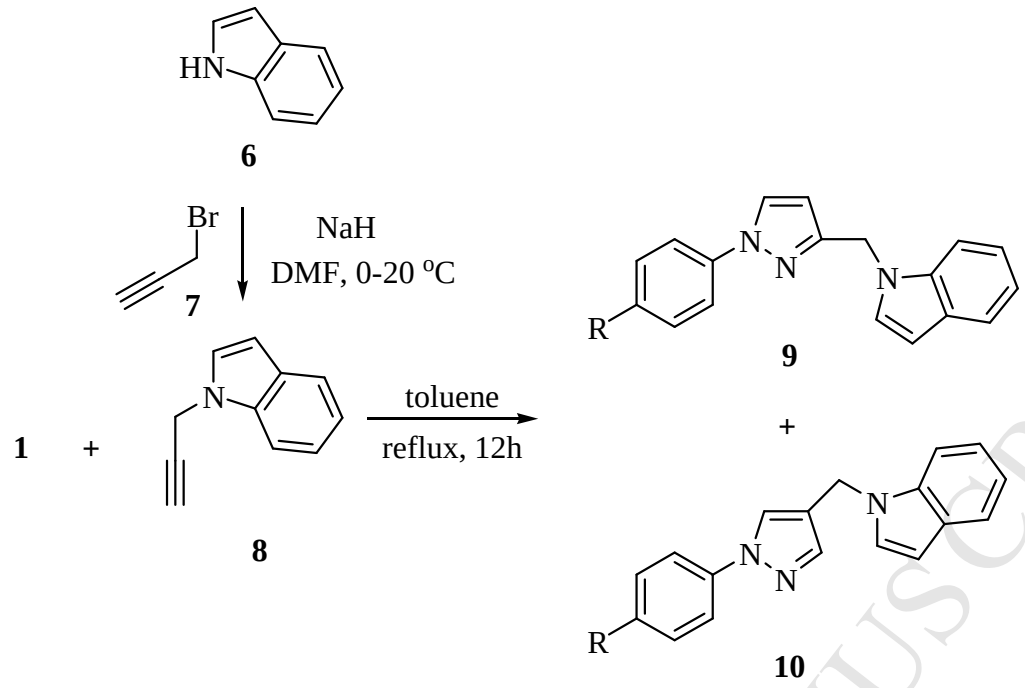

	R	Yield **9** (%)	Yield **10** (%)	~Ratio	Yield (%)
a	H	18	36	1:2	54
b	4-Me	28	42	2:3	70
c	4-I	20	5	4:1	25
d	4-Cl	35	7	5:1	42
e	4-OMe	10	40	1:4	50
f	4-F	20	10	2:1	30
g	3,4-OCH_2O	20	10	2:1	30

Scheme 4. Synthesis of propynylindole **8** and cycloaddition to *N*-aryl sydnones **1** affording regioisomeric products **9** and **10**.

While proton and carbon resonances were in accord with those previously reported for some related indoly pyrazoles,[28-30] this did not seem to provide a sufficiently reliable basis for structural assignment, particularly as analysis of the proton data was incomplete owing to many overlapping resonances (see Experimental section). Fortunately, many of the products were crystalline and we were able to resort to X-ray crystallographic analysis, specifically of products **9d** and **10d**. Exact structures of the regioisomers were established by the X-ray ORTEP views of the single crystals (Figures 1 and 2).

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Crystallographic data have been deposited at the CCDC, reference numbers 934162 (**9d**) and 934163 (**10d**), respectively.

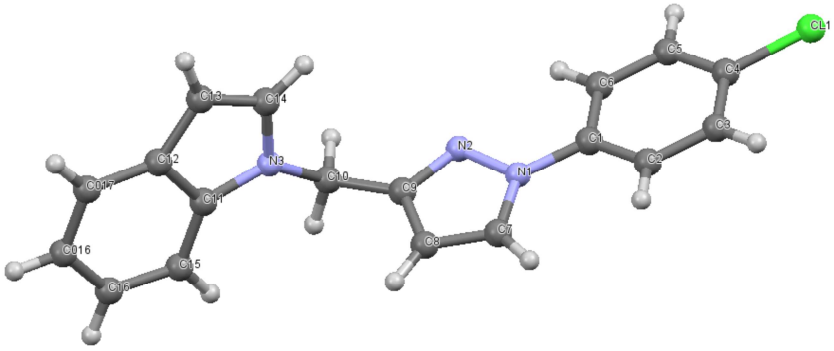

Figure 1. ORTEP diagram of pyrazole isomer **9d**, showing the indole attached to the 3-position.

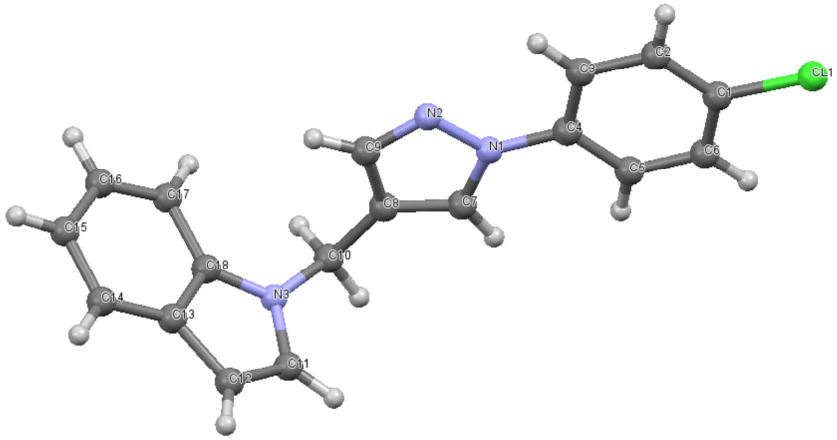

Figure 2. ORTEP diagram of pyrazole isomer **10d**, with the indole attached to the 4-position.

Neither ORTEP diagram revealed any unusual features in these structures. Comparative NMR data then allowed structural assignments to be made to all the remaining products with certainty (See Figs. 3-6 in the Experimental section under compounds **9c** and **10c**).

By examining the ratios of the regioisomers based on the reaction yields, it is seen that, in the case of electron donating groups on the sydnone *N*-aryl substituent, the regioisomers **10** are the major products while regioisomers **9** are minor products. The reverse is true when there is an electron withdrawing halogen atom at the 4-position of the phenyl group and the regioisomers **9** are the major products and the regioisomers **10** the minor. However, the reasons behind the relative differences between the 4-methoxy and 3,4-dimethoxy are not obvious. These regioselectivities are somewhat unusual, given the typical propensity for the formation of very largely or exclusively 3-substituted pyrazoles shown by such cycloadditions.[3,4] Some recent exceptions have come to light when using 2-pyridyl- and 2-pyrimidinyl-1-alkynes as the dipolarophiles,[4] although it is not obvious why the present indolic analogues react with a similar lack of selectivity. At least, these results provide something of a predictive pattern for future use in pyrazole synthesis. In contrast, the complete regioselectivity shown by the alkynol **4**, which gave only products **5** (Scheme 3),

3. Conclusions

In summary, we report a practical catalyst-free protocol that allows access to a variety of substituted indolyl pyrazoles, cyclopropyl-(1-substituted-phenyl)-1*H*-pyrazol-3-yl)methanols and 2-(4-substituted phenyl)-3,3a-dihydro-2*H*-[1]benzothieno[3,2-*c*]pyrazole 4,4-dioxides using [1,3]-dipolar cycloaddition reactions of mesoionic *N*-aryl sydnones. The reactions proceed in moderate yields and the regioselectivities vary substantially depending on the nature of the 4-substituents on the phenyl ring in sydnones **1**, in the case of the sydnone-propynylindole cycloadditions, where the major-minor ratio are largely reversed by replacing electron releasing substituents with electron withdrawing ones. However, the remaining two types of cycloaddition studied, with an alkynyl cyclopropylmethanol and benzothiophene dioxide, lead to only one regioisomeric cycloadduct, the nature of which is unaffected by the aryl 4-substituent.

4. Experimental

4.1. General

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were obtained from KBr pellets or neat on NaCl plates for liquids and were recorded on Perkin Elmer 1600 FTIR and Shimadzu spectrophotometers. Mass spectra were recorded on a Fisons VG Platform II spectrometer and on a Waters Synapt spectrometer using the ionization modes specified. NMR spectra were recorded on Varian and Bruker spectrometers operating at 500, 400, 300 and 250 MHz for ^{1}H and at 125, 100 MHz and 75 for ^{13}C , respectively, all at 25 ºC, as specified for each data set. All chemical shifts are reported in ppm downfield from TMS. Coupling constants (*J*) are reported in Hz. Routine TLC analyses were carried out on pre-coated silica gel plates with fluorescent indicator. Flash column chromatography was performed on silica gel (230-400 Mesh ASTM). A rotary TLC apparatus (Chromatotron) was utilized for further separation and purifications. Stain solutions of potassium permanganate and iodine were used for visualization of the TLC spots.

4.2. *2-(4-Substituted phenyl)-3,3a-dihydro-2H-[1]benzothieno[3,2-c]pyrazole 4,4-dioxides* **3a-g**:

General procedure

A mixture of benzo[b]thiophene 1,1-dioxide **2** (83 mg, 0.5 mmol) and a substituted sydnone **1** (0.5 mmol) was refluxed in toluene (10 mL) for 12 h. After completion of the reaction, as monitored by TLC (*n*-hexane-EtOAc, 1:1), the solvent was removed under reduced pressure. The crude product was then purified by column chromatography to give compounds **3**.

4.2.1. *2-Phenyl-3,3a-dihydro-2H-[1]benzothieno[3,2-c]pyrazole 4,4-dioxide* **3a**

Yield: 50 mg (35%); yellow powder. Mp 135–137 °C; R_f = 0.49 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3061, 2924, 1653, 1597, 1500, 1465, 1375, 1296 (SO_2 asym), 1145 (SO_2 sym), 1062, 1001, 752 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83-7.79 (m, 2H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.35

(t, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.98 (t, *J* = 7.2 Hz, 1H), 5.04 (dd, *J* = 13.6, 10.4 Hz, 1H), 4.50 (t, *J* = 10.4 Hz, 1H), 4.14 (dd, *J* = 13.6, 10.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.9, 145.1, 143.5, 134.3, 131.2, 130.1, 129.6, 123.2, 122.9, 121.7, 114.0, 66.8, 50.3. HRMS: *m/z* (ESI-TOF, $[M+H]^+$) calcd for $C_{15}H_{13}N_2O_2S$: 285.0698. Found: 285.0701.

4.2.2. *2-(4-Methylphenyl)-3,3a-dihydro-2H-[1]benzothieno[3,2-c]pyrazole 4,4-dioxide* **3b**

Yield: 49 mg (33%); yellow oil. R_f = 0.50 (*n*-hexane-EtOAc, 1:1). IR (KBr): 2928, 1653, 1516, 1460, 1379, 1307 (SO_2 asym), 1168 (SO_2 sym), 1112, 954, 817 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84-7.78 (m, 2H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.14 (d, *J* = 8.6 Hz, 2H), 7.04 (d, *J* = 8.6 Hz, 2H), 5.03 (dd, *J* = 13.6, 10.4 Hz, 1H), 4.48 (t, *J* = 10.4 Hz, 1H), 4.10 (dd, *J* = 13.6, 10.4 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.6, 142.8, 142.7, 134.0, 131.0, 130.8, 129.9, 129.8, 122.9, 122.6, 113.9, 66.6, 50.4, 20.6. HRMS: *m/z* (ESI-TOF, $[M+H]^+$) calcd for $C_{16}H_{15}N_2O_2S$: 299.0854. Found: 299.0852.

4.2.3. *2-(4-Iodophenyl)-3,3a-dihydro-2H-[1]benzothieno[3,2-c]pyrazole 4,4-dioxide* **3c**

Yield: 78 mg (38%); yellow oil. R_f = 0.47 (*n*-hexane-EtOAc, 1:1). IR (KBr): 2924, 1683, 1586, 1490,1381, 1305 (SO_2 asym), 1265, 1166 (SO_2 sym), 1146, 1070, 825, 833 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81 (t, *J* = 6.7 Hz, 2H), 7.65 (td, *J* = 7.6, 3.2 Hz, 1H), 7.62-7.55 (m, 2H), 6.89 (dt, *J* = 9.7, 4.7 Hz, 2H), 5.04 (dd, *J* = 13.6, 10.7 Hz, 1H), 4.47 (app. t, *J* = 10.7 Hz, 1H), 4.10 (dd, *J* = 13.6, 10.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 146.0, 144.7, 144.2, 138.2, 134.3, 131.5, 129.8, 123.3, 122.9, 116.0, 83.8 (C-I), 66.9 (C-SO_2), 50.1. HRMS: *m/z* (ESI-TOF, $[M+H]^+$) calcd for $C_{15}H_{12}IN_2O_2S$: 410.9664. Found: 410.9664.

4.2.4. *2-(4-Chlorophenyl)-3,3a-dihydro-2H-[1]benzothieno[3,2-c]pyrazole 4,4-dioxide* **3d**

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Yield: 64 mg (40%); orange solid. Mp 163-165 °C. R_f = 0.45 (*n*-hexane-EtOAc, 1:1). IR (KBr): 2926, 1683, 1653, 1593, 1492, 1465, 1379, 1303 (SO_2 asym), 1165 (SO_2 sym), 1145, 1124, 825, 767 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.82 (t, *J* = 7.0 Hz, 2H), 7.71 (t, *J* = 6.7 Hz, 1H), 7.60 (t, *J* = 6.7 Hz, 1H), 7.25 (d, *J* = 8.7 Hz, 2H), 7.11-7.04 (m, 2H), 5.06 (dd, *J* = 13.7, 10.5 Hz, 1H), 4.49 (t, *J* = 10.5 Hz, 1H), 4.12 (dd, *J* = 13.7, 10.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.0, 144.1, 143.7, 134.3, 131.4, 129.8, 129.5, 126.7, 123.3, 122.9, 115.2, 66.9 (C-SO_2), 50.4. HRMS: *m/z* (ESI-TOF, $[M+H]^+$) calcd for $C_{15}H_{12}ClN_2O_2S$: 319.0308. Found: 319.0308.

4.2.5. *2-(4-Methoxyphenyl)-3,3a-dihydro-2H-[1]benzothieno[3,2-c]pyrazole 4,4-dioxide* **3e**

Yield: 55 mg (35%); yellow oil. R_f = 0.46 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3450, 1653, 1510, 1460, 1303 (SO_2 asym), 1244, 1145 (SO_2 sym), 1124, 1070, 1035, 827, 763 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.81 (t, *J* = 7.6 Hz, 2H), 7.73-7.20 (m, 2H), 7.11 (d, *J* = 8.7 Hz, 2H), 6.89-6.82 (m, 2H), 5.04 (dd, *J* = 14.0, 10.8 Hz, 1H), 4.48 (t, *J* = 10.5 Hz, 1H), 4.08 (dd, *J* = 14.0, 10.5 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.1, 145.8, 139.4, 134.2, 133.8, 132.5, 131.0, 123.1, 122.8, 115.7, 114.9, 66.9 (C-SO_2), 55.8 (OCH_3), 51.4. HRMS: m/z (ESI-TOF, $[M+H]^+$) calcd for $C_{16}H_{15}N_2O_3S$: 315.0803. Found: 315.0808.

4.2.6. *2-(4-Fluorophenyl)-3,3a-dihydro-2H-[1]benzothieno[3,2-c]pyrazole 4,4-dioxide* **3f**

Yield: 68 mg (45%); yellow powder. Mp 170–172 °C; R_f = 0.45 (*n*-hexane-EtOAc, 1:1). IR (KBr): 2928, 1653, 1508, 1375, 1303 (SO_2 asym), 1224, 1145 (SO_2 sym), 1070, 825, 748 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.82 (t, *J* = 7.0 Hz, 1H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.12-7.01 (m, 5H), 5.05 (dd, *J* = 13.7, 10.5 Hz, 1H), 4.49 (t, *J* = 10.5 Hz, 1H), 4.10 (dd, *J* = 13.7, 10.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3 (*J* = 245.2 Hz, C-F), 145.9, 143.9, 141.7, 134.3, 131.3, 129.9, 123.4, 123.2, 116.0, 115.3, 67.0 (C-SO_2), 51.0. HRMS: (ESI-TOF, $[M+H]^+$) calcd for $C_{15}H_{12}FN_2O_2S$: 303.0604. Found: 303.0602.

4.2.7. *2-(1,3-Benzodioxol-5-yl)-3,3a-dihydro-2H-[1]benzothieno[3,2-c]pyrazole 4,4-dioxide* **3g**

Yield: 49 mg (30%); orange solid. Mp 155–157 °C; R_f = 0.46 (*n*-hexane-EtOAc, 1:1). IR (KBr): 2924, 1683, 1587, 1506, 1489, 1303 (SO_2 asym), 1234, 1213, 1145 (SO_2 sym), 1037, 935, 812, 736 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.83-7.78 (m, 2H), 7.69 (t, *J* = 6.7 Hz, 1H), 7.58 (t, *J* = 6.7 Hz, 1H), 6.89 (dd, *J* = 4.6, 2.6 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 6.42 (dd, *J* = 8.4, 2.3 Hz, 1H), 5.95 (s, 2H), 5.06 (dd, *J* = 13.7, 10.5 Hz, 1H), 4.42 (t, *J* = 10.5 Hz, 1H), 4.06 (dd, *J* = 13.7, 10.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.7, 145.9, 143.2, 142.9, 140.8, 134.2, 131.1, 130.0, 123.1, 122.8, 108.5, 106.0, 101.4, 97.6, 66.9 (C-SO_2), 51.3. HRMS: (ESI-TOF, $[M+H]^+$) calcd for $C_{16}H_{13}N_2O_4S$: 329.0596. Found: 329.0591.

4.3. *1-Cyclopropylprop-2-yn-1-ol* **4**[22]

Cyclopropylcarboxaldehyde (700 mg, 10 mmol) was added dropwise into a solution of ethynylmagnesium bromide (22 ml of a 0.5M solution in THF, 11 mmol) in dry THF at 0 °C. The reaction mixture was left to warm up to room temperature. After completion of the reaction, as indicated by TLC (*n*-hexane-EtOAc, 1:1), saturated aqueous ammonium chloride was added to the reaction mixture which was then extracted with ethyl acetate (3 x 20 mL). The combined organic solutions were dried over Na_2SO_4 and the solvents evaporated. The crude oily product was then purified by column chromatography on silica gel using *n*-hexane-EtOAc (4:1) to give **4** as brown oil; yield: 768 mg (80%). R_f = 0.67 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3373, 2966, 2110, 1712, 1452, 1438, 1381, 1317, 1207, 1078, 997, 945 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.13 (d, *J* = 5.8 Hz, 1H), 2.51-2.27 (m, 2H), 1.20 (tdt, *J* = 8.1, 6.6, 5.0 Hz, 1H), 0.62-0.31 (m, 4H).

4.3.1 *Cyclopropyl(1-substituted-1H-pyrazol-3-yl)methanols* **5a-g**: *General procedure.*

A mixture of 1-cyclopropylprop-2-yn-1-ol **4** (48 mg, 0.5 mmol) and a substituted sydnone **1** (0.5 mmol) was refluxed in toluene for 12h. After completion of the reaction, as monitored by TLC (hexane-EtOAc,

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1:1), the solvent was removed under reduced pressure. The crude product was purified by column chromatography to give regioisomers **5** as the only isolable products.

4.3.1.1. *Cyclopropyl(1-phenyl-1H-pyrazol-3-yl)methanol* **5a**

Yield: 36 mg (33%); yellow oil. R_f = 0.32 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3385, 1600, 1525, 1502, 1390, 1251, 1228, 1035, 754, 680 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 2.4 Hz, 1H), 7.61-7.59 (m, 2H), 7.40-7.34 (m, 2H), 7.24-7.18 (m, 1H), 6.42 (d, *J* = 2.4 Hz, 1H), 4.16 (d, *J* = 8.3 Hz, 1H), 2.55 (br s, 1H, OH), 1.30-1.13 (m, 1H), 0.62–0.32 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.4 (C-3, C=N), 137.8, 127.1 (C-5), 125.4, 124.1, 116.9, 102.6 (C-4), 70.7 (C-OH), 15.3, 0.9. LC-MS (ES^+): *m/z* (%) 215 (M+H, 25), 197 (M-H_2O, 100). HRMS: (ESI-TOF, M+Na) calcd for $C_{13}H_{14}N_2ONa$: 237.1005. Found: 237.1004.

4.3.1.2. *Cyclopropyl(1-p-tolyl-1H-pyrazol-3-yl)methanol* **5b**

Yield: 36 mg (35%); yellow oil. R_f = 0.34 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3408, 2922, 1739, 1612,1533, 1514, 1388, 1259,1035, 817 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 2.3 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 6.40 (d, *J* = 2.3 Hz, 1H), 4.15 (d, *J* = 8.3 Hz, 1H), 2.51 (br s, 1H, OH), 2.31 (s, 3H), 1.30-1.17 (m, 1H), 0.63–0.34 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.3 (C-3, C=N), 136.6, 130.3, 128.1 (C-5), 119.5, 104.9 (C-4), 73.5 (C-OH), 21.3, 18.0, 3.6, 2.6. LC-MS (ES^+): *m/z* (%) 229 (M+H, 78), 211 (M-H_2O, 100). HRMS: (ESI-TOF, M+Na) calcd for $C_{14}H_{16}N_2ONa$: 229.1341. Found: 229.1346.

4.3.1.3. *Cyclopropyl(1-(4-iodophenyl)-1H-pyrazol-3-yl)methanol* **5c**

Yield: 64 mg (40%); light yellow oil. R_f = 0.32 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3408, 2924, 1589, 1529, 1491,1383, 1251, 1033, 1004, 943, 823 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 2.5 Hz, 1H), 7.65 (d, *J* = 6.8 Hz, 2H), 7.38 (d, *J* = 6.8 Hz, 2H), 6.43 (d, *J* = 2.5 Hz, 1H), 4.13 (d, *J* = 8.4 Hz, 1H), 2.51 (br s, 1H, OH), 1.31-1.08 (m, 1H), 0.66-0.32 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.7 (C-3, C=N), 136.1, 125.2 (C-5), 118.4, 103.1 (C-4), 88.0 (C-I), 70.6 (C-OH), 15.3, 0.9, 0.0. LC-MS

(ES$^+$): *m/z* (%): 341 (M+H, 53), 323 (M-H_2O, 100). HRMS: (ESI-TOF, M+Na) calcd for $C_{13}H_{13}IN_2ONa$: 341.0151. Found: 341.0138.

4.3.1.4. *1-(4-Chlorophenyl)-1H-pyrazol-3-yl)(cyclopropyl)methanol* **5d**

Yield: 53 mg (43%); brown oil. R_f = 0.32 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3381, 1597, 1533, 1498, 1386, 1096, 1033, 1010, 947, 829, 738 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 2.4 Hz, 1H), 7.54 (dt, *J* = 9.6, 2.8 Hz, 2H), 7.33 (dt, *J* = 9.6, 2.8 Hz, 2H), 6.43 (d, *J* = 2.4 Hz, 1H), 4.13 (d, *J* = 8.3 Hz, 1H), 2.58 (br s, 1H, OH), 1.33-1.10 (m, 1H), 0.68-0.30 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.7 (C-3, C=N), 136.3, 129.5, 127.2, 125.3 (C-5), 117.9, 103.0 (C-4), 70.6 (C-OH), 15.3, 0.9. LC-MS (ES$^+$): *m/z* (%) 249 (M+H, 18), 231 (M-H_2O, 100). HRMS: (ESI-TOF, M+Na) calcd for $C_{13}H_{13}ClN_2ONa$: 271.0614. Found 271.0627.

4.3.1.5. *Cyclopropyl(1-(4-methoxyphenyl)-1H-pyrazol-3-yl)methanol* **5e**

Yield: 40 mg (33%); yellow oil. R_f = 0.23 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3385, 1658, 1525, 1514, 1249, 1031, 829, 798 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 2.4 Hz, 1H), 7.50 (d, *J* = 6.8 Hz, 2H), 6.87 (d, *J* = 6.8 Hz, 2H), 6.39 (d, *J* = 2.4 Hz, 1H), 4.14 (d, *J* = 8.3 Hz, 1H), 3.77 (s, 3H), 2.54 (br s, 1H, OH), 1.35-1.13 (m, 1H), 0.67-0.31 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.0 (C-3, C=N), 153.9 (C-OCH_3), 131.7, 125.5 (C-5), 122.4, 118.6, 112.2, 102.1 (C-4), 70.7 (C-OH), 53.3 (OCH_3), 15.3, 0.9. LC-MS (ES$^+$): m/z (%) 245 (M+H, 27), 227 (M-H_2O, 100). HRMS: (ESI-TOF, M+Na) calcd for $C_{14}H_{16}ClN_2O_2$: 267.1109. Found: 267.1112.

4.3.1.6. *Cyclopropyl(1-(4-fluorophenyl)-1H-pyrazol-3-yl)methanol* **5f**

Yield: 44 mg (38%); yellow oil. R_f = 0.30 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3381, 1533, 1512, 1388, 1232, 1035, 835, 752 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 2.4 Hz, 1H), 7.56 (dd, *J* = 12.0, 4.5 Hz, 2H), 7.07 (t, *J* = 8.0 Hz, 2H), 6.42 (d, *J* = 2.4 Hz, 1H), 4.14 (d, *J* = 8.4 Hz, 1H), 2.49 (br s, 1H, OH), 1.31-1.10 (m, 1H), 0.66-0.33 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.4 (C-F) (d, *J* = 247.0 Hz), 157.0 (C-3, C=N), 128.2, 121.3 (C-5), 116.7, 116.4, 105.4 (C-4), 73.4 (C-OH), 18.0, 3.6, 2.7.

LC-MS (ES^+): m/z (%) 233 (M+H, 48), 215 (M-H_2O, 100). HRMS: *m/z* (ESI-TOF, M+Na) calcd for $C_{13}H_{13}FN_2O$: 255.0910. Found: 255.0915.

4.3.1.7. *(1-(Benzo[d][1,3]dioxol-5-yl)-1H-pyrazol-3-yl)(cyclopropyl)methanol* **5g**

Yield: 39 mg (30%); brown oil. R_f = 0.27 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3431, 1527, 1512, 1467, 1247, 1228, 1037, 933, 810 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, *J* =2.4 Hz, 1H), 7.13 (d, *J* = 2.2 Hz, 1H), 7.01 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 6.39 (d, *J* = 2.4 Hz, 1H), 5.95 (s, 2H), 4.13 (d, *J* = 8.3 Hz, 1H), 2.48 (br s, 1H, OH), 1.30-1.10 (m, 1H), 0.66-0.32 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.3 (C-3, C=N), 146.2, 144.0, 125.6 (C-5), 110.3, 106.0 (C-4), 102.3 (OCH_2O), 99.6, 99.4, 70.7 (C-OH), 27.4, 15.3, 0.9, 0.0. LC-MS (ES^+): m/z (%) 259 (M+H, 50), 241 (M-H_2O, 100). HRMS: *m/z* (ESI-TOF, M+Na) calcd for $C_{14}H_{14}N_2O_3Na$: 281.0902. Found: 281.0906.

4.4. *The preparation of 1-(prop-2-ynyl)-1H-indole* **8**

A procedure has been followed, which was used in the literature for a similar compound.[31] Thus, indole **6** (1.170 g, 10 mmol) in dry DMF (2 mL) was added dropwise to a suspension of NaH (0.40 g, 10 mmol) in dry DMF (5 mL) maintained at 0 °C and then the reaction mixture was stirred at room temperature for 8h, followed by the addition of propargyl bromide **7** (1.190 g, 10 mmol) in dry DMF (1 mL). After completion of reaction (monitored by TLC), the mixture was poured into cold water (30 mL) and the organic products extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and the dichloromethane evaporated. The crude oily product was purified by column chromatography on silica gel using *n*-hexane-EtOAc (8:1) to give **8** as a yellow solid; yield: 1.160 g (75%). Mp 65-69 °C; (lit.[32] mp. 36-37 °C). R_f = 0.67 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3292, 3055, 2123, 1612, 1514, 1483, 1464, 1396, 1336, 1315, 1259, 1186, 1012, 931, 883, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.55 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.29 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.15 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.11-7.01 (m, 2H), 6.44 (dd, *J* = 3.2, 0.8 Hz, 1H), 4.73 (d, *J* = 2.6 Hz, 2H), 2.27 (t, *J* = 2.6 Hz, 1H).

4.4.1. *Preparation of pyrazolyl-1H-indoles **9** and **10** General procedure.*

A solution of 1-(prop-2-ynyl)-1*H*-indole **8** (76 mg, 0.5 mmol) and a 4-aryl sydnone **1** (0.5 mmol) was refluxed in toluene (10 mL) for 12 h. After completion of the reaction, as indicated by TLC monitoring (*n*-hexane-EtOAc, 1:1), the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, 230-400 Mesh ASTM) to give, separately, regioisomers **9** which were eluted first as less polar fractions and **10** as second, more polar fractions.

4.4.1.1. *((1-Phenyl-1H-pyrazol-3-yl)methyl)-1H-indole* **9a**

Yield: 25 mg (18%); white powder. Mp 110-112 °C; R_f = 0.58 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3442, 1641, 1530, 1485, 1463, 1390, 1330, 1315, 1259, 1188, 1153, 1074, 1045, 754, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 2.4 Hz, 1H), 7.62-7.50 (m, 3H), 7.44-7.30 (m, 3H), 7.26-7.17 (m, 1H), 7.17-7.09 (m, 2H), 7.09-6.99 (m, 1H), 6.45 (dd, *J* = 3.1, 0.7 Hz, 1H, Hc), 6.02 (d, *J* = 2.4 Hz, 1H, Hb), 5.32 (s, 2H, Ha). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.2, 140.4, 136.6, 129.9, 129.1, 128.4 (2C; coincident), 126.9, 122.0, 121.3, 119.9, 119.5, 110.1, 106.8, 102.1, 44.7. HRMS: (ESI-TOF, $[M+H]^+$) calcd for $C_{18}H_{16}N_3$: 274.1344. Found: 274.1349.

4.4.1.2. *1-((1-Phenyl-1H-pyrazol-4-yl)methyl)-1H-indole* **10a**

Yield: 49 mg (36%); light yellow solid. Mp 105-107 °C; R_f = 0.44 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3442, 1642, 1600, 1567, 1504, 1460, 1396, 1333, 1313, 1265, 1217, 1186, 1109, 1042, 1012, 958, 902, 854, 798 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.61-7.55 (m, 3H), 7.54 (m, 1H), 7.50 (dd, *J* = 9.2, 1.6 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.20-7.09 (m, 3H), 7.07-7.02 (m, 2H), 6.45 (dd, *J* = 2.8, 0.4 Hz, 1H, Hb), 5.18 (s, 2H, Ha). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.4, 140.2, 136.3, 129.8, 129.2, 127.9, 127.0, 125.8, 122.1, 121.5, 120.4, 120.0, 119.5, 109.8, 102.1, 41.2. HRMS: *m/z* (ESI-TOF, $[M+H]^+$) calcd for $C_{18}H_{16}N$: 274.1344. Found: 274.1354.

4.4.1.3. *1-((1-p-Tolyl-1H-pyrazol-3-yl)methyl)-1H-indole* **9b**

Yield: 40 mg (28%); yellow solid. Mp 95-97 °C; R_f = 0.57 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3435, 1638, 1527, 1511, 1441, 1383, 1354, 1297, 1238, 1198, 1058, 1004, 950, 810, 736 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 2.4 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.18-7.10 (m, 4H), 7.03 (t, *J* = 8.0 Hz, 1H), 6.46 (d, *J* = 3.2 Hz, 1H, Hc), 6.02 (d, *J* = 2.4 Hz, 1H, Hb), 5.33 (s, 2H, Ha), 2.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.9, 139.4, 136.8, 135.9, 133.1, 132.5, 130.3, 128.4, 122.0, 121.4, 119.9, 119.5, 110.1, 106.5, 102.0, 44.7, 21.3. HRMS: (ESI-TOF, $[M+H]^+$) calcd for $C_{19}H_{18}N_3$: 288.1501. Found: 288.1501.

4.4.1.4. *1-((1-p-Tolyl-1H-pyrazol-4-yl)methyl)-1H-indole* **10b**

Yield: 61 mg (42%); dark yellow solid. Mp 75–77 °C; R_f = 0.40 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3449, 1612, 1569, 1518, 1485, 1464, 1402, 1315, 1257, 1122, 1083, 1037, 1012, 957, 883, 813, 738 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.62-7.51 (m, 3H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 1H), 7.16-7.01 (m, 5H), 6.45 (dd, *J* = 3.2, 0.8 Hz, 1H, Hb), 5.17 (s, 2H, Ha), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.2, 138.1, 136.9, 136.3, 130.3, 129.1, 127.9, 125.8, 122.1, 121.5, 120.1, 120.0, 119.4, 109.8, 102.1, 41.2, 21.3. HRMS: *m/z* (ESI-TOF, $[M+H]^+$) calcd for $C_{19}H_{18}N_3$: 288.1501. Found: 288.1491.

4.4.1.5. *1-((1-(4-Iodophenyl)-1H-pyrazol-3-yl)methyl)-1H-indole* **9c**

Yield: 40 mg (20%); light yellow solid. Mp 136–138 °C; R_f = 0.61 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3435, 1637, 1587, 1383, 1298, 1240, 1197, 1059, 1004, 946, 815, 765, 750, 665 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) (Fig. 3): δ = 7.66 (d, *J* = 9.2 Hz, 2H), 7.63 (d, *J* = 2.4 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.36 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 2H), 7.13 (td, *J* = 10.0, 7.2, 1.2 Hz, 2H), 7.04 (td, *J* = 8.8, 8.0, 1.2 Hz, 1H), 6.46 (dd, *J* = 3.2, 0.8 Hz, 1H, Hc), 6.03 (d, *J* = 2.4 Hz, 1H, Hb), 5.31 (s, 2H, Ha). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6, 140.0, 138.8, 136.6, 129.1, 128.4, 128.2, 122.2, 121.2, 121.1,

119.9, 110.1, 107.2, 102.2, 91.0, 44.6. HRMS: m/z (ESI-TOF, $[M+H]^+$) calcd for $C_{18}H_{15}IN_3$: 400.0311. Found: 400.0317.

4.4.1.6. *1-((1-(4-Iodophenyl)-1H-pyrazol-4-yl)methyl)-1H-indole* **10c**

Yield: 10 mg (5%): yellow solid. Mp 125–127 °C; R_f = 0.55 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3428, 1647, 1492, 1460, 1394, 1332, 1311, 1257, 1195, 1168, 1082, 1041, 1011, 952, 860, 812, 738 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.8 Hz, 2H), 7.59-7.55 (m, 2H), 7.28 (t, *J* = 10.8 Hz, 3H), 7.20-7.01 (m, 4H), 6.46 (d, *J* = 2.8 Hz, 1H, Hb), 5.18 (s, 2H, Ha). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.7, 139.9, 138.8, 136.3, 129.1, 127.9, 125.5, 122.2, 121.5, 121.1, 121.0, 120.1, 109.7, 102.3, 91.1 (C-I), 41.2. HRMS: *m/z* (ESI-TOF, $[M+H]^+$) calcd for $C_{18}H_{15}IN_3$: 400.0311. Found: 400.0311.

4.4.1.7. *1-((1-(4-Chlorophenyl)-1H-pyrazol-3-yl)methyl)-1H-indole* **9d**

Yield: 54 mg (35%); yellow solid. Mp 105-107 °C; R_f = 0.64 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3422, 1615, 1597, 1530, 1498, 1464, 1383, 1309, 1256, 1174, 1093, 1051, 1010, 948, 830, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 2.4 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.32 (d, *J* = 9.2 Hz, 2H), 7.17-7.10 (m, 2H), 7.03 (td, *J* = 7.9, 0.9 Hz, 1H), 6.46 (d, *J* = 4.0 Hz, 1H, Hc), 6.03 (d, *J* = 2.4 Hz, 1H, Hb), 5.31 (s, 2H, Ha). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.5, 138.9, 136.6, 132.3, 129.9, 129.1, 128.4, 128.3, 122.1, 121.4, 120.6, 119.9, 110.1, 107.2, 102.2, 44.6. HRMS: *m/z* (ESI-TOF, $[M+H]^+$) calcd for $C_{18}H_{15}ClN_3$: 308.0955. Found: 308.0948.

4.4.1.8. *1-((1-(4-Chlorophenyl)-1H-pyrazol-4-yl)methyl)-1H-indole* **10d**

Yield: 11 mg (7%); yellow solid. Mp 108–110 °C; R_f = 0.55 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3435, 1639, 1500, 1471, 1408, 1309, 1215, 1122, 1092, 1037, 1012, 952 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.59 (s, 1H), 7.57 (d, *J* = 4.0 Hz, 2H), 7.45 (dt, *J* = 10.0, 5.2, 3.2 Hz, 2H), 7.31-7.26 (m, 2H), 7.14 (td, *J* = 8.4, 7.2, 1.2 Hz, 2H), 7.09-7.02 (m, 2H), 6.46 (dd, *J* = 3.2, 0.8 Hz, 1H, Hb), 5.18 (s, 2H, Ha). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.6, 138.7, 136.3, 132.5, 129.9, 129.1, 127.9, 125.7, 122.2, 121.5,

120.9, 120.6, 120.0, 109.7, 102.3, 41.2. HRMS: *m/z* (ESI-TOF, $[M+H]^+$) calcd for $C_{18}H_{15}ClN_3$: 308.0955. Found: 308.0945.

4.4.1.9. *1-((1-(4-Methoxyphenyl)-1H-pyrazol-3-yl)methyl)-1H-indole* **9e**

Yield: 15 mg (10%); light yellow solid. Mp 93-96 °C; R_f = 0.44 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3442, 1637, 1597, 1533, 1514, 1464, 1446, 1390, 1359, 1301, 1247, 1190, 1112, 1051, 1033, 962, 837, 768 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 2.4 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 9.2 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.17-7.09 (m, 2H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 9.2 Hz, 2H), 6.46 (d, *J* = 3.2 Hz, 1H, Hc), 6.02 (d, *J* = 2.4 Hz, 1H, Hb), 5.32 (s, 2H, Ha), 3.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7, 150.7, 136.6, 134.2, 129.1, 128.5, 128.4, 122.0, 121.3, 119.8, 114.9, 110.1, 106.3, 102.0, 56.0 (OCH_3), 44.7 (one quaternary coincident). HRMS: *m/z* (ESI-TOF, $[M+H]^+$) calcd for $C_{19}H_{18}N_3O$: 304.1450. Found: 304.1442.

4.4.1.10. *1-((1-(4-Methoxyphenyl)-1H-pyrazol-4-yl)methyl)-1H-indole* **10e**

Yield: 61 mg (40%); light yellow solid. Mp 106-108 °C; R_f = 0.28 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3435, 1646, 1566, 1518, 1464, 1452, 1402, 1292, 1247, 1203, 1174, 1109, 1087, 1047, 1024, 958, 868, 836, 788, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 8.0 Hz, 1H), 7.53 (s, 2H), 7.40 (dt, *J* = 12.4, 10.0, 3.2 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 1H), 7.17-7.01 (m, 3H), 6.84 (dt, *J* = 12.4, 8.0, 3.2 Hz, 2H), 6.46 (dd, *J* = 3.2, 0.4 Hz, 1H, Hb), 5.18 (s, 2H, Ha), 3.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7 (C-OCH_3), 140.0, 136.3, 134.0, 129.1, 127.9, 125.9, 122.1, 121.4, 121.1, 119.9, 114.8, 109.8, 102.1, 55.9 (OCH_3), 41.2 (one quaternary coincident). HRMS: *m/z* (ESI-TOF, $[M+H]^+$) calcd for $C_{19}H_{18}N_3O$: 304.1450; found: 304.1451.

4.4.1.11. *1-((1-(4-Fluorophenyl)-1H-pyrazol-3-yl)methyl)-1H-indole* **9f**

Yield: 26 mg (20%); light yellow solid. Mp 94-96 °C; R_f = 0.63 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3442, 1647, 1533, 1510, 1464, 1429, 1392, 1330, 1315, 1238, 1188, 1097, 1051, 1043, 1009, 952, 838, 755 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 2.5 Hz, 1H), 7.57-7.48 (m, 3H), 7.37 (d, *J* = 8.7 Hz,

1H), 7.15-7.00 (m, 5H), 6.46 (dd, *J* = 3.2, 0.7 Hz, 1H, Hc), 6.03 (d, *J* = 2.2 Hz, 1H, Hb), 5.31 (s, 2H, Ha). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 161.1 (d, *J* = 246.3 Hz, C-F), 150.9, 136.4, 136.3, 136.2, 128.7, 128.1, 128.0, 121.6, 121.0, 120.9, 119.5, 116.3, 116.2, 109.7, 106.5, 101.7, 44.2 (one quaternary coincident). HRMS: *m/z* (ESI-TOF, $[M+H]^+$) calcd for $C_{18}H_{15}FN_3$: 292.1250. Found: 292.1249.

4.4.1.12. *1-((1-(4-Fluorophenyl)-1H-pyrazol-4-yl)methyl)-1H-indole* **10f**

Yield: 14 mg (10%); yellow oil. R_f = 0.44 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3442, 1642, 1516, 1485, 1462, 1400, 1313, 1264, 1228, 1153, 1097, 1035, 1010, 954, 835, 815, 738 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.59 (t, *J* = 1.0 Hz, 1H), 7.53 (d, *J* = 3.0 Hz, 2H), 7.50-7.40 (m, 2H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.17–7.11 (td, *J* = 8.2, 7.0, 2.2 Hz, 2H), 7.09–6.96 (m, 3H), 6.46 (dd, *J* = 3.0, 0.7 Hz, 1H, Hb), 5.18 (s, 2H, Ha). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.1 (d, *J* = 244.6 Hz, C-F), 140.0, 136.2, 135.9, 127.5, 125.5, 121.8, 121.1, 120.9, 120.8, 119.6, 116.2, 116.1, 109.4, 101.8, 40.8. HRMS: *m/z* (ESI-TOF, $[M+H]^+$) calcd for $C_{18}H_{15}FN_3$: 292.1250. Found: 292.1248.

4.4.1.13. *1-((1-(Benzo[d][1,3]dioxol-5-yl)-1H-pyrazol-3-yl)methyl)-1H-indole* **9g**

Yield: 32 mg (20%); white solid. Mp 121-123 °C; R_f = 0.58 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3431, 1631, 1529, 1504, 1462, 1384, 1334, 1313, 1265, 1249, 1109, 1037, 934, 875, 739 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 2.4 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.15-7.09 (m, 3H), 7.02 (t, *J* = 8.0 Hz, 1H), 6.96 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.45 (d, *J* = 3.2 Hz, 1H, Hc), 5.99 (d, *J* = 2.4 Hz, 1H, Hb), 5.92 (s, 2H, OCH_2O), 5.29 (s, 2H, Ha). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.8, 148.8, 146.7, 136.6, 135.3, 129.1, 128.6, 128.4, 122.0, 121.3, 119.9, 112.9, 110.1, 108.7, 106.5, 102.3, 102.2, 102.1, 44.6. HRMS: *m/z* (ESI-TOF, $[M+H]^+$) calcd for $C_{19}H_{16}N_3O_2$: 318.1243. Found: 318.1242.

4.4.1.14. *1-((1-(Benzo[d][1,3]dioxol-5-yl)-1H-pyrazol-4-yl)methyl)-1H-indole* **10g**

Yield: 16 mg (10%); brown oil. R_f = 0.45 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3442, 1642, 1508, 1464, 1396, 1334, 1311, 1265, 1247, 1201, 1105, 1037, 966, 935, 881, 802, 738 cm^{-1}. ^{1}H NMR (400 MHz,

$CDCl_3$): δ = 7.57 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.17-7.02 (m, 4H), 6.90 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.46 (dd, *J* = 3.2, 0.7 Hz, 1H, Hb), 5.92 (s, 2H), 5.18 (s, 2H, Ha). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.7, 146.7, 140.0, 136.3, 135.2, 129.1, 127.9, 126.1, 122.1, 121.5, 120.1, 120.0, 112.9, 109.8, 108.6, 102.2, 102.1, 101.9, 41.2. HRMS:*m/z* (ESI-TOF, $[M+H]^+$) calcd for $C_{19}H_{16}N_3O_2$: 318.1243; found: 318.1238.

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