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A ring-closing metathesis approach to eight-membered benzannelated scaffolds and subsequent internal alkene isomerizations

Abu Taher [a], Blessing A. Aderibigbe [b], Garreth L. Morgans [b], Lee G. Madeley [b], Setshaba D. Khanye [b], Leandi van der Westhuizen [a], Manuel A. Fernandes [b,†], Vincent J. Smith [a,†], Joseph P. Michael [b], Ivan R. Green [a], Willem A.L. van Otterlo [a,b,*]

[a] Department of Chemistry and Polymer Science, Stellenbosch University, Stellenbosch, 7602 Western Cape, South Africa
[b] Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, PO Wits, 2050 Johannesburg, South Africa

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ABSTRACT

A set of eight-membered benzannelated heterocycles containing two heteroatoms (*O*,*O*, *NR*,*NR* and *O*,*NR* where R=protecting group) was synthesized by ring-closing metathesis from the corresponding *ortho*-bis-allyl precursors. In this manner, 7-methoxy-2,5-dihydro-1,6-benzodioxocine, 1,2,5,6-tetrahydro-1,6-benzodiazocines, 5,6-dihydro-2*H*-1,6-benzoxazocines and 5,6,9,10-tetrahydropyrido[2,3-*b*][1,4]diazocine were synthesized. A number of these compounds were then treated with the catalyst [RuClH(CO)(PPh_3)$_3$] to facilitate isomerization of the alkene into conjugation with the heteroatoms in the eight-membered ring. Quite surprisingly, an equal ratio of regioisomers was obtained, even if the heteroatoms were different.

1. Introduction

Ring-closing metathesis (RCM) has become an established method to synthesize medium sized ring systems including five-, six-, seven- and eight-membered hetero- and carbo-cycles.[1] Probably the most significant contributor to the surge in synthetic strategies delivering useful unsaturated heterocycles has been the availability and extensive use of the so-called 'Grubbs catalysts'.[2] The ready application of this robust group of catalysts has also led to the generation of benzo-fused compounds with varying rings sizes (see, for example, benzo-fused five-,[3] six-,[4] seven-[5] and eight-membered[6] systems) and the synthesis of this class of compounds using RCM has been a topic of interest in our group.[7]

The importance of eight-membered benzo-fused compounds, particularly those with one or more heteroatoms in the heterocyclic core, has also been increasing. Examples of compounds being investigated in the medicinal chemistry realm include compounds, such as **1** (NK1 antagonists)[8] and **2** (nefopam, a potent non-sedative analgesic)[9] (Fig. 1). Compounds from the natural product world also contain this motif. See, for example, the compound porritoxin **3**,[10] extracted from *Alternaria porri*, which inhibits the growth of

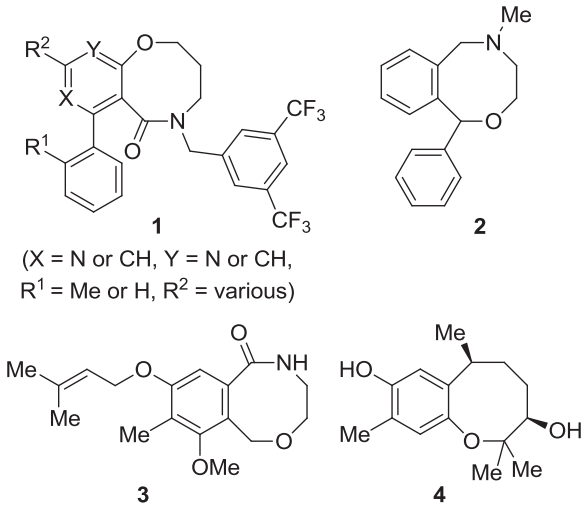

Fig. 1. Representative structures of natural and synthetic compounds containing a benzo-fused eight-membered ring system with one or more heteroatoms.

* Corresponding author. E-mail addresses: wvo@sun.ac.za, Willem.vanOtterlo@wits.ac.za (W.A.L. van Otterlo).
† For X-ray crystallography.

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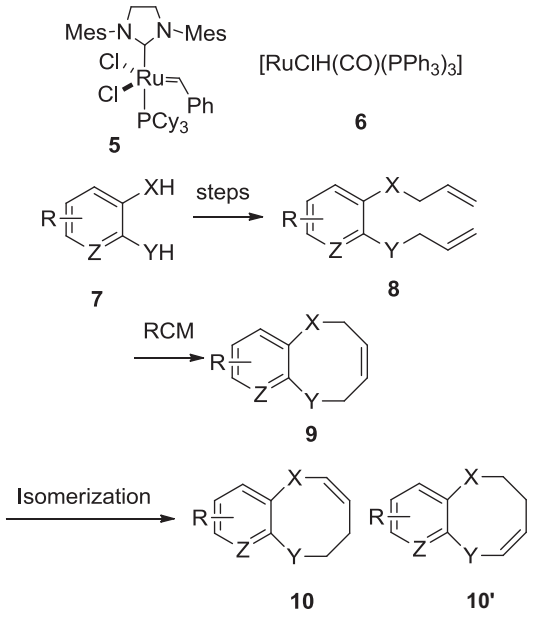
seedlings; and heliannuol A **4**,[11] a member of a well populated sesquiterpenoid family with well-documented allelochemical bioactivities.[12]

An additional point of interest, in terms of eight-membered benzo-fused rings, is that as the benzannelated ring system increases in size, so too does the conformational space that can be occupied increase, particularly when compared to that occupied by similar six- and seven-membered systems.[13] As medicinal chemists have increasingly started to appreciate that the flexibility of molecules is important in overcoming resistance from amino acid mutations in and near the active site, this could make the eight-membered benzo-fused heterocycles worthy of more investigation.[14] It can be argued that one of the reasons for the comparative rarity of medicinal investigations into eight-membered systems is due to the increased difficulty of their controlled synthesis. This paper aims to make a contribution in this regard. It should be noted that in recent years a number of papers describing the application of RCM to eight-membered ring systems have been published,[15] and we trust our work will add value to this area.

Along with the increase of synthetic applications of RCM have been the reports of isomerizations associated with the methodology. On the one hand, these reports could describe this problematic side-reaction leading to a decrease in yield of the desired compound, on the other as a useful strategy to move the resulting alkene from the RCM into a new targeted position. The identification of metathesis products resulting from 'pre-' or 'post-'metathetic isomerizations has thus seen much investigation and this work has been summarized in recent reviews.[16] Examples are known where isomerization prior to the RCM results in cycles containing one less carbon atom than expected, in most cases an undesired result. In fact, it has been shown that in slow metathetic transformations the presence of a ruthenium hydride, originating from the decomposition of the actual Grubbs catalyst, is responsible for the isomerization of the terminal alkenes to the more thermodynamically stable internal regioisomers.[17] Other work, focussing on the isomerization of the alkene functionality after the metathesis event, has also elicited interest.[18] For instance, seminal work by the research groups headed by Schmidt,[16c,19] Snapper[20] and other more recent work,[21] have demonstrated how useful the RCM-isomerization strategy can be.

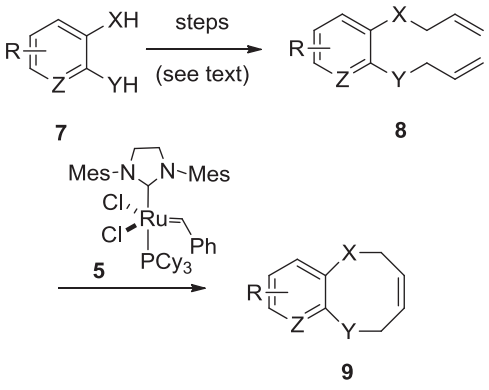
Of interest to note is that the intentional isomerization of cyclic alkenes after metathesis has mainly been applied to the smaller ring systems, with seven-membered rings often being the upper limit tested. With this particular background in mind we thus disclose our results concerning the generally facile metathetic construction of eight-membered benzo-fused heterocyclic systems containing two heteroatoms with the Grubbs second generation catalyst **5** (i.e., transformation **8** → **9** in Scheme 1), from *ortho*-bis-allyl substrates generated from the commercially available **7**. This would be followed by the intentional post-metathetic isomerization of the resultant eight-membered products to afford alkenes now in conjugation to a heteroatom (i.e., transformation **9** → **10** & **10′**, Scheme 1). The isomerizations were not performed by an in situ procedure, as has so successfully been utilized by Schmidt and co-workers,[19] but by a sequential isomerization performed with the ruthenium hydride **6**, previously utilized in our group. The compounds thus formed by this approach were studied by spectroscopic methods and in several cases their structures were confirmed by single crystal X-ray crystallographic studies.



Scheme 1. Proposed route for the synthesis of eight-membered pyrido- and benzo-fused compounds and the subsequent isomerization reactions (X, Y=*N*R and/or *O*, where R=Boc, Bz, Ac or Ts; Z=*N* or CH_2, R=H or OMe).

2. Results and discussion

To access the eight-membered benzannelated ring systems **9** it was initially necessary to synthesize a range of *ortho*-bis-allyl analogues **8**. Scheme 2 illustrates how the benzo- and pyrido-bisallyl systems **8** were synthesized in general, utilizing a variety of protection and allylation strategies from the diamino, dihydroxy or aminohydroxy compounds **7** (see Experimental section for specific details). To probe the scope of the reactions, 3-methoxycatechol (*O*,*O*-**7**) and 1,2-diaminobenzene (*N*,*N*-**7**) were initially utilized; the latter's amino groups protected as the *tert*-butyl carbamate **7b**, the phenyl benzamide **7c**, the tosyl sulfonamide **7d** and as the acetamide **7e**. The *ortho*-bis-allyl derivatives were then readily synthesized to afford compounds **8a**–**e** in acceptable yields. Next, the respective pyrido *ortho*-bis-allyl equivalents were generated from pyridine-2,3-diamine and 2-chloro-pyridin-3-ol[22] to give in hand compounds **8f**–**g**. Finally, 2-aminophenol (*N*,*O*-**7**) was *N*-protected with the Boc, benzoyl and tosyl groups and converted into the *ortho*-bis-allyl equivalents **8h**, **8i** and **8j**, respectively.



Scheme 2. For information concerning structure (i.e., X, Y and Z) and results of the RCM reactions (**8** → **9**), see Table 1. For other conditions see Experimental section.

The first key-step involved exposure of these *ortho*-bis-allyl precursors to the Grubbs second generation catalyst **5**, surprisingly with mixed results. In general, the benzene derivatives readily afforded their respective eight-membered systems **9** as expected and Table 1 (Scheme 2) summarizes these synthetic results. The yields for ring systems **9a**–**e** ranged from moderate (49% for **9b**) to excellent (97% for **9c**). It should be noted that for **9c** the best results were obtained when a catalytic amount of *p*-toluenesulfonic acid was added to the reaction mixture. In contrast, the pyrido *ortho*-bis-allyl derivatives **8f** and **8g** gave mixed results when subjected to the ring-closing conditions. In our hands, we were unable to cyclize 2,3-bis(allyloxy)pyridine **8f**[22] using standard metathesis conditions. Believing that perhaps coordination with the pyrido nitrogen was effectively interrupting the

Table 1
Results for RCM reactions

Entry	X	Y	Z	Yield of ring-closed products **9** (%)
a[a]	O	O	CH	60
b	NBoc	NBoc	CH	49
c	NBz	NBz	CH	97
d	NTs	NTs	CH	92
e	NAc	NAc	CH	80
f	O	O	N	—
g	NTs	NTs	N	94
h	O	NBoc	CH	58
i	O	NBz	CH	78
j	O	NTs	CH	70

[a] Compounds **8**/**9a** also contained an OMe group in position.

metathetic catalytic cycle, it was decided to complex the basic nitrogen as done by other researchers; however, additives, such as titanium isopropoxide,[23] *p*-toluenesulfonic acid[24] and hydrochloric acid[25] were unfortunately ineffective in facilitating ring-closure. Of interest was that the bis-tosyl derivative **8g** did however facilely ring close in excellent yield of 94%. This could mean that the additional steric hindrance of the two bulky sulfonamide groups pre-organizes the allyl groups in such a way as to discourage chelation with the basic nitrogen atom of the pyridine ring, thus allowing for RCM to occur. The exact reason why chelation of this group did not result in the cyclization of substrate **8f** is still a puzzle. Finally, the benzazocine compounds with the nitrogen atom protected as the Boc **9h**, benzoyl **9i** or tosyl derivative **9j** were all readily prepared in acceptable to good yields.

In addition, as part of our studies into the solid-state structures of the eight-membered ring systems, crystal structures of compounds **9b** and **9c** were successfully determined—see the ORTEP structures in Fig. 2. It was further decided to reduce the alkene functionality found in diazocine **9b**, to afford the saturated analogue **11**, which was also studied by single crystal X-ray diffraction (Scheme 3 and Fig. 2). The effective reduction of the alkene was evident in the new saturated four-carbon bridge in the structure of **11**.

With a number of the eight-membered ring-closed products **9** in hand, it was decided to investigate the possibility of controlled isomerization of the alkene functionality within the heterocyclic ring (Scheme 4). To the best of our knowledge the isomerization of alkenes in eight-membered ring systems has seen very little investigation; Schmidt and co-workers have performed a post-metathetic isomerization on an eight-membered glycoside derivative after converting the Grubbs second generation catalyst into a ruthenium hydride with sodium borohydride,[19b] while Stevens and co-workers successfully utilized [RuClH(CO)(PPh_3)$_3$] **6** on a number of 1-phosphonylated 2-benzazocine systems.[6a]

A number of the eight-membered benzannelated ring-systems were thus subjected to an induced isomerization process by application of the ruthenium hydride [RuClH(CO)(PPh_3)$_3$] **6**, a catalyst reliably used in our previous research.[26] The first system to be investigated was the substrate, 7-methoxy-2,5-dihydro-1,6-benzodioxocine **9a**. Application of the isomerization catalyst **6** to this compound afforded, after chromatography, a 1:1 mixture of the regioisomers **10a** and **10′a**, which we were unable to separate from each other. Of interest here is that it appears that the methoxy group did not in any way seem to bias the regiochemical outcome of the isomerization.

Secondly, application of the hydride catalyst **6** to the protected benzo[*b*][1,4]diazocine skeletons gave good results. Use of [RuClH(CO)(PPh_3)$_3$] **6** on the Boc-protected diazocine derivative **9b** afforded the isomerized product **10b** after 2 h in a good yield of 81%, the structure of which was confirmed by NMR spectroscopy. In addition, under similar conditions, 1,6-bis(toluene-4-sulfonyl)-1,2,5,6-tetrahydro-benzo[*b*][1,4]diazocine **9d** gratifyingly afforded the isomerized **10d** in a reasonable yield of 61% (for an alternative synthesis of this compound see reference 14c). For this compound,

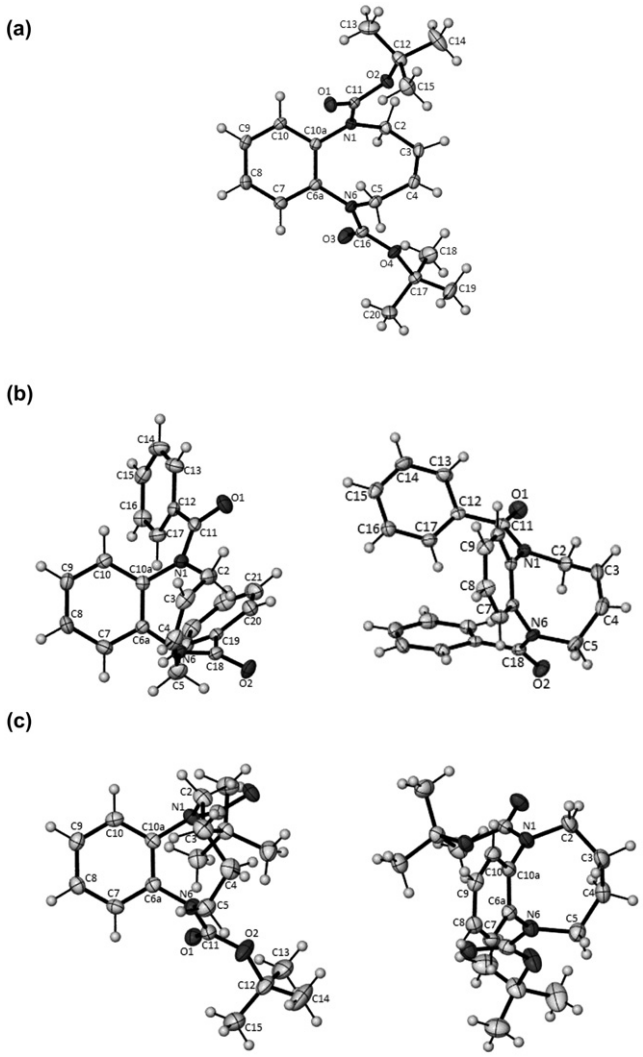
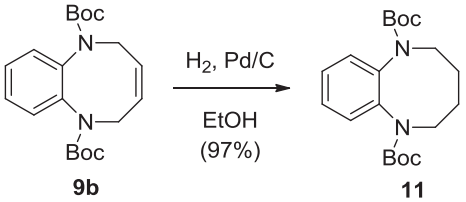


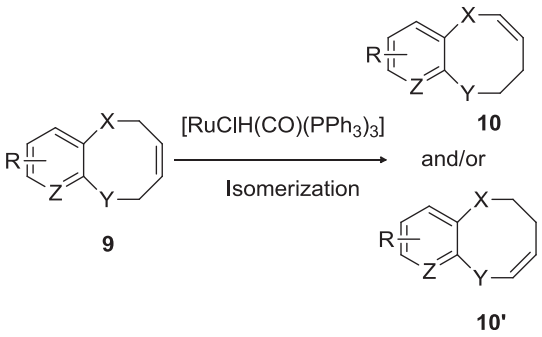
Fig. 2. ORTEP diagrams of the X-ray crystal structures of compounds a) **9b**, b) **9c** (two orientations) and c) **11** (two orientations), with all thermal ellipsoids at 50% probability.

the isomerization process was confirmed by the fact that the two simple signals due to the symmetrical $-TsNCH_2CH{=}CHCH_2NTs-$ system now appeared as four separate peaks representing two different sets of CH_2 and CH= groups, respectively. The loss of symmetry was also reflected in a more complicated carbon NMR spectrum. The isomerization of the double bond was finally confirmed by the crystal structure in which the alkene was now clearly in conjugation with the nitrogen atom (Fig. 3a).

Next, the only pyrido-derivative in hand, namely 5,10-bis-tosyl-5,6,9,10-tetrahydro-pyrido[2,3-*b*][1,4]diazocine **9g**, was investigated with regard to catalyst **6**. The isomerization reaction was complete after 18 h (TLC) giving two regioisomeric products in a ratio of 45:55 (from ^{1}H NMR spectroscopy), and with an overall yield of 89%. Careful flash silica gel column chromatography then afforded a clean sample of the isomerized product with the higher R_f value, on which



Scheme 3. Reduction of alkene **9b** to afford **11**.



Scheme 4. For information concerning structure (i.e., X, Y and Z) and results of the isomerization reactions, see Table 2. For other conditions see Experimental section.

a single crystal X-ray analysis was successfully performed (Fig. 3b), allowing for the rigorous identification of the regioisomer **10g**.

When the isomerization conditions were applied to the *O*,*N*Ts-system **9j**, once again NMR spectroscopic analysis of the product indicated a mixture of regioisomers, which were assigned as **10j** and **10′j**, respectively. Unexpectedly, the ratio of these compounds was again 1:1, in effect indicating that the catalyst was not differentiating between the oxygen atom and the much bulkier *N*-tosyl environment. Careful selection of the crystals afforded from a slow recrystallization, allowed for the single crystal X-ray structural determination of both regioisomers **10j** and **10′j** (Fig. 3c and d), and facilitated a comparison of their solid state conformations.

3. Conclusion

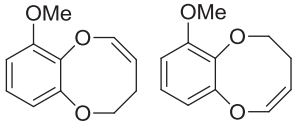
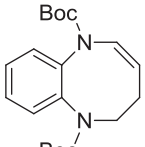
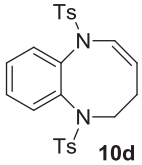
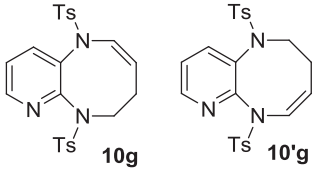
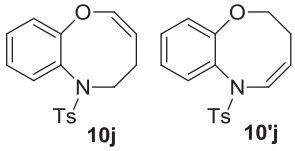
In this paper it has been demonstrated that i) the RCM methodology is readily applicable for the synthesis of a number of eight-membered benzannelated bis-heteroatom-containing heterocycles, although a pyridine nitrogen *ortho* to an *O*-allyl groups appears to hinder the ring closure, and that ii) the alkene group in a number of the compounds synthesized could be isomerized into conjugation with the heteroatoms by the application of the isomerization catalyst [RuClH(CO)(PPh_3)$_3$] **6**. Of interest, was that the ruthenium hydride did not appear to discriminate in terms of regioselectivity, as neither bulk of protecting groups nor a difference in heteroatoms seemed to affect the 1:1 mixture of regioisomers obtained.

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 300, Bruker DRX 400, Varian Inova 400 or Varian Inova 300 spectrometers at the frequency indicated. Infra-red spectra were recorded on Bruker IFS 25, Bruker Vector 22 or Thermo Nicolet Nexus 470 Fourier transform spectrometers. Mass spectra were recorded on a Kratos MS 9/50, VG 70E MS or VG 70 SEQ mass spectrometer or alternatively a Waters API Q-TOF Ultima, GCT Premier or SYNAPT G2 mass spectrometer. Macherey-Nagel Kieselgel 60 (particle size 0.063–0.200 mm) was used for conventional silica gel

Table 2
Results regarding isomerization reactions performed

Entry[a]	Substrate	X	Y	Z	Yield (ratio)	Structure of product(s)
a[b]	**9a**	O	O	CH	63 (1:1)	 **10a** **10'a**
b	**9b**	NBoc	NBoc	CH	81	 **10b**
c	**9d**	NTs	NTs	CH	61	 **10d**
d	**9g**	NTs	NTs	N	89 (45:55)	 **10g** **10'g**
e	**9j**	O	NTs	CH	78 (1:1)	 **10j** **10'j**

[a] Numbering according to Table 1.
[b] Compounds **9a** contained an OMe group in position.

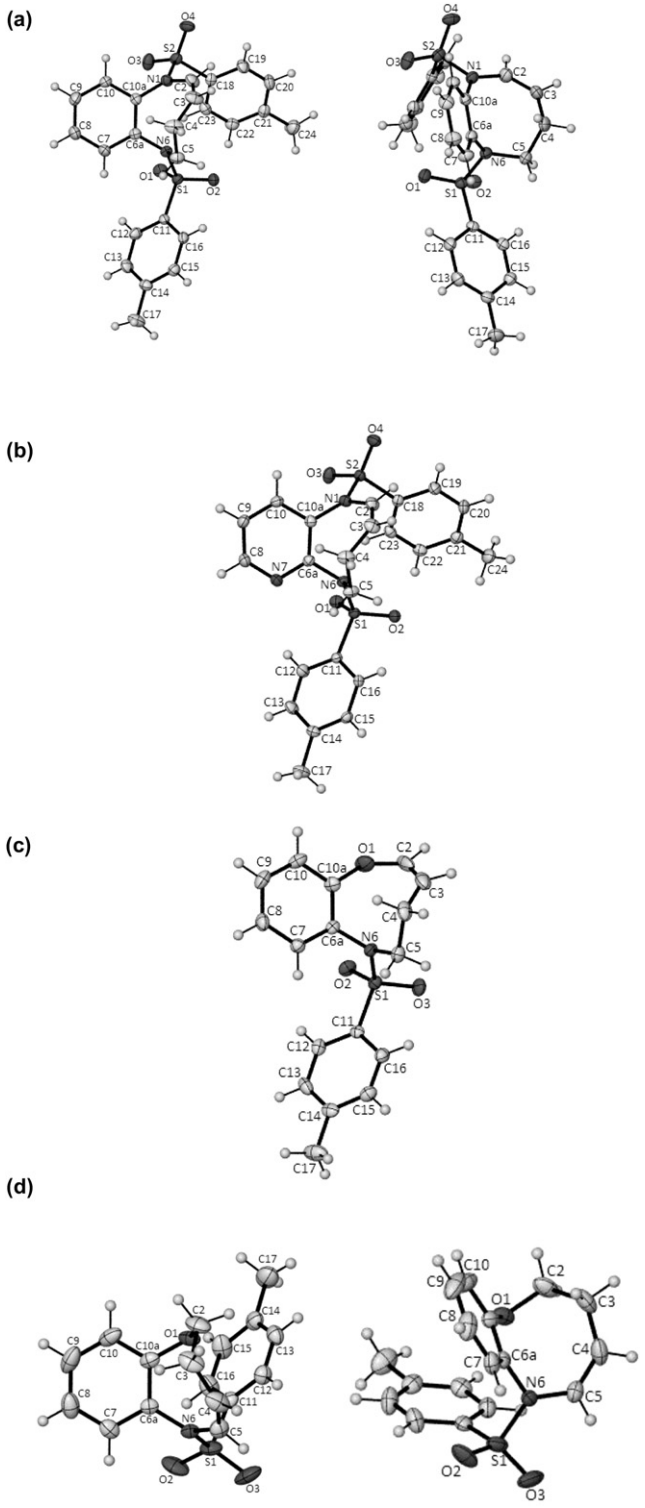


Fig. 3. ORTEP diagrams of the X-ray crystal structures of compounds a) **10d** (two orientations, note methyl carbon 24 is disordered over two positions at 50:50), b) **10g**, c) **10j** and d) **10′j** (two orientations), with thermal ellipsoids at 50% probability.

chromatography. All solvents used for reactions and chromatography were distilled prior to use. Reactions were performed under a blanket of inert gas (Ar or N_2) unless specified. Melting points are uncorrected.

2,3-Bis(allyloxy)pyridine **8f** was synthesized according to the procedures described by Jarvis and Anderson.[22]

*4.1.1. 1,2-Bis(allyloxy)-3-methoxybenzene (**8a**).* 3-Methoxy-1,2-benzenediol (0.498 g, 3.56 mmol) was dissolved in acetone (20 mL) and K_2CO_3 (1.97 g, 14.3 mmol) and allyl bromide (1.72 g, 14.2 mmol) were added. The reaction mixture was then heated at reflux for 18 h. After cooling, H_2O (30 mL) was added and the crude product was then extracted with EtOAc (3×100 mL). The combined filtrate was then dried with $MgSO_4$ to afford the product as an yellow oil, which was purified by column chromatography (20% EtOAc/hexane) to afford the desired compound **8a** as a light yellow oil (0.60 g, 76%). R_f (30% EtOAc/hexane) 0.72; IR ν_{max} (film)/cm^{-1} 1647, 1475, 1104; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=3.83 (s, 3H, OCH_3), 4.53 (d, 2H, *J* 6.0 Hz, OCH_2), 4.57 (d, 2H, *J* 5.2 Hz, OCH_2), 5.16–5.44 (m, 4H, 2× CH=CH_2), 5.99–6.18 (m, 2H, 2× CH_2C*H*=), 6.67 (d, 2H, *J* 8.6 Hz, 2× ArH), 6.92–6.98 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=55.9 (OCH_3), 69.8 (OCH_2), 74.0 (OCH_2), 105.4 (CH_2), 107.1 (CH_2), 117.1 (CH), 117.4 (CH), 123.4 (CH), 133.4 (CH), 134.5 (CH), 137.7 (C), 152.6 (C), 153.8 (C); *m*/*z* (EI): 220 (M^+, 65%), 205 (27), 179 (96), 41 (100); HRMS: M^+, calcd for $C_{13}H_{16}O_3$ 220.1099, found 220.1098.

*4.1.2. 7-Methoxy-2,5-dihydro-1,6-benzodioxocine (**9a**).*[5b] Bis(allyloxy) benzene **8a** (0.140 g, 0.635 mmol) was dissolved in toluene (10 mL), after which Grubbs second generation catalyst **5** (10 mol %, 0.054 g, 0.063 mmol) was added and the reaction mixture stirred at 60 °C for a further 18 h. The solvent was removed under a high vacuum and silica gel column chromatography (10% EtOAc/hexane) was performed on the crude product to afford the desired cyclized compound **9a** as an yellow oil (0.072 g, 60%). R_f (20% EtOAc/hexane) 0.46; IR: ν_{max} (film)/cm^{-1} 1585, 1474, 1314, 1270, 1245, 1099; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=3.82–3.85 (br m, 3H, OCH_3), 4.87–5.00 (m, 2H, OCH_2), 4.96–4.99 (m, 2H, OCH_2), 5.88–5.91 (m, 2H, CH=CH), 6.54–6.57 (m, 2H, 2× ArH), 6.86–6.92 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=55.9 (OCH_3), 67.9 (OCH_2), 70.8 (OCH_2), 105.1 (CH), 113.6 (CH), 123.6 (CH), 126.9 (CH), 132.1 (CH), 136.6 (C), 149.2 (C), 153.5 (C); *m*/*z* (EI): 192 (M^+, 87%), 151 (47), 110 (90), 94 (100); HRMS: M^+, calcd for $C_{11}H_{12}O_3$ 192.0786, found 192.0785.

*4.1.3. 10-Methoxy-2,3-dihydro-1,6-benzodioxocine and 7-methoxy-2,3-dihydro-1,6-benzodioxocine (**10a** & **10′a**).* Benzodioxocine **9a** (0.0590 g, 0.307 mmol) was dissolved in toluene (4 mL) and [RuClH(CO)(PPh_3)$_3$] **6** (6 mol %, 0.016 g, 0.020 mmol) was added. The reaction mixture was then heated at reflux for 48 h. The solvent was removed under high vacuum and silica gel column chromatography (20% EtOAc/hexane) was performed to afford an inseparable mixture of regioisomers **10a** and **10′a** as an yellow oil (0.037 g, 63%). R_f (20% EtOAc/hexane) 0.23; IR: ν_{max} (film)/cm^{-1} 1651, 1591, 1472, 1315, 1270, 1247, 1116, 1090; ^{1}H NMR (300 MHz, $CDCl_3$, combined): δ (ppm)=2.18–2.29 (m, 4H, 2× OCH_2CH_2), 3.77 and 3.78 (s, 6H, 2× OCH_3), 4.04 and 4.18 (t, 4H, *J* 5.6 Hz, 2× OCH_2), 4.57–4.64 and 4.75–4.81 (m, 2H, 2× OCH=C*H*), 6.36 and 6.47 (d, 2H, *J* 7.1 Hz, 2× O*CH*=CH), 6.55–6.61 (m, 4H, 4× ArH), 6.84–6.93 (m, 2H, 2× ArH); ^{13}C NMR (75 MHz, $CDCl_3$, combined): δ (ppm)=23.9 (CH_2), 25.3 (CH_2), 56.1 (OCH_3), 56.2 (OCH_2), 66.0 (CH_2), 68.6 (CH_2), 103.7 (CH), 106.7 (CH), 107.3 (CH), 107.8 (CH), 113.5 (CH), 114.6 (CH), 123.6 (CH), 124.2 (CH), 126.8 (C), 132.1 (C), 136.7 (C), 145.2 (2× CH), 149.5 (C), 152.4 (C), 153.8 (C); *m*/*z* (EI): 192 (M^+, 29%), 153 (39), 136 (30), 107 (42), 89 (49), 77 (100), 51 (38); HRMS: M^+, calcd for $C_{11}H_{12}O_3$ 192.0786, found 192.0781.

*4.1.4. Di-tert-butyl 1,2-phenylenebis(allylcarbamate) (**8b**).* Di-*tert*-butyl 1,2-phenylenedicarbamate[27] (0.930 g, 3.01 mmol) was dissolved in DMF (20 mL), to which NaH (60% in oil, 0.389 g, 9.73 mmol) and allyl bromide (0.84 mL, 9.7 mmol) were added. The reaction mixture was then stirred at rt for 18 h. H_2O (50 mL) was then added and the reaction mixture was extracted with EtOAc

(4×50 mL). The organic fractions were combined, dried ($MgSO_4$) and reduced in vacuo, after which column chromatography was performed (20% EtOAc/hexane) to afford the product **8b** as an yellow oil (0.770 g, 66%). The NMR spectra showed evidence for the existence of rotamers in solution, by way of peak broadening. R_f (20% EtOAc/hexane) 0.53; IR: ν_{max} (film)/cm^{-1} 1701, 1599, 1500, 1454, 1388, 1307, 1251, 1149; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)= 1.25 and 1.36 (2× br s, 18H, 6× CH_3), 3.63 (br s, 2H, NCH_2), 4.47 (br s, 2H, NCH_2), 5.08–5.11 (br m, 4H, 2× CH=CH_2), 5.89–5.91 (br m, 2H, 2× CH_2CH=), 7.06–7.09 (m, 2H, 2× ArH), 7.22 (br s, 2H, 2× ArH); ^{13}C NMR (75 MHz, $CDCl_3$, quaternary C not observed in spectrum): δ (ppm)=28.2 (6× CH_3), 51.3 and 52.8 (br, 2× CH_2), 80.2 (br, 2× C–O), 117.4 (br, 2× CH_2), 127.7 (br, 2× CH), 131.0 (br, 2× CH), 133.5 (br, 2× CH), 154.3 (br, 2× C=O); *m*/*z* (EI): 388 (M^+, 5%), 276 (21), 187 (30), 159 (33), 57 (100); HRMS: M^+, calcd for $C_{22}H_{32}N_2O_4$ 388.2362, found 388.2371.

*4.1.5. Di(tert-butyl)-2,5-dihydro-1,6-benzodiazocine-1,6-dicarboxylate (**9b**).* Bis(allylcarbamate) **8b** (0.120 g, 0.309 mmol) was dissolved in toluene (5 mL) and Grubbs second generation catalyst **5** (10 mol %, 0.026 g, 0.031 mmol) was added, after which the reaction mixture was stirred for 18 h at 60 °C. The solvent was removed on the high vacuum and silica gel column chromatography was then performed (20% EtOAc/hexane) to afford the cyclized compound **9b** as a white solid (0.055 g, 49%). The NMR spectra showed evidence for the existence of rotamers in solution, by way of peak broadening. Mp: 113–116 °C; R_f (20% EtOAc/hexane) 0.47; IR: ν_{max} (film)/cm^{-1} 1701, 1499, 1454, 1368, 1246, 1165; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)= 1.43 (br s, 18H, 6× CH_3), 4.08 (br s, 4H, 2× NCH_2), 5.86 (br s, 2H, CH=CH), 7.12–7.14 (br m, 2H, 2× ArH), 7.15–7.30 (br m, 2H, 2× ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=28.2 (6× CH_3), 45.7 (2× CH_2), 80.6 (2× C–O), 125.3 (2× C), 128.5 (2× CH), 129.2 (2× CH), 136.5 (2× CH), 154.6 (br, 2× C=O); *m*/*z* (EI): 360 (M^+, 6%), 248 (29), 204 (48), 159 (33), 57 (100); HRMS: M^+, calcd for $C_{20}H_{28}N_2O_4$ 360.2049, found 360.2069.

X-ray crystal structure details of compound **9b**: crystallized from 20% EtOAc/hexane, formula: $C_{20}H_{28}N_2O_4$, M=360.44, colour of crystal: colourless, needle, crystal size 0.22×0.15×0.07 mm, a=5.966(5) Å, b=11.293(5) Å, c=14.888(5) Å, α=86.038(5)°, β=88.040(5)°, γ=88.792(5)°, V=999.9(10) Å^3, ρ_{calcd}=1.197 Mg/m^3, μ=0.083 mm^{-1}, F(000)=388, Z=2, triclinic, space group P–1, T=173(2) K, 12,980 reflections collected, 4908 independent reflections, θ_{max} 28.28°, 235 refined parameters, maximum residual electron density 0.259 and −0.279 e Å^{-3}. R_1=0.0492, wR_2=0.1146. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC-901912.

*4.1.6. Di(tert-butyl) 2,3-dihydro-1,6-benzodiazocine-1,6-dicarboxylate (**10b**).* 1,6-Benzodiazocine **9b** (0.080 g, 0.222 mmol) was dissolved in d_8-toluene and ruthenium isomerization catalyst **6** (0.011 g, 5 mol %, 0.011 mmol) was added. The reaction mixture was then heated at 95 °C for 2 h at which point ^1H NMR spectroscopy confirmed that the reaction was complete. The solvent was subsequently removed under high vacuum and silica gel column chromatography was performed (30% EtOAc/hexane) to afford the desired compound **10b** as a white crystalline solid (0.065 g, 81%). Mp: 78–80 °C; R_f (20% EtOAc/hexane) 0.50; IR: ν_{max} (film)/cm^{-1} 2973, 1700, 1390, 1297, 1155, 1069; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=1.47 (br s, 18H, 6× CH_3), 1.74–1.83 (m, 2H, CH_2), 3.53 (br s, 2H, NCH_2), 4.66–4.63 (m, 1H, CH=C$H$$CH_2$), 6.93 (d, 1H, J 12.0 Hz, NCH=CH), 7.08–7.11 (br m, 1H, ArH), 7.24–7.35 (m, 3H, 3× ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=22.0 (CH_2), 27.9 (3× CH_3), 28.2 (3× CH_3), 45.9 (CH_2), 79.8 (C–O), 81.8 (C–O), 104.1 (CH), 127.3 (CH), 128.4 (CH), 128.5 (CH), 128.9 (CH), 130.0 (CH), 136.1 (C), 137.4 (C), 152.7 (C=O), 154.6 (C=O); *m*/*z* (EI): 383 (M^++Na, 100%), 360 (M^+, 9), 327 (6), 305 (48), 249 (16); HRMS $(M+H)^+$: calcd for $C_{20}H_{29}N_2O_4$ 361.2127, found 361.2117.

*4.1.7. Di(tert-butyl) 2,3,4,5-tetrahydro-1,6-benzodiazocine-1,6-dicarboxylate (**11**).* Hydrogenation was performed by stirring 10% Pd/C (0.070 g, 0.05 mol) in EtOH (20 mL), followed by the addition of compound **9b** (0.0480 g, 0.133 mmol) under H_2 pressure (5 atm) for 20 h. The crude product was then filtered under vacuum through a Celite plug using EtOH (50 mL), after which the solvent was removed under a vacuum. Silica gel column chromatography was then performed (30% EtOAc/hexane) to afford the product **11** as a white solid (0.047 g, 97%). The NMR spectra showed evidence for the existence of rotamers in solution, by way of peak broadening. Mp: 100–103 °C; R_f (30% EtOAc/hexane) 0.42; IR: ν_{max} (film)/cm^{-1} 1699, 1598, 1502, 1454, 1385, 1280, 1252; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=1.44 (br s, 18H, 6× CH_3), 1.67 (br s, 4H, 2× CH_2CH_2), 3.65 (br s, 4H, 2× NCH_2), 7.23 (br s, 2H, 2× ArH), 7.33–7.39 (m, 2H, 2× ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=26.5 (2× CH_2), 28.2 (6× CH_3), 50.9 (br s, 2× NCH_2), 79.7 (2× C–O), 128.0 (2× CH), 129.3 (2× CH), 140.4 (2× C), 154.8 (2× C=O); *m*/*z* (EI): 362 (M^+, 27%), 206 (71), 162 (26), 57 (100); HRMS: M^+, calcd for $C_{20}H_{30}N_2O_4$ 362.2206, found 362.2203.

X-ray crystal structure details of compound **11**: crystallized from 30% EtOAc/hexane, formula: $C_{20}H_{30}N_2O_4$, M=362.46, colour of crystal: colourless, needle, crystal size 0.34×0.25×0.24 mm, a=9.1809(14) Å, b=23.088(4) Å, c=9.9199(16) Å, β=91.996(10)°, V=2101.5(6) Å^3, ρ_{calcd}=1.146 Mg/m^3, μ=0.080 mm^{-1}, F(000)=784, Z=4, monoclinic, space group P2(1)/n, T=173(2) K, 21,655 reflections collected, 5072 independent reflections, θ_{max} 28.00°, 236 refined parameters, maximum residual electron density 0.209 and −0.210 e Å^{-3}. R_1=0.0456, wR_2=0.1005. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC-901916.

*4.1.8. N-Allyl-N-{2-[allyl(benzoyl)amino]phenyl}benzamide (**8c**).* To a solution of *N*-[2-(benzoylamino)phenyl]benzamide[28] (1.00 g, 3.16 mmol) in DMSO (20 mL) was added NaH (60% in oil, 0.520 g, 13.0 mmol), followed by allyl bromide (1.09 mL, 12.4 mmol) 5 min later. The reaction mixture was then stirred at rt for 20 h under N_2, after which H_2O (10 mL) was added. The mixture was then extracted using EtOAc (3×100 mL) and the combined fractions were dried ($MgSO_4$). Silica gel column chromatography was next performed (20% EtOAc/hexane) to afford the product **8c** as a white solid (1.01 g, 81%). The NMR spectra showed evidence for the existence of rotamers in solution, by way of significant peak broadening. Mp: 132–135 °C; R_f (20% EtOAc/hexane) 0.33; IR: ν_{max} (film)/cm^{-1} 1651, 1596, 1577, 1494, 1448, 1426, 1373, 1308, 1217; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=3.90–4.20 [br m, 2H, 2× NC(H)H], 4.37 [br s, 2H, 2× NC(H)H], 5.11 (br s, 4H, 2× CH=CH_2), 5.86 (br s, 2H, 2× CH_2CH=), 7.26–7.40 (m, 14H, 14× ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=52.1 (br, 2× CH_2), 116.3 (br, 2× CH_2), 126.8 (CH), 126.9 (CH), 127.8 (br, 2× CH), 129.4 (br, 2× CH), 130.6 (CH) 134.2 (2× CH), 136.0 (br, 2× C), 140.2 (2× C), 168.3 (br, 2× C=O); *m*/*z* (EI): 396 (M^+, 7%), 291 (45), 275 (98), 105 (100), 77 (57); HRMS: M^+, calcd for $C_{26}H_{24}N_2O_2$ 396.1837, found 396.1842.

*4.1.9. 1,6-Dibenzoyl-1,2,5,6-tetrahydro-1,6-benzodiazocine (**9c**).* Dibenzamide **8c** (0.190 g, 0.479 mmol) was dissolved in toluene (20 mL) and *p*-toluenesulfonic acid (0.009 g, 0.052 mmol) was added, followed by Grubbs second generation catalyst **5** (10 mol %, 0.017 g, 0.020 mmol). The reaction mixture was then stirred for 23 h at rt, after which the solvent was removed under vacuum. Silica gel column chromatography was performed on the crude material (30% EtOAc/hexane) to give the cyclized product **9c** as a white solid (0.170 g, 97%). Mp: 195–198 °C; R_f (30% EtOAc/hexane) 0.12; IR: ν_{max} (film)/cm^{-1} 1731, 1642, 1575, 1493, 1474, 1363, 1294, 1261, 1096;

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=4.74 (br s, 4H, 2× NCH_2), 5.79 (br s, 2H, CH=CH), 6.89–7.00 (m, 6H, 6× ArH), 7.08–7.13 (m, 4H, 4× ArH), 7.22–7.27 (m, 4H, 4× ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=45.4 (2× CH_2), 126.9 (2× CH), 127.9 (4× CH), 128.7 (4× CH), 129.0 (2× CH), 129.8 (2× CH), 130.0 (2× CH), 135.5 (2× C), 137.4 (2× C), 169.6 (2× C=O); *m*/*z* (EI): 368 (M^+, 10%), 247 (45), 105 (100), 77 (49); HRMS: M^+, calcd for $C_{24}H_{20}N_2O_2$ 368.1524, found 368.1539.

X-ray crystal structure details of compound **9c**: crystallized from 30% EtOAc/hexane, formula: $C_{24}H_{20}N_2O_2$, M=368.42, colour of crystal: colourless, needle, crystal size 0.36×0.18×0.15 mm, a=15.201(5) Å, b=8.703(5) Å, c=15.347(5) Å, β=112.263(5)°, V=1879.0(14) Å^3, ρ_{calcd}=1.302 Mg/m^3, μ=0.08 mm^{-1}, F(000)=776, Z=4, monoclinic, space group P2(1)/c, T=173(2) K, 11,690 reflections collected, 4662 independent reflections, θ_{max} 28.30°, 253 refined parameters, maximum residual electron density 0.22 and −0.27 e Å^{-3}. R_1=0.0487, wR_2=0.1049. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC-901913.

*4.1.10. N-Allyl-N-(2-{allyl[(4-methylphenyl)sulfonyl]amino}phenyl)-4-methylbenzenesulfonamide (**8d**).* 4-Methyl-*N*-(2-{[(4-methylphenyl) sulfonyl]amino}phenyl)benzenesulfonamide[29] (1.00 g, 2.40 mmol) was dissolved in acetone (20 mL) and treated with allyl bromide (1.00 mL, 9.60 mmol) and K_2CO_3 (1.33 g, 9.60 mmol). The reaction mixture was stirred at reflux for 18 h, after which the reaction was filtered (cotton wool plug) and the filtrate concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (10–30% EtOAc/hexane) to afford diallyl **8d** (1.10 g, 92%) as light brown crystals. Mp: 141–143 °C; R_f (30% EtOAc/hexane) 0.50; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=2.47 (s, 6H, $ArCH_3$), 4.40 (br d, 4H, *J* 5.5 Hz, 2× CH_2CH=), 4.99–5.09 (m, 4H, 2× CH=CH_2), 5.71–5.84 (m, 2H, 2× CH=CH), 6.97–7.00 (m, 2H, 2× ArH), 7.23–7.26 (m, 2H, 2× ArH), 7.35 (d, 4H, *J* 8.1 Hz, 2× ArH), 7.81 (d, 4H, *J* 8.1 Hz, 2× ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 21.6 (2× CH_3), 54.6 (2× CH_2), 119.5 (2× CH), 128.3 (2× CH), 128.6 (2× CH), 129.6 (2× CH), 131.3 (2× CH), 132.7 (2× C), 137.4 (2× C), 139.3 (2× CH), 143.7 (2× C); *m*/*z* (EI): 496 (M^+, 1%), 285 (46), 264 (23), 219 (81), 185 (27), 171 (51), 155 (32), 131 (51), 91 (35), 69 (100).

*4.1.11. 1,6-Bis[(4-methylphenyl)sulfonyl]-1,2,5,6-tetrahydro-1,6-benzodiazocine (**9d**).* The benzenesulfonamide **8d** (0.104 g, 0.202 mmol) was reacted with Grubbs second generation catalyst **5** (0.0086 g, 0.010 mmol, 5 mol %) in toluene (10 mL). The reaction mixture was then carried out at rt for 5 h under N_2. The solvent was removed to give **9d** (0.090 g, 92%) as white-coloured crystals after column chromatography (10–30% EtOAc/hexane). Mp: 203–205 °C. See reference 31 for a reported crystal structure. The reaction was also performed on a bigger scale (0.80 mmol) to afford the cyclized product in a yield of 96%. ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=21.6 (CH_3), 47.7 (CH_2), 127.8 (CH), 128.2 (CH), 128.7 (CH), 128.9 (CH), 129.2 (CH), 136.2 (C), 136.5 (C), 144.9 (C). The rest of the spectra compared well with that available in the literature.[14a,30]

*4.1.12. 1,6-Bis[(4-methylphenyl)sulfonyl]-1,2,3,6-tetrahydro-1,6-benzodiazocine (**10d**).* Benzodiazocine **9d** (0.280 g, 0.597 mmol) was dissolved in toluene (5 mL) at rt and [RuClH(CO)(PPh_3)$_3$] **6** (0.022 g, 0.024 mmol, 4 mol %) was added. The reaction mixture was then stirred for a further 20 h at 100 °C. The solvent was removed under vacuum and silica gel column chromatography was performed (30% EtOAc/hexane) to afford the desired compound **10d** as a light brown-coloured solid (0.170 g, 61%). Mp: 134–138 °C; R_f (40% EtOAc/hexane) 0.42; IR: ν_{max} (film)/cm^{-1} 1654, 1493, 1449, 1351, 1163, 1084; The rest of the spectra compared well with that available in the literature.[14c]; *m*/*z* (EI): 468 (M^+, 12%), 313 (38), 159 (100), 131 (21), 91 (41); HRMS: M^+, calcd for $C_{24}H_{24}N_2O_4S_2$ 468.1178, found 468.1172.

X-ray crystal structure details of compound **10d**: crystallized from EtOAc/hexane, formula: $C_{24}H_{24}N_2O_4S_2$, M=468.57, colour of crystal: colourless, needle, crystal size 0.18×0.08×0.08 mm, a=16.2510(15) Å, b=8.8288(8) Å, c=17.4649(17) Å, β=115.060(6)°, V=2269.9(4) Å^3, ρ_{calcd}=1.371 Mg/m^3, μ=0.269 mm^{-1}, F(000)=984, Z=4, monoclinic, space group P2(1)/c, T=173(2) K, 15,943 reflections collected, 4955 independent reflections, θ_{max} 27.00°, 290 refined parameters, maximum residual electron density 0.282 and −0.401 e Å^{-3}. R_1=0.0447, wR_2=0.0999. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC-902341.

*4.1.13. N-{2-[Acetyl(allyl)amino]phenyl}-N-allylacetamide (**8e**).* *N*-[2-(Acetylamino)phenyl]acetamide **7e**[32] (0.478 g, 2.49 mmol) was dissolved in dry acetone (15 mL) and the temperature of the mixture was lowered to −14 °C (ice and salt slurry bath), followed by the sequential addition of NaH (60% in oil, 0.191 g, 4.97 mmol) and allyl bromide (0.66 g, 0.47 mL, 5.5 mmol). The reaction mixture was then stirred at rt for 24 h under N_2. The reaction mixture was then quenched with H_2O (100 mL) and extracted with EtOAc (3×50 mL), after which the combined fractions were dried ($MgSO_4$). After filtration, the solvent was then removed under reduced pressure and the resulting crude residue purified through a silica gel column (EtOAc) to afford the desired product **8e** as a white, low melting point solid (0.626 g, 92%). Mp: 25–26 °C; R_f (100% EtOAc) 0.27; IR: ν_{max} (ATR)/cm^{-1}: 2916, 1645, 1594, 1499, 1441, 1378, 1333, 1298, 1281, 1250, 1228; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=2.04 (s, 6H, 2× CH_3), 3.78 [br m, 2H, CH=C*H*(H)], 5.20 [br m, 2H, CH=C*H*(H)], 5.26–5.44 (m, 4H, NCH_2CH=CH_2), 6.02–6.23 (m, 2H, C*H*=CH_2), 7.47 (m, 2H, 2× ArH), 7.71 (m, 2H, 2× ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=22.7 (2× CH_3), 49.9 (2× CH_2), 118.1 (2× CH), 129.0 (2× CH), 131.9 (2× CH), 132.5 (2× CH), 138.7 (2× C), 169.8 (2× C=O); *m*/*z* (EI): 272 (M^+, 2%), 230 (22), 213 (100), 187 (46), 172 (20), 159 (48), 145 (32), 119 (34), 92 (8), 77 (9); HRMS: M^+, calcd for $C_{16}H_{20}N_2O_2$ 272.1525, found: 272.1526.

*4.1.14. 1,6-Diacetyl-1,2,5,6-tetrahydro-1,6-benzodiazocine (**9e**).* Bisacetamide **8e** (0.141 g, 0.518 mmol) and Grubbs second generation catalyst **5** (0.0352 g, 0.0414 mmol, 8 mol %) were dissolved in distilled, degassed toluene (15 mL). The reaction mixture was then stirred at 90 °C for 18 h under Ar. The reaction mixture was then evaporated under reduced pressure and the resultant crude product was purified by silica gel column chromatography (10% EtOAc/hexane–100% EtOAc) to afford the cyclized **9e** as a dark oil (0.101 g, 80%). Note that the NMR spectra showed evidence for the existence of rotamers in solution. R_f (100% EtOAc) 0.28; IR: ν_{max} (ATR)/cm^{-1}: 2931, 1712, 1662, 1599, 1500, 1362, 1304, 1283, 1223; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=1.82–2.00 (m, 6H, 2× CH_3), 3.47–5.19 (br m, 4H, 2× NCH_2), 5.82–6.11 (m, 2H, CH=CH), 7.24–7.50 (br m, 4H, 4× ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=22.4 (2× CH_3), 45.2 (2× CH_2), 128.7 (2× CH), 129.1 (br, 2× CH), 130.1 (br, 2× CH_2), 139.1 (br, 2× C), 169.2 (2× C=O). *m*/*z* (EI): 244 (M^+, 34%), 230 (8), 202 (100), 184 (82), 159 (93), 143 (64), 119 (84), 93 (6), 92 (16), 77 (18), 65 (9); HRMS: M^+, calcd for $C_{14}H_{16}N_2O_2$ 244.1212, found: 244.1212.

*4.1.15. N-Allyl-N-(3-{allyl[(4-methylphenyl)sulfonyl]amino}-2-pyridinyl)-4-methylbenzenesulfonamide (**8g**).* 2,3-Diaminopyridine **7g** (1.00 g, 9.16 mmol) was dissolved in pyridine (15 mL), after which *p*-toluenesulfonyl chloride (5.24 g, 27.5 mmol) was added. The reaction mixture was then stirred at 60 °C for 23 h under N_2. After completion of the reaction the reaction mixture was poured into ice-cold H_2O (100 mL), after which the resultant brown precipitate was collected by filtration. The filter cake was washed

with copious amounts of H_2O, after which it was dried and purified by way of recrystallization (95% ethanol). The material obtained (1.91 g, 50%) was used directly in the next reaction as NMR spectroscopy revealed that the product 4-methyl-*N*-(2-{[(4-methylphenyl)sulfonyl]amino}-3-pyridinyl)benzenesulfonamide was not entirely pure. This compound (0.500 g, 1.19 mmol) was dissolved in acetone (30 mL), after which K_2CO_3 (1.32 g, 9.58 mmol, in two equal portions, the second after 10 h) and allyl bromide (0.434 g, 3.59 mmol, in two equal portions, the second after 10 h) were added. The reaction mixture was then heated at reflux for 24 h. After completion of the reaction, as monitored by TLC, the K_2CO_3 was removed by filtration and the solvent was removed under reduced pressure to afford a residue. This was purified by column chromatography (15% EtOAc/hexane) to give the desired product **8g** as white solid (0.260 g, 44%). Mp: 144–145 °C; R_f (30% EtOAc/hexane) 0.55; IR: ν_{max} (ATR)/cm^{-1} 2988, 1452, 1339, 1157, 1059, 879; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.44 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.25 (d, 2H, *J* 8.0 Hz, CH_2), 4.40 (d, 2H, *J* 8.0 Hz, CH_2), 4.90–5.10 (m, 4H, 2× CH=C*H*$_2$), 5.67–5.83 (m, 2H, 2× C*H*=CH_2), 7.22–7.35 (m, 5H, 5× ArH), 7.47–7.50 (m, 1H, ArH), 7.85 (d, 4H, *J* 8.0 Hz, 4× ArH), 8.38 (d, 1H, *J* 4.0 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)=21.8 (CH_3), 21.9 (CH_3), 53.7 (CH_2), 54.1 (CH_2), 118.7 (CH), 120.6 (CH), 123.5 (CH), 128.4 (2× CH), 129.3 (2× CH), 129.4 (2× CH), 130.0 (2× CH), 132.4 (CH), 132.8 (CH), 135.2 (C), 136.7 (C), 137.2 (C), 140.3 (CH), 143.9 (C), 144.3 (C), 148.0 (CH), 153.0 (C); *m*/*z* (EI): 498 ($M+H^+$, 100%), 483 (3); HRMS $(M+H)^+$ calcd for $C_{25}H_{27}N_3O_4S_2$ 498.1521, found 498.1520.

*4.1.16. 5,10-Bis-[(4-methylphenyl)sulfonyl]-5,6,9,10-tetrahydropyrido [2,3-b][1,4]diazocine (**9g**).* The *ortho*-bis-allyl compound **8g** (0.100 g, 0.201 mmol) was dissolved in toluene (5 mL) and Grubbs second generation catalyst **5** (0.009 g, 0.010 mmol, 5 mol %) was added. The reaction mixture was then stirred at rt for 5 h under N_2. After completion of the reaction, confirmed by TLC, the solvent was removed on the high vacuum and column chromatography was performed on the residue (20% EtOAc/hexane) to afford the cyclized compound **9g** as a white solid (0.089 g, 94%). Spectroscopic data for this compound corresponded well with that in the literature.[30]

*4.1.17. 5,10-Bis[(4-methylphenyl)sulfonyl]-5,8,9,10-tetrahydropyrido [2,3-b][1,4]diazocine (**10g**) and 5,10-bis[(4-methylphenyl)sulfonyl]-5,6,7,10-tetrahydropyrido[2,3-b][1,4]diazocine (**10′g**).* The diazocine **9g** (0.0840 g, 0.179 mmol) was dissolved in toluene (5 mL) and the solution was degassed with N_2. $[RuClH(CO)(PPh_3)_3]$ **2** (0.0085 g, 0.0090 mmol, 5 mol %) was added and the reaction mixture was stirred at 90 °C for 18 h. After completion of the reaction, as monitored by TLC, the solvent was removed under vacuum and column chromatography was performed (15% EtOAc/hexane) to afford the desired product as an inseparable mixture of regioisomers **10g** and **10′g** (45:55) and as a white solid (0.075 g, 89%). Mp: 182–184 °C; R_f (40% EtOAc/hexane) 0.45; IR: ν_{max} (ATR)/cm^{-1} 2928, 1655, 1439, 1337, 1156; ^1H NMR ($CDCl_3$, 400 MHz, combined assignments) δ 1.73 (dd, 2H, *J* 13.6, 5.7 Hz, CH_2), 1.87 (dd, 2H, *J* 13.8, 5.7 Hz, CH_2), 2.41 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.43 (3H, CH_3), 3.10 (t, 2H, *J* 5.9 Hz, NCH_2), 3.47 (t, 2H, *J* 5.9 Hz, NCH_2), 4.71 (dd, 1H, *J* 18.1, 8.2 Hz, NCH=C*H*), 4.83 (dd, 1H, *J* 18.0, 8.1 Hz, NCH=C*H*), 6.56 (d, 1H, *J* 9.9 Hz, NC*H*=CH), 6.72 (d, 1H, *J* 10.0 Hz, NC*H*=CH), 7.27–7.33 (m, 10H, Ar), 7.76 (d, 1H, *J* 1.8 Hz, Ar), 7.79 (d, 2H, *J* 6.7 Hz, Ar), 7.82 (d, 2H, *J* 8.3 Hz, Ar), 7.86 (d, 2H, *J* 8.3 Hz, Ar), 7.93 (d, 2H, *J* 8.3 Hz, Ar), 8.01 (dd, 1H, *J* 8.0, 1.8 Hz, Ar), 8.32 (dd, 1H, *J* 4.7, 1.8 Hz, Ar), 8.45 (dd, 1H, *J* 4.7, 1.8 Hz, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 17.1 (CH_2), 17.1 (CH_2), 17.1 (CH_3), 17.2 (CH_3), 17.8 (CH_3), 18.2 (CH_3), 42.5 (CH_2), 42.7 (CH_2), 101.8 (CH), 102.1 (C), 118.9 (CH), 119.0 (C), 123.4 (CH), 123.5 (C), 123.6 (CH), 123.9 (CH), 123.9 (CH), 124.6 (CH), 124.7 (C), 124.7 (CH), 124.8 (CH), 125.3 (CH), 125.4 (CH), 128.1 (CH), 130.9 (CH), 131.3 (CH), 131.6 (C), 133.4 (C), 135.9 (CH), 136.2 (C), 139.1 (CH), 139.2 (C), 139.6 (C), 140.1 (CH), 143.0 (C), 143.9 (C), 144.5 (CH), 146.7 (C); *m*/*z* (EI): 470 ($M+H^+$, 100%); HRMS: *m*/*z* calcd for $C_{23}H_{23}N_3O_4S_2$ $[M+H]^+$ 470.1208, found 470.1210.

X-ray crystal structure details of compound **10g**: crystallized from EtOAc/MeCN/hexane, formula: $C_{23}H_{23}N_3O_4S_2$, *M*=469.56, colour of crystal: colourless, needle, crystal size 0.25×0.25×0.06 mm, *a*=16.695(2) Å, *b*=8.5195(10) Å, *c*=17.160(2) Å, β=114.496(2)°, *V*=2220.9(5) $Å^3$, ρ_{calcd}=1.404 Mg/m^3, μ=0.276 mm^{-1}, *F*(000)=984, *Z*=4, monoclinic, space group P2(1)/c, *T*=100(2) K, 13,901 reflections collected, 5268 independent reflections, θ_{max} 28.7°, 291 refined parameters, maximum residual electron density 0.96 and −0.64 e $Å^{-3}$. R_1=0.046, wR_2=0.123. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC-901932.

*4.1.18. tert-Butyl-2,5-dihydro-6H-1,6-benzoxazocine-6-carboxylate (**9h**).* *tert*-Butyl allyl[2-(allyloxy)phenyl]carbamate **8h**[7b] (0.080 g, 0.276 mmol) was dissolved in toluene (3 mL) and Grubbs second generation catalyst **5** (10 mol %, 0.023 g, 0.027 mmol) was added. The reaction mixture was then stirred for a further 18 h at rt. The crude product was then passed through a silica gel column (10% EtOAc/hexane) to afford the cyclized product as a brown solid (0.042 g, 58%). Note that the NMR spectra showed evidence for the existence of rotamers in solution. Mp: 65–68 °C; R_f (20% EtOAc/hexane) 0.56; IR: ν_{max} (film)/cm^{-1} 1700, 1496, 1451, 1388, 1315, 1239, 1166; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=1.41 (br s, 9H, 3× CH_3), 4.34 (br s, 2H, NCH_2), 4.71 (d, 2H, *J* 6.6 Hz, OCH_2), 5.78–5.92 (m, 2H, CH=CH), 6.92–6.97 (m, 2H, 2× ArH), 7.11–7.17 (m, 2H, 2× ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=28.2 (3× CH_3), 48.9 (CH_2), 65.1 (br, CH_2), 80.5 [*C*(CH_3)$_3$], 120.8 (CH), 121.8 (CH), 125.5 (C), 127.9 (CH), 129.8 (2× CH), 132.6 (CH), 136.6 (C), 154.7 (C=O); *m*/*z* (EI): 261 (M^+, 41%), 218 (3), 148 (48), 117 (100), 68 (56), 57 (62); HRMS: M^+, calcd for $C_{15}H_{19}NO_3$ 261.1322, found 261.1321.

*4.1.19. 6-Benzoyl-5,6-dihydro-2H-1,6-benzoxazocine (**9i**).* *N*-Allyl-*N*-[2-(allyloxy)phenyl]benzamide **8i**[7b] (0.201 g, 0.685 mmol) and Grubbs second generation catalyst **5** (0.029 g, 0.034 mmol, 5 mol %) were dissolved in distilled, degassed toluene (15 mL). The reaction mixture was then stirred at 90 °C for 18 h under Ar. After cooling, the reaction mixture was diluted with a 10% EtOAc/hexane mixture and filtered through a compacted Celite plug (washed 3×20 mL, 10% EtOAc/hexane) to remove the catalyst. The solvent was then removed under reduced pressure and the resulting crude residue purified through a silica gel column (15% EtOAc/hexane) to afford the cyclized product **9i** as a low melting point solid (0.142 g, 78%). Mp: 29–30 °C; R_f (20% EtOAc/hexane) 0.13; IR: ν_{max} (ATR)/cm^{-1}: 1645, 1497, 1360, 1325, 1274, 1249; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=4.20–5.48 (br m, 4H, NCH_2 and OCH_2), 5.68–5.77 (m, 1H, OCH_2CH), 5.85–5.91 (m, 1H, NCH_2CH), 6.70–6.75 (m, 2H, 2× ArH), 6.89 (br dd, 1H, *J* 8.2, 0.6 Hz, ArH), 7.06–7.14 (m, 1H, ArH), 7.14–7.27 (m, 3H, 3× ArH), 7.38 (br d, 2H, *J* 7.6 Hz, 2× ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=49.1 (br, NCH_2), 65.2 (OCH_2), 121.3 (br, CH), 122.3 (br, CH), 124.7 (CH), 127.4 (br, CH), 127.6 (br, CH), 128.1 (br, 2× CH), 129.4 (br, 2× CH), 130.1 (br, CH), 131.4 (CH), 132.8 (C), 135.6 (C), 153.1 (C), 171.2 (C=O). *m*/*z* (EI): 265 (M^+, 4%), 251 (30), 234 (5), 146 (6), 131 (24), 105 (100), 77 (42), 51 (9); HRMS: M^+, calcd for $C_{17}H_{15}NO_2$ 265.1103, found: 265.1117.

*4.1.20. 6-[(4-Methylphenyl)sulfonyl]-5,6-dihydro-2H-1,6-benzoxazocine (**9j**).* *N*-Allyl-*N*-(2-(allyloxy)phenyl)-4-methylbenzenesulfonamide **8j**[7b] (0.150 g, 0.437 mmol) was reacted with 5 mol % of Grubbs second generation catalyst **5** (0.013 g, 0.022 mmol) in toluene (10 mL). The reaction mixture was then stirred at rt for 5 h under N_2. The solvent was removed to give **9j** (0.096 g, 70%) as white crystals after column chromatography (5% EtOAc/hexane). Mp: 103–105 °C; IR: ν_{max} (film)/cm^{-1} 1595, 1150; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=2.42 (s, 3H,

$ArCH_3$), 4.38 (d, 2H, *J* 6.1 Hz, CH_2), 4.76 (d, 2H, *J* 4.8 Hz, CH_2), 5.63–5.70, (m, 1H, *H*C=CH), 5.76–5.81 (m, 1H, HC=C*H*), 6.90 (d, 1H, *J* 8.2 Hz, ArH), 6.91–7.02 (m, 1H, ArH), 7.16–7.26 (m, 4H, 4× ArH), 7.51 (d, 2H, *J* 8.1 Hz, 2× ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)=21.6 (CH_3), 49.4 (CH_2), 68.5 (CH_2), 122.0 (CH), 123.3 (CH), 127.6 (CH), 128.7 (CH), 129.1 (C), 129.3 (CH), 129.4 (CH), 129.7 (CH), 130.4 (C), 135.5 (CH), 143.5 (C), 154.1 (C–O); *m*/*z* (EI): 315 (M^+, 41%), 160 (100), 120 (12), 91 (15), 41 (24); HRMS: M^+, calcd for $C_{17}H_{17}NO_3S$ 315.0929, found 315.0939.

*4.1.21. 6-[(4-Methylphenyl)sulfonyl]-3,6-dihydro-2H-1,6-benzoxazocine and 6-[(4-methylphenyl)sulfonyl]-5,6-dihydro-4H-1,6-benzoxazocine (**10j** & **10′j**).* Benzoxazocine **9j** (0.037 g, 0.12 mmol) was dissolved in d_8-toluene at rt and [RuClH(CO)(PPh_3)$_3$] **6** (0.001 g, 0.011 mmol) was added. The reaction mixture was then heated at 60–70 °C in an oil bath for a further 18 h after which the solvent was removed under high vacuum. Silica gel column chromatography (5% EtOAc/hexane) was then performed to afford the desired product as an equimolar mixture of regioisomers **10j** and **10′j** as a white solid (0.029 g, 78%). Mp: 101–104 °C; R_f (10% EtOAc/hexane) 0.35; IR: ν_{max} (film)/cm^{-1} 1649, 1597, 1492, 1350, 1305, 1254, 1165, 1086; ^{1}H NMR (300 MHz, $CDCl_3$, combined compounds): δ (ppm)= 1.89–1.97 and 1.99–2.03 (2× m, 2× 2H, 2× CH_2). 2.41 and 2.43 (2× s, 2× 3H, 2× CH_3), 3.42 (t, 2H, *J* 5.8 Hz, OCH_2), 3.73 (t, 2H, *J* 5.5 Hz, NCH_2), 4.44–4.48 (m, 1H, NC*H*=CH), 4.81–4.87 (m, 1H, OCH=C*H*)], 6.14 (d, 1H, *J* 7.5 Hz, NCH=), 6.86–7.27 (m, 12H, 11× ArH and OCH=), 7.47–7.54 (m, 3H, 3× ArH), 7.67–7.70 (m, 2H, 2× ArH); ^{13}C NMR (75 MHz, $CDCl_3$, 3 signals not observed in aromatic region): 21.5 and 21.6 (CH_3), 22.1 and 22.7 (CH_2), 45.7 (NCH_2), 71.2 (OCH_2), 100.9 (CH), 106.7 (CH), 121.4 (CH), 123.4 (CH), 124.6 and 124.9 (CH), 127.5 and 127.6 (CH), 129.1 (CH), 129.3 (CH), 129.9 (CH), 130.0 (CH), 130.8 (CH), 131.6 (CH), 132.1 (CH), 135.8 (C), 137.9 (C), 143.2 (C), 143.6 (C), 144.0 (C), 154.3 (C); *m*/*z* (EI): 315 (M^+, 36%), 160 (100); HRMS: M^+, calcd for $C_{17}H_{17}NO_3S$ 315.0929, found 315.0914.

X-ray crystal structure details of compound **10j**: crystallized from MeOH, formula: $C_{17}H_{17}NO_3S$, *M*=315.38, colour of crystal: colourless, needle, crystal size 0.35×0.18×0.14 mm, *a*=10.167(5) Å, *b*=9.085(5) Å, *c*=17.170(5) Å, β=104.047(5)°, *V*=1538.5(12) Å^3, ρ_{calcd}=1.362 Mg/m^3, μ=0.222 mm^{-1}, *F*(000)=664, *Z*=4, monoclinic, space group P2(1)/n, *T*=173(2) K, 10,102 reflections collected, 3796 independent reflections, θ_{max} 28.28°, 199 refined parameters, maximum residual electron density 0.365 and −0.322 e Å^{-3}. R_1=0.0459, wR_2=0.1057. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC-901914.

X-ray crystal structure details of compound **10′j**: crystallized from MeOH, formula: $C_{17}H_{17}NO_3S$, *M*=315.38, colour of crystal: colourless, needle, crystal size 0.22×0.12×0.08 mm, *a*=7.8540(11) Å, *b*=16.538(3) Å, *c*=12.3164(18) Å, β=103.092(8)°, *V*=1558.2(4) Å^3, ρ_{calcd}=1.344 Mg/m^3, μ=0.220 mm^{-1}, *F*(000)=664, *Z*=4, monoclinic, space group P2(1)/n, *T*=173(2) K, 9372 reflections collected, 3402 independent reflections, θ_{max} 27.00°, 200 refined parameters, maximum residual electron density 0.285 and −0.375 e Å^{-3}. R_1=0.0494, wR_2=0.0965. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC-901915.

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