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Microwave-assisted regioselective [1,3]-dipolar cycloaddition of 3-methyl-2-(substitutedbenzylidene)-5-oxopyrazolidin-2-ium-1-ides to benzothiophene 1,1-dioxide

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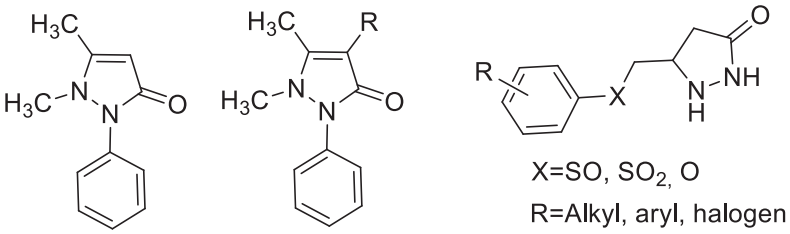
Abstract: A series of pyrazolidinium ylides was reacted with benzothiophene 1,1-dioxide to afford (*3R,5S,5aS,10bS*)-3-methyl-5-substitutedphenyl-2,3,5,5a-tetrahydrobenzo[4,5]thieno[3,2-c]pyrazolo[1,2-a]pyrazol-1(*10bH*)-one 6,6-dioxides under microwave irradiation and their structures were identified by means of spectral/physical characteristics including X-ray diffraction data and HRMS measurements.

Key words: Microwave-assisted synthesis, pyrazolidinium, ylide, 1,3-dipolar cycloaddition, benzothiophene dioxide

1. Introduction

Heterocyles containing pyrazolone rings have been attracting continuing interest due to their diverse medicinal chemistry applications, for example as antipyretic and antiparasitic agents. Recently, some sulfanyl pyrazolone derivatives, which can be used against amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, a fatal neurodegenerative disease causing muscle loss and paralysis, were reported (Figure 1).[1–12]



Antipyrine

R=N(CH$_3$)$_2$: Aminopyrine

R= CH(CH$_3$)$_2$: Isopropylantipyrine

R= N(CH$_3$)CH$_2$SO$_3$Na : Sulpyrine

Figure 1. Some biologically important pyrazolone derivatives.

Pyrazolidium ylides have been studied rarely in terms of 1,3-dipolar cycloaddition. 1,3-Dipolar cycloaddition of these dipoles to phenyl acetylene, ethyl propiolate, maleimides, and fullerenes is reported.[13–17]

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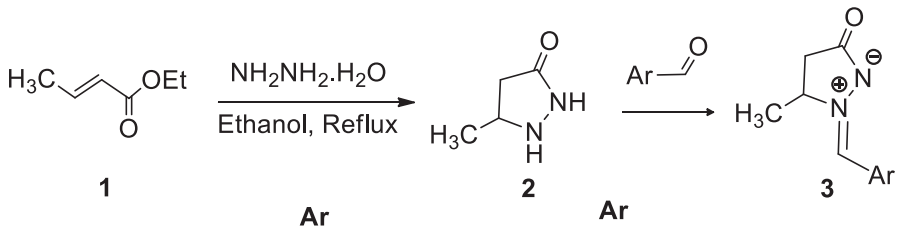
The dipolarophilic reagent used in this work, benzothiophene 1,1-dioxide, is also rarely utilized in dipolar cycloadditions.[18–20] Recently, we performed cycloaddition of sydnones to benzothiophene dioxide.[21]

Taking account of the above considerations and our continuing interest[22] in the cycloadditions of various ylides, we herein focused on the cycloaddition of oxopyrazolidinium ylides to benzothiophene 1,1-dioxide under microwave irradiation conditions routinely utilized in organic synthesis including cycloaddition and multicomponent reactions.[23–28]

2. Results and discussion

The major starting 1,3-dipolar compounds, the pyrazolidinum ylides **3a**–**l**, were prepared by reacting ethyl but-2-enoate with hydrazine hydrate then with substituted benzaldehydes carrying both electron withdrawing and electron donating groups, according to the procedure previously reported,[29] and their structures were confirmed by spectral/physical characteristics (Scheme 1).



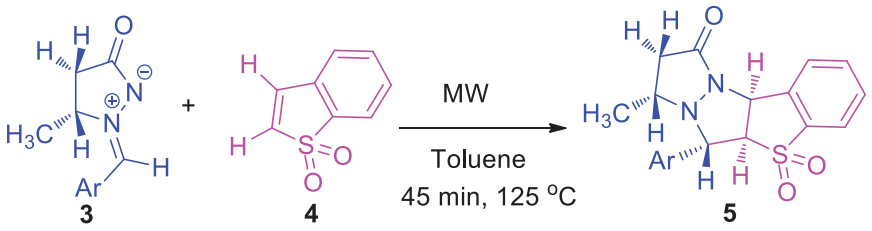
1 **2** **3**

	Ar		Ar
a	C_6H_5	**g**	4-CF_3-C_6H_5
b	4-CH_3-C_6H_5	**h**	4-CN-C_6H_5
c	3-CH_3-C_6H_5	**i**	4-F-C_6H_5
d	4-CH_3O-C_6H_5	**j**	4-Cl-C_6H_5
e	3-CH_3O-C_6H_5	**k**	4-NO_2-C_6H_5
f	4-CH_3S-C_6H_5	**l**	4-$N(CH_3)_2$-C_6H_5

Scheme 1. Synthesis of oxopyrazolidinium ylides **3a**–**l**.

The electron deficient dipolarophile benzothiophene 1,1-dioxide **4** underwent cycloaddition with oxopyrazolidinium ylides **3a**–**l** under microwave heating and gave the regioisomers **5a**–**l** in good yields as the only isolable regioisomeric products (Scheme 2). Even if prolonged reflux conditions were applied, no reaction occurred at all between the ylides and benzothiophene dioxide.

Typical characteristics of these cycloadducts carrying four stereocenters in their IR spectra are the carbonyl absorptions of the pyrazolidinone at around 1685–1695 cm^{-1} and the symmetric and asymmetric stretching vibrations of SO_2 moiety at around 1150 and 1300 cm^{-1}, respectively. In the proton NMR spectra of these cycloadducts, the most deshielded aliphatic hydrogen (H_a) originating from benzothiophene 1,1-dioxide is that attached to the bridge carbon adjacent to the nitrogen with the ring carbonyl group and appeared at around 5.77 ppm as a doublet. Another bridge proton (H_b) originating from benzothiophene 1,1-dioxide and spatially *trans* to the sulfone group and H_c resonated at around 4.35 ppm as a triplet. The H_c proton that originated from the ylide azomethine group appears as a doublet at around 4.20 ppm with a J value of 8.8 Hz. H_d is split into a septet due to adjacent methyl and methylene protons (H_e and H_f) at around 3.24 ppm (Figure 2a). The most deshielded aromatic protons (H_g) are those attached to the carbon, which are closer to



	Ar	Yield %		Ar	Yield %
a	C_6H_5	56	**g**	4-CF_3-C_6H_5	71
b	4-CH_3-C_6H_5	71	**h**	4-CN-C_6H_5	67
c	3-CH_3-C_6H_5	76	**i**	4-F-C_6H_5	70
d	4-CH_3O-C_6H_5	88	**j**	4-Cl-C_6H_5	69
e	3-CH_3O-C_6H_5	89	**k**	4-NO_2-C_6H_5	71
f	4-CH_3S-C_6H_5	75	**l**	4-$N(CH_3)_2$-C_6H_5	71

Scheme 2. 1,3-Dipolar cycloaddition of pyrazolidinium ylides **3a**–**l** with benzothiophene 1,1-dioxide **4** leading to **5a**–**l**.

the sulfone group spatially and came out at around 8.40 ppm as doublets. As for ^{13}C NMR data, we observe the pyrazolone carbonyl carbon resonating at around 170 ppm, while the bridge methine (C1) adjacent to sulfone resonates at around 73.5 ppm, another bridge carbon (C2) appears at 60.5 ppm and C3 carrying an aromatic group at 68.2 ppm, while pyrazolone C4 carbon, which is attached to the methyl group, arises at 55.8 ppm (Figure 2b).

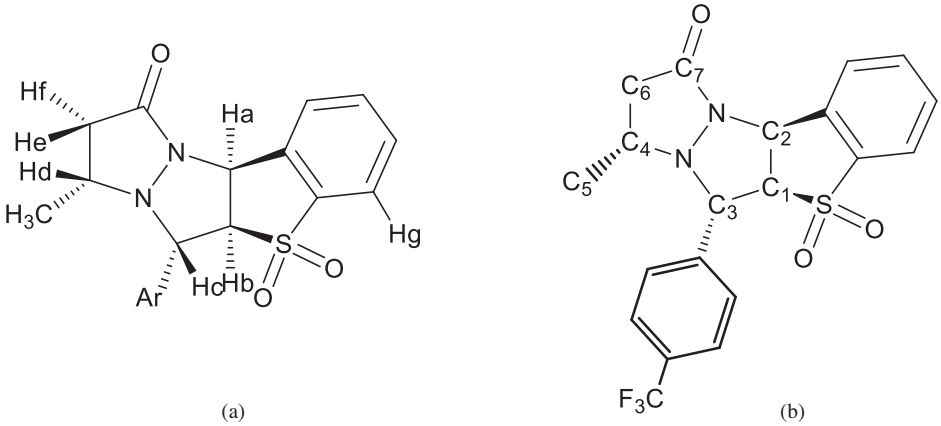


Figure 2. (**a**) Proton assignments in the ^{1}H NMR spectrum of **5a**–**l**; (**b**) assignment of carbons of **5h**.

Exact regiochemistry and stereochemistry of the cycloadducts were resolved by means of X-ray diffraction data obtained from a fine single crystal of **5i** (Figure 3). It is clearly seen that aryl and methyl groups are *cis*; H_b and H_c protons are *trans*. H_b and H_d obtain their *cis* stereochemistry from benzothiophene 1,1-dioxide.

Formation of these single regioisomers coincides with the outcome of a previous observation in which azomethine ylide generated from isatine in which ylide approach to the dipolarophile occurred through the less hindered site.[18] In the case of benzothiophene-*S*-oxide–ylide cycloaddition, a contrasting situation was reported.[29] In this regard, in our current case, regioisomers **5a**–**l** were generated by approach of the dipolarophile benzothiophene 1,1-dioxide, which may be attributed to the possible resonance structure having the higher electron deficiency on the number 2 carbon and likely less hindrance (Scheme 3).

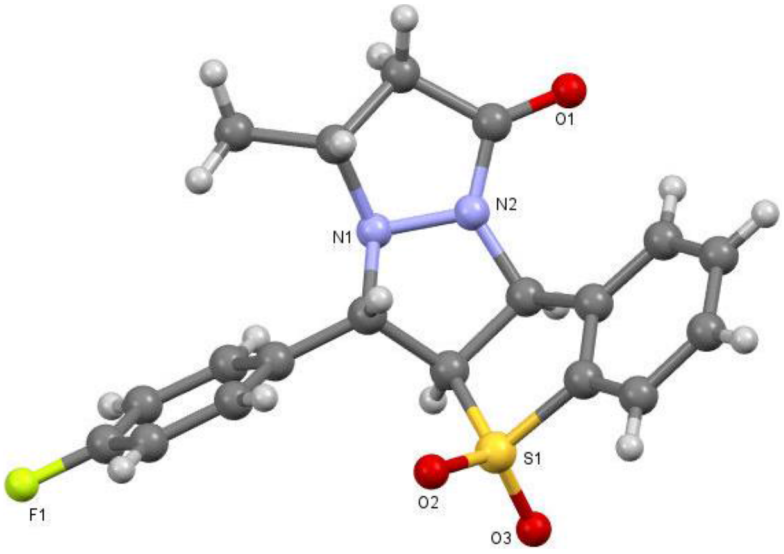
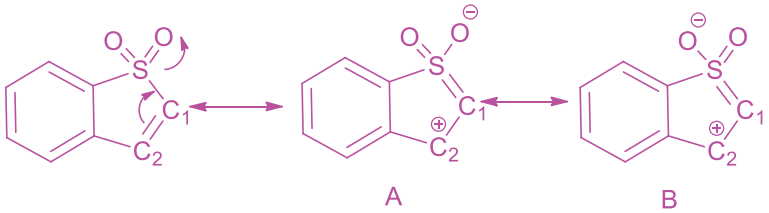
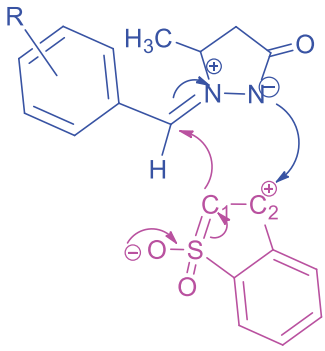


Figure 3. X-ray ORTEP diagram of **5i**.



Scheme 3. Resonance structures of benzothiophene 1,1-dioxide.

Considering the fact that the electron deficiency is higher in no. 2 carbon of benzothiophene 1,1-dioxide we may think of drawing an anticipated transition state configuration based on the approaching 1,3-dipolar azomethine ylide to the electron poor and electron rich ends of the dipolarophile benzothiophene dioxide (Scheme 4).



Scheme 4. Transition state configuration of the cycloaddition.

3. Conclusions

In summary, we demonstrate a practical method that allows access to a series of substituted benzothiophene fused pyrazolones carrying substituted aryl groups using [1,3]-dipolar cycloaddition reactions of 3-methyl ox-

opyrazolidinium ylides to electron deficient dipolarophile benzothiophene 1,1-dioxide. The reactions result in good yields and are regioselective under microwave irradiation.

4. Experimental

4.1. General

Melting points were determined on a Meltemp apparatus and are uncorrected. Infrared spectra were obtained from KBr pellets or neat on NaCl plates for liquids and were recorded on a Shimadzu 8000 FTIR spectrophotometer. LC-MS spectra were recorded on an Agilent spectrometer and HRMS on a Waters Synapt spectrometer using the ionization modes specified. NMR spectra were recorded on JEOL and VARIAN spectrometers operating at 400 MHz for ^{1}H and at 100 MHz for ^{13}C, respectively, all at 25 °C, 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. Preparation of oxopyrazolidinium ylides 3a–l: general procedure[30]

Ethyl 3-butenoate (5.15 g, 45.0 mmol) was added dropwise to a solution of hydrazine monohydrate (1.4 g, 45.0 mmol) in ethanol (80 mL) and the reaction mixture was refluxed overnight at 78 °C; the intermediate pyrazolidin-3-one formed. Then substituted benzaldehyde (60.0 mmol) was added to the solution. After stirring overnight at room temperature, the solvent was removed under reduced pressure. The resultant residue was purified by column chromatography on silica gel using MeOH/EtOAc (1/10, v/v) to afford 2-arylidene-3-methyl-5-oxopyrazolidin-2-ium-1-ides (**3a**–**l**).

4.2.1. 2-Benzylidene-3-methyl-5-oxopyrazolidin-2-ium-1-ide 3a

Light yellow solid, mp 148–150 °C. R_f: 0.08 (EtOAc) IR (KBr, cm^{-1}): 1654 (C=O), 1585, 1454, 1350, 1319, 1095, 1026, 759. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (dd, J = 1.7, 7.8 Hz, 2H), 7.70 (s, 1H), 7.52–7.45 (m, 3H), 4.82–4.74 (m, 1H), 2.79 (dd, J = 9.1, 16.3 Hz, 1H), 2.20 (dd, J = 4.1, 16.3 Hz, 1H), 1.52 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 183.40 (C=O), 131.94, 131.64, 131.53, 130.62, 129.21, 66.05, 37.59, 22.57.

4.2.2. 3-Methyl-2-(4-methylbenzylidene)-5-oxopyrazolidin-2-ium-1-ide 3b

Yellow solid, mp 129–132 °C. R_f: 0.08 (EtOAc). IR (KBr, cm^{-1}): 1654 (C=O), 1585, 1435, 1342, 1315, 1184, 1091, 813. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 7.5 Hz, 2H), 7.32–7.22 (m, 2H), 7.07 (d, J = 10.3 Hz, 1H), 4.72–4.62 (m, 1H), 3.45 (d, J = 10.7 Hz, 1H), 2.98 (m, 1H), 2.38 (s, 3H), 1.64 (dd, J = 6.7, 11.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.44 (C=O), 143.00 (C=N), 131.80, 129.79, 129.69, 126.75, 65.96, 37.60, 22.59, 21.88.

4.2.3. 3-Methyl-2-(3-methylbenzylidene)-5-oxopyrazolidin-2-ium-1-ide 3c

Light yellow solid, mp 136–138 °C. R_f: 0.10 (EtOAc) IR (KBr, cm^{-1}): 1662 (C=O), 1585, 1342, 1292, 1095, 1026, 1026, 786. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 9.0 Hz, 2H), 7.00 (s, 1H), 6.65 (d, J = 9.3 Hz,

2H), 4.61–4.54 (m, 1H), 3.07 (d, J = 8.6 Hz, 1H), 3.05 (s, 2.42 (dd, J = 4.2, 16.4 Hz, 1H), 1.59 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.76 (C=O), 152.65 (C=N), 134.31, 134.26, 116.91, 111.28, 64.77, 39.86, 22.59, 21.88.

4.2.4. 2-(4-Methoxybenzylidene)-3-methyl-5-oxopyrazolidin-2-ium-1-ide 3d

Yellow solid, mp 114–116 °C. R_f: 0.04 (EtOAc) IR (KBr, cm^{-1}): 1662 (C=O), 1597, 1508, 1346, 1308, 1261, 1172, 1091, 1026, 732. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 9.0 Hz, 2H), 7.05 (s, 1H), 6.93 (d, J = 9.1 Hz, 2H), 4.70–4.58 (m, 1H), 3.84 (s, 3H(–OCH_3)), 2.98 (dd, J = 9.2, 16.4 Hz, 1H), 2.42 (dd, J = 4.2, 16.4 Hz, 1H), 1.63 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz) δ 183.43, 162.61, 134.00, 132.35, 122.58, 114.43, 65.63, 55.53, 37.74, 22.71.

4.2.5. 2-(3-Methoxybenzylidene)-3-methyl-5-oxopyrazolidin-2-ium-1-ide 3e

Light yellow solid, mp 93–96 °C. R_f: 0.08 (EtOAc) IR (KBr, cm^{-1}): 1662 (C=O), 1589, 1435, 1323, 1099, 1026, 918, 786. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.38–7.33 (m, 1H), 7.07 (s, 1H), 7.02 (dd, J = 1.7, 8.3 Hz, 1H), 4.78–4.62 (m, 1H), 3.84 (s, 3H), 3.02 (dd, J = 9.1, 16.5 Hz, 1H), 2.46 (dd, J = 4.1, 16.5 Hz, 1H), 1.67 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz) δ 183.58 (C=O), 159.72, 130.54, 130.13, 129.83, 124.51, 118.82, 115.65, 66.45, 55.66, 37.46, 22.63.

4.2.6. 3-Methyl-2-(4-(methylthio)benzylidene)-5-oxopyrazolidin-2-ium-1-ide 3f

Yellow solid, mp 120–122 °C. R_f: 0.04 (EtOAc) IR (KBr, cm^{-1}): 1654 (C=O), 1589, 1427, 1311, 1284, 1091, 1026, 819. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, J = 8.7 Hz, 2H), 7.64 (s, 1H), 7.36 (d, J = 8.7 Hz, 2H), 4.81–4.67 (m, 1H), 2.77 (dd, J = 9.1, 16.3 Hz, 1H), 2.50 (s, 3H, SCH_3)), 2.18 (dd, J = 4.2, 16.3 Hz, 1H), 1.50 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz) δ 182.85 (C=O), 143.54, 131.80, 130.33, 126.80, 125.39, 65.62, 37.72, 22.49, 14.37 (SCH_3).

4.2.7. 3-Methyl-5-oxo-2-(4-(trifluoromethyl)benzylidene)pyrazolidin-2-ium-1-ide 3g

White solid, mp 197–199 °C. R_f: 0.14 (EtOAc) IR (KBr, cm^{-1}): 1670 (C=O), 1593, 1562, 1438, 1319, 1111, 1068, 1018, 837. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 8.6 Hz, 2H), 7.69 (d, J = 8.3 Hz, 2H), 7.11 (s, 1H), 4.79–4.71 (m, 1H), 3.04 (dd, J = 9.1, 16.6 Hz, 1H), 2.49 (dd, J = 4.1, 16.6 Hz, 1H), 1.71 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.75 (C=O), 132.84, 132.42, 131.59, 130.00, 129.14, 125.74, 67.07, 37.13, 22.65.

4.2.8. 2-(4-Cyanobenzylidene)-3-methyl-5-oxopyrazolidin-2-ium-1-ide 3h

Yellow solid, mp 202–204 °C. R_f: 0.09 (EtOAc) IR (KBr, cm^{-1}): 2225(−C≡N), 1666 (C=O), 1581, 1427, 1338, 1311, 1099, 1030, 960, 833. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 8.6 Hz, 2H), 7.72 (d, J = 8.6 Hz, 2H), 7.09 (s, 1H), 4.83–4.70 (m, 1H), 3.04 (dd, J = 9.1, 16.7 Hz, 1H), 2.50 (dd, J = 4.1, 16.7 Hz, 1H), 1.71 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.74 (C=O), 133.09, 132.46, 131.49, 129.98, 118.36, 114.23, 67.07, 37.14, 22.65.

4.2.9. 2-(4-Fluorobenzylidene)-3-methyl-5-oxopyrazolidin-2-ium-1-ide 3i

Light yellow solid, mp 163–165 °C. R_f: 0.08 (EtOAc) IR (KBr, cm^{-1}): 1662 (C=O), 1597, 1578, 1346, 1307, 1234, 1161, 1091, 840. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (dd, J = 5.7, 9.0 Hz, 2H), 7.72 (s, 1H), 7.36 (t, J = 9.0 Hz, 2H), 4.84–4.70 (m, 1H), 2.79 (dd, J = 9.1, 16.3 Hz, 1H), 2.20 (dd, J = 4.2, 16.3 Hz, 1H), 1.51 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 183.40 (C=O), 162.37, 134.18, 130.85, 127.44, 116.40, 65.97, 37.60, 22.52.

4.2.10. 2-(4-Chlorobenzylidene)-3-methyl-5-oxopyrazolidin-2-ium-1-ide 3j

White solid, mp 128–131 °C. R_f: 0.08 (EtOAc) IR (KBr, cm^{-1}): 1666 (C=O), 1589, 1489, 1427, 1307, 1091, 1026, 821, 732. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 8.8 Hz, 2H), 7.42 (dd, J = 3.7, 8.8 Hz, 2H), 7.06 (s, 1H), 4.78–4.62 (m, 1H), 3.01 (dd, J = 9.1, 16.5 Hz, 1H), 2.46 (ddd, J = 2.5, 5.5, 16.5 Hz, 1H), 1.67 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.69 (C=O), 137.98, 132.81, 129.56, 129.26, 127.84, 66.56, 37.41, 22.53.

4.2.11. 3-Methyl-2-(4-nitrobenzylidene)-5-oxopyrazolidin-2-ium-1-ide 3k

Bright yellow solid, mp 125–128 °C. R_f: 0.08 (EtOAc) IR (KBr, cm^{-1}): 1705 (C=O), 1600, 1523, 1342, 1195, 1103, 1026, 848, 817. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 9.1 Hz, 2H), 8.34 (d, J = 9.1 Hz, 2H), 7.85 (s, 1H), 4.91–4.81 (m, 1H), 2.84 (dd, J = 9.0, 16.5 Hz, 1H), 2.27 (dd, J = 4.2, 16.5 Hz, 1H), 1.56 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.71 (C=O), 140.56, 132.09, 131.23, 124.95, 124.33, 67.06, 37.43, 22.66.

4.2.12. 2-(4-(Dimethylamino)benzylidene)-3-methyl-5-oxopyrazolidin-2-ium-1-ide 3l

Orange solid, mp 177–180 °C. R_f: 0.07 (EtOAc) IR (KBr, cm^{-1}): 1651 (C=O), 1600, 1531, 1361, 1319, 1188, 1087, 1022, 945, 821. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 9.0 Hz, 2H), 7.00 (s, 1H), 6.65 (d, J = 9.3 Hz, 2H), 4.61–4.54 (m, 1H), 3.07 (d, J = 8.6 Hz, 1H), 3.05 (s, 6H, $N(CH_3)_2$), 2.42 (dd, J = 4.2, 16.4 Hz, 1H), 1.59 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.76 (C=O), 152.65, 134.31, 134.26, 116.91, 111.28, 64.77, 39.86, 37.91, 22.45.

4.3. Synthesis of cycloaddition products 5a–l: general procedure

A solution of benzo[b]thiophene 1,1-dioxide **4** (0.25 mmol, 42 mg) and substituted pyrazolidinium ylides **3a**–**l** (0.25 mmol) in toluene was subjected to microwave irradiation at 125 °C for 45 min. After completion of the reaction, as indicated by TLC (n-hexane/EtOAc, 1:1), the solvent was removed under reduced pressure. The crude product was purified by column chromatography to give compounds **5a**–**l**.

4.3.1. (*1S,4aR,9bR,10S*)-1-Methyl-10-phenyl-1,2,9b,10-tetrahydrobenzo[4,5]thieno[2,3-c]pyrazolo[1,2-a]pyrazol-3(4aH)-one 5,5-dioxide 5a

White solid, yield: 50 mg, 52%: mp 200–202 °C; R_f 0.33 (EtOAc:n-hexane, 1:1). IR (KBr): 2978, 2928, 1689 (C=O), 1454, 1408, 1315 (SO_2 asym), 1192, 1149 (SO_2 sym), 1122, 756, 732, 702 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 7.9 Hz, 1H), 7.75–7.71 (m, 1H), 7.69 (dd, J = 1.3, 7.8 Hz, 1H), 7.64–7.61 (m, 1H),

7.56 (dd, J = 1.6, 8.0 Hz, 2H), 7.44–7.34 (m, 3H), 5.67 (d, J = 8.4 Hz, 1H), 4.38 (t, J = 8.6 Hz, 1H), 4.14 (d, J = 8.8 Hz, 1H), 3.30–3.20 (m, 1H), 2.73 (dd, J = 7.2, 16.4 Hz, 1H), 2.56 (ddd, J = 1.1, 11.9, 16.4 Hz, 1H), 0.79 (d, J = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.30 (C=O), 138.62, 135.30, 134.40, 132.48, 131.37, 129.40, 129.16, 128.49, 121.56, 73.33 (C–SO_2), 69.07 (N–C–Ar), 60.37 (C–bridge), 55.73 (CH_3–C–N), 44.57 (CH_2–CO), 17.91. HRMS (ESI) calcd for $C_{19}H_{19}N_2O_3S$: 354.1116 $(M + H)^+$, Found 355.1120.

4.3.2. (*1S,4aR,9bR,10S*)-1-Methyl-10-(*p*-tolyl)-1,2,9b,10-tetrahydrobenzo[4,5]thieno[2,3-c]pyrazolo[1,2-a]pyrazol-3(4aH)-one 5,5-dioxide 5b

Light yellow solid, yield: 65 mg, 71%: mp 151–153 °C; R_f 0.36 (EtOAc:n-hexane, 1:1) IR (KBr, cm^{-1}): 2978, 2928, 2855, 1694 (C=O), 1516, 1454, 1408, 1315 (SO_2 asym), 1192, 1153 (SO_2 sym), 1122, 829, 763, 736. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 7.9 Hz, 1H), 7.72–7.55 (m, 3H), 7.41 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 5.63 (d, J = 8.4 Hz, 1H), 4.35 (t, J = 8.6 Hz, 1H), 4.07 (d, J = 8.8 Hz, 1H), 3.28–3.14 (m, 1H), 2.70 (dd, J = 7.2, 16.3 Hz, 1H), 2.52 (ddd, J = 1.1, 11.9, 16.4 Hz, 1H), 2.34 (s, 3H), 0.77 (d, J = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.26 (C=O), 139.17, 138.66, 134.33, 132.65, 132.31, 131.32, 131.26, 129.77, 128.33, 121.50, 73.28 (C–SO_2), 68.90 (N–C–Ar), 60.26 (C-bridge), 55.70 (CH_3–C–N), 44.62 (CH_2–CO), 21.31, 18.02. HRMS (ESI) calcd for $C_{20}H_{21}N_2O_3S$: 369.1273 $(M + H)^+$, Found 369.1273.

4.3.3. (*1S,4aR,9bR,10S*)-1-methyl-10-(*m*-tolyl)-1,2,9b,10-tetrahydrobenzo[4,5]thieno[2,3-c]pyrazolo[1,2-a]pyrazol-3(4aH)-one 5,5-dioxide 5c

White solid, yield: 70 mg, 76%: mp 169–171 °C; R_f: 0.36 (EtOAc:n-hexane, 1:1) IR (KBr, cm^{-1}): 2978, 2928, 1693 (C=O), 1408, 1315 (SO_2 asym), 1192, 1153 (SO_2 sym), 1064, 914, 763, 732. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 7.9 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.68 (dd, J = 1.3, 7.7 Hz, 1H), 7.64–7.58 (m, 1H), 7.34 (d, J = 9.1 Hz, 2H), 7.30–7.23 (m, 2H), 5.65 (d, J = 8.4 Hz, 1H), 4.38 (t, J = 8.6 Hz, 1H), 4.10 (dd, J = 3.5, 7.9 Hz, 1H), 3.30–3.16 (m, 1H), 2.73 (dd, J = 7.2, 16.4 Hz, 1H), 2.55 (ddd, J = 1.1, 11.9, 16.4, Hz, 1H), 2.37 (s, 3H), 0.79 (d, J = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.32 (C=O), 138.84, 138.67, 135.27, 134.35, 132.45, 131.37, 131.31, 130.11, 129.01, 125.54, 121.54, 73.33 (C–SO_2), 69.09 (N–C–Ar), 60.30 (C-bridge), 55.79 (CH_3–C–N), 44.59 (CH_2–CO), 21.51, 18.01. HRMS (ESI) calcd for $C_{20}H_{21}N_2O_3S$: 369.1037 $(M + H)^+$, Found 369.1037.

4.3.4. (*1S,4aR,9bR,10S*)-10-(4-Methoxyphenyl)-1-methyl-1,2,9b,10-tetrahydrobenzo[4,5]thieno[2,3-c]pyrazolo[1,2-a]pyrazol-3(4aH)-one 5,5-dioxide 5d

White solid, yield: 85 mg, 88%: mp 161–163 °C; R_f: 0.26 (EtOAc:n-hexane, 1:1) IR (KBr, cm^{-1}): 2974, 2931, 1689 (C=O), 1612, 1516, 1408, 1311 (SO_2 asym), 1253, 1226, 1122 (SO_2 sym), 1030, 837, 763. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 7.9 Hz, 1H), 7.74–7.65 (m, 2H), 7.61 (d, J = 7.4 Hz, 1H), 7.45 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 5.65 (d, J = 8.4 Hz, 1H), 4.34 (t, J = 8.6 Hz, 1H), 4.06 (d, J = 8.9 Hz, 1H), 3.81 (s, 3H), 3.26–3.16 (m, 1H), 2.71 (dd, J = 7.2, 16.4 Hz, 1H), 2.54 (ddd, J = 1.0, 12.0, 16.4 Hz, 1H), 0.78 (d, J = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.19 (C=O), 160.35, 138.60, 134.41, 132.75, 131.27, 129.66, 126.94, 121.52, 114.50, 73.07 (C-SO_2), 68.72 (N–C–Ar), 60.27 (C-bridge), 55.65 (OCH_3), 55.40 (CH_3–C–N), 44.67 (CH_2–CO), 17.95. HRMS (ESI) calcd for $C_{20}H_{21}N_2O_4S$: 385.1222 $(M + H)^+$, Found 385.1238.

4.3.5. (*1S,4aR,9bR,10S*)-10-(3-Methoxyphenyl)-1-methyl-1,2,9b,10-tetrahydrobenzo[4,5]thieno [2,3-c]pyrazolo[1,2-a]pyrazol-3(4aH)-one 5,5-dioxide 5e

Light yellow oil, yield: 85 mg, 89%: R_f: 0.24 (EtOAc:*n*-hexane, 1:1) IR (KBr, cm^{-1}): 2974, 2931, 1693 (C=O), 1600, 1492, 1454, 1311 (SO_2 asym), 1153 (SO_2 sym), 1037, 910, 732. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 7.9 Hz, 1H), 7.73 (d, J = 7.7 Hz, 1H), 7.69 (dd, J = 1.3, 7.8 Hz, 1H), 7.64–7.59 (m, 1H), 7.33–7.28 (m, 1H), 7.17–7.11 (m, 2H), 6.90 (ddd, J = 1.0, 2.6, 8.3 Hz, 1H), 5.65 (d, J = 8.4 Hz, 1H), 4.37 (t, J = 8.5 Hz, 1H), 4.12 (d, J = 9.3 Hz, 1H), 3.83 (s, 3H), 3.30–3.20 (m, 1H), 2.74 (dd, J = 7.2, 16.4 Hz, 1H), 2.57 (ddd, J = 1.1, 11.8, 16.4 Hz, 1H), 0.84 (d, J = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.36 (C=O), 160.10, 138.67, 136.93, 134.37, 132.31, 131.38, 131.35, 130.20, 121.55, 120.68, 114.98, 113.65, 73.39 (C–SO_2), 68.91 (N–C–Ar), 60.37 (C-bridge), 55.80 (OCH_3), 55.45 (CH_3–C–N), 44.54 (CH_2–CO), 18.04. HRMS (ESI) calcd for $C_{20}H_{21}N_2O_4S$: 385.1222 $(M + H)^+$, Found 385.1238.

4.3.6. (*1S,4aR,9bR,10S*)-1-Methyl-10-(4-(methylthio)phenyl)-1,2,9b,10-tetrahydrobenzo[4,5]thieno[2,3-c]pyrazolo[1,2-a]pyrazol-3(4aH)-one 5,5-dioxide 5f

Light yellow solid, yield: 75 mg, 75%: mp 156–158 °C; R_f 0.31 (EtOAc:*n*-hexane, 1:1) IR (KBr, cm^{-1}): 2978, 2924, 1693 (C=O), 1597, 1492, 1408, 1311 (SO_2 asym), 1192, 1149 (SO_2 sym), 1122, 1033, 829, 736. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 7.5 Hz, 1H), 7.75–7.66 (m, 2H), 7.62 (d, J = 7.4 Hz, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H), 5.66 (d, J = 8.4 Hz, 1H), 4.34 (t, J = 8.6 Hz, 1H), 4.10 (dd, J = 2.6, 8.0 Hz, 1H), 3.28–3.19 (m, 1H), 2.73 (dd, J = 7.2, 16.4 Hz, 1H), 2.61–2.55 (m, 1H), 2.49 (s, 3H), 0.82 (d, J = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.23 (C=O), 140.25, 138.57, 134.44, 132.55, 131.65, 131.34, 128.85, 126.74, 121.55, 73.17 (C–SO_2), 68.71 (N–C–Ar), 60.40 (C-bridge), 55.71 (CH_3–C–N), 44.57 (CH_2–CO), 17.99, 15.54. HRMS (ESI) calcd for $C_{20}H_{21}N_2O_3S_2$: 401.0994 $(M + H)^+$, Found 401.0978.

4.3.7. (*1S,4aR,9bR,10S*)-1-Methyl-10-(4-(trifluoromethyl)phenyl)-1,2,9b,10-tetrahydrobenzo[4,5] thieno[2,3-c]pyrazolo[1,2-a]pyrazol-3(4aH)-one 5,5-dioxide 5g

White solid, yield: 76 mg, 71%: mp 165–167 °C; R_f 0.36 (EtOAc:Hex, 1:1) IR (KBr, cm^{-1}): 2978, 2935, 1697 (C=O), 1620, 1423, 1323 (SO_2 asym), 1165, 1122 (SO_2 sym), 1064, 1018, 848, 736. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 7.9 Hz, 1H), 7.74–7.69 (m, 4H), 7.68–7.64 (m, 2H), 7.62 (d, J = 7.6 Hz, 1H), 5.65 (d, J = 8.3 Hz, 1H), 4.32 (t, J = 8.5 Hz, 1H), 4.20 (d, J = 8.7 Hz, 1H), 3.30–3.19 (m, 1H), 2.73 (dd, J = 7.1, 16.4 Hz, 1H), 2.56 (ddd, J = 1.0, 11.8, 16.5 Hz, 1H), 0.79 (d, J = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.24 (C=O), 145.13–145.15 (quarternary C in Ph ring, J_{para} = 3.8 Hz), 139.85, 138.39, 134.52, 132.35, 131.66, 131.44, 131.36, 128.86, 127.9–119.8 (CF_3 carbon, J= 271.0 Hz) 126.13, 121.57, 119.8–119.9 (β-C to CF_3, J_{meta} = 10.8 Hz), 116.3–116.5 (α-C to CF_3, J_{ortho} = 32.5 Hz), 73.46 (C–SO_2), 68.26 (N–C–Ar), 60.50 (C-bridge), 55.68 (CH_3–C–N), 44.48 (CH_2–CO), 18.08 (CH_3). HRMS (ESI) calcd for $C_{20}H_{18}F_3N_2O_3S$: 423.0990 $(M + H)^+$, Found 423.0992.

4.3.8. 4-((*1S,4aR,9bR,10S*)-1-methyl-5,5-dioxido-3-oxo-1,2,3,4a,9b,10-hexahydrobenzo[4,5]thieno [2,3-c]pyrazolo[1,2-a]pyrazol-10-yl)benzonitrile 5h

White solid, yield: 65 mg, 67%: mp 230–232 °C; R_f 0.21 (EtOAc:*n*-hexane, 1:1) IR (KBr, cm^{-1}): 2974, 2928, 2229 (C=N), 1689 (C=O), 1408, 1315 (SO_2 asym), 1192, 1149 (SO_2 sym), 1122, 1064, 848, 736. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 7.8 Hz, 1H), 7.79–7.73 (m, 2H), 7.72 (d, J = 2.1 Hz, 3H), 7.69 (dd, J = 5.7, 1.7 Hz, 1H), 7.66–7.61 (m, 1H), 5.66 (d, J = 8.3 Hz, 1H), 4.30 (t, J = 8.5 Hz, 1H), 4.20 (d, J = 8.7 Hz, 1H), 3.32–3.18 (m, 1H), 2.75 (dd, J = 7.1, 16.4 Hz, 1H), 2.58 (ddd, J = 1.0, 11.8, 16.4 Hz, 1H), 0.81 (d, J = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.21 (C=O), 141.12, 138.27, 134.62, 132.94, 132.24, 131.53, 131.37, 129.24, 121.62, 118.27, 113.38 (C≡N), 73.40 (C–SO_2), 68.10 (C-bridge), 60.59 (N–C–Ar), 55.67 (CH_3–C–N), 44.42 (CH_2–CO), 18.07 (CH_3). HRMS (ESI) calcd for $C_{20}H_{18}N_3O_3S$: 380.1069 $(M + H)^+$, Found 380.1065.

4.3.9. (*1S,4aR,9bR,10S*)-10-(4-Fluorophenyl)-1-methyl-1,2,9b,10-tetrahydrobenzo[4,5]thieno[2,3-c]pyrazolo[1,2-a]pyrazol-3(4aH)-one 5,5-dioxide 5i

White solid, yield: 65 mg, 70%: mp 174–176 °C; R_f: 0.29 (EtOAc:*n*-hexane, 1:1) IR (KBr, cm^{-1}): 2982, 2935, 1685 (C=O), 1508, 1454, 1408, 1315 (SO_2 asym), 1226, 1122 (SO_2 sym), 844, 763. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 7.9 Hz, 1H), 7.75–7.71 (m, 1H), 7.69 (dd, J = 7.7, 1.4 Hz, 1H), 7.64–7.59 (m, 1H), 7.57–7.53 (m, 2H), 7.10 (t, J = 8.6 Hz, 2H), 5.65 (d, J = 8.4 Hz, 1H), 4.32 (t, J = 8.7 Hz, 1H), 4.11 (d, J = 8.9 Hz, 1H), 3.27–3.17 (m, 1H), 2.73 (dd, J = 7.2, 16.4 Hz, 1H), 2.56 (ddd, J = 1.1, 11.9, 16.4 Hz, 1H), 0.79 (d, J = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.17 (C=O), 138.51, 134.51, 132.56, 131.37, 131.19, 130.25, 130.17, 121.56, 116.30, 116.08, 73.29 (C–SO_2), 68.34 (C-bridge), 60.39 (N–C–Ar), 55.64 (CH_3–C–N), 44.61 (CH_2–CO), 17.98 (CH_3). HRMS (ESI) calcd for $C_{19}H_{18}FN_2O_3S$: 373.1023 $(M + H)^+$, Found 373.1022.

4.3.10. (*1S,4aR,9bR,10S*)-10-(4-Chlorophenyl)-1-methyl-1,2,9b,10-tetrahydrobenzo[4,5]thieno[2,3-c]pyrazolo[1,2-a]pyrazol-3(4aH)-one 5,5-dioxide 5j

White solid, yield: 67 mg, 69%: mp 180–182 °C; R_f: 0.29 (EtOAc:*n*-hexane, 1:1) IR (KBr, cm^{-1}): 2978, 2931, 1685 (C=O), 1492, 1408, 1315 (SO_2 asym), 1192, 1149 (SO_2 sym), 910, 732. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 7.9 Hz, 1H), 7.76–7.72 (m, 1H), 7.70 (dd, J = 7.7, 1.4 Hz, 1H), 7.65–7.59 (m, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.6 Hz, 2H), 5.65 (d, J = 8.4 Hz, 1H), 4.31 (t, J = 8.7 Hz, 1H), 4.11 (dd, J = 2.7, 8.0 Hz, 1H), 3.29–3.18 (m, 1H), 2.74 (dd, J = 7.2, 16.4 Hz, 1H), 2.57 (ddd, J = 16.4, 11.9, 1.1, Hz, 1H), 0.81 (d, J = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.19 (C=O), 138.44, 135.31, 134.52, 133.98, 132.48, 131.41, 131.35, 129.78, 129.42, 121.58, 73.29 (C–SO_2), 68.30 (C-bridge), 60.49 (N–C–Ar), 55.65 (CH_3–C–N), 44.57 (CH_2–CO), 18.03 (CH_3). HRMS (ESI) calcd for $C_{19}H_{18}ClN_2O_3S$: 389.0727 $(M + H)^+$, Found 389.0724.

4.3.11. (*1S,4aR,9bR,10S*)-1-Methyl-10-(4-nitrophenyl)-1,2,9b,10-tetrahydrobenzo[4,5]thieno[2,3-c] pyrazolo[1,2-a]pyrazol-3(4aH)-one 5,5-dioxide 5k

Orange oil, yield: 70 mg, 71%: R_f: 0.24 (EtOAc:*n*-hexane, 1:1). IR (KBr, cm^{-1}): 2978, 2928, 1697 (C=O), 1523, 1454, 1408, 1350, 1315 (SO_2 asym), 1192, 1153 (SO_2 sym), 860, 736. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 7.8 Hz, 1H), 8.27 (d, J = 8.8 Hz, 2H), 7.80 (d, J = 8.7 Hz, 2H), 7.77–7.69 (m, 2H), 7.64 (t, J = 7.5

Hz, 1H), 5.67 (d, J = 8.1 Hz, 1H), 4.32 (dd, J = 8.1, 8.6 Hz, 1H), 4.26 (d, J = 8.7 Hz, 1H), 3.34–3.20 (m, 1H), 2.76 (dd, J = 7.1, 16.4 Hz, 1H), 2.59 (dd, J = 11.8, 16.4 Hz, 1H), 0.82 (d, J = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.23 (C=O), 148.56, 143.06, 138.26, 134.64, 132.23, 131.55, 131.37, 129.45, 124.34, 121.63, 73.46 (C–SO_2), 67.91 (C-bridge), 60.64 (N–C–Ar), 55.69 (CH_3–C–N), 44.41 (CH_2–CO), 18.11 (CH_3). HRMS (ESI) calcd for $C_{19}H_{18}N_3O_5S$: 400.0967 $(M + H)^+$, Found 400.0949.

4.3.12. (*1S,4aR,9bR,10S*)-10-(4-(Dimethylamino)phenyl)-1-methyl-1,2,9b,10-tetrahydrobenzo [4,5]thieno[2,3-c]pyrazolo[1,2-a]pyrazol-3(4aH)-one 5,5-dioxide 5l

White solid, yield: 70 mg, 71%: mp 205–207 °C; R_f: 0.20 (EtOAc:n-hexane, 1:1). IR (KBr, cm^{-1}): 2978, 2928, 1685 (C=O), 1612, 1523, 1408, 1311 (SO_2 asym), 1192 (SO_2 sym), 910, 825, 732. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 7.9 Hz, 1H), 7.76–7.65 (m, 3H), 7.60 (t, J = 7.7 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 5.65 (d, J = 8.4 Hz, 1H), 4.35 (t, J = 8.6 Hz, 1H), 4.02 (d, J = 9.0 Hz, 1H), 3.24–3.16 (m, 1H), 2.98 (s, 6H), 2.71 (dd, J = 7.2, 16.3 Hz, 1H), 2.54 (dd, J = 12.0, 16.3 Hz, 1H), 0.80 (d, J = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.28 (C=O), 145.49, 138.66, 136.64, 136.26, 134.37, 132.93, 131.29, 131.21, 129.36, 121.52, 72.87 (C–SO_2), 68.97 (C-bridge), 60.17 (N–C–Ar), 55.64 (CH_3–C–N), 44.71 (CH_2–CO), 18.00 (CH_3). HRMS (ESI) calcd for $C_{21}H_{24}N_3O_3S$: 398.1538 $(M + H)^+$, Found 398.1537.

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Supporting information

Crystallographic data of **5i** have been deposited at the CCDC, with reference number 1024964, and can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif.

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