Sequential Aza-Claisen Rearrangement and Ring-Closing Metathesis as a Route to 1-Benzazepine Derivatives

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Abstract: A synthetic strategy based on sequential application of aza-Claisen rearrangement and ring-closing metathesis reaction as key steps has been developed for the synthesis of various 1-benzazepine derivatives of pharmaceutical relevance.

Key words: aza-Claisen rearrangement, benzazepine, ring-closing metathesis

Recent studies have revealed that N-substituted 1-benzazepines can act as powerful vasopressin V_2 receptor antagonists, and therefore have the potential for use in the treatment of heart diseases.[1] Some of the most promising derivatives of this class are OPC-31260[2] (**1**, Figure 1) and tolvaptan[3] (**2**), currently undergoing clinical trials. In addition, several other 1-benzazepine derivatives display promising biological activities towards a number of important targets such as enzymes (e.g., compound **3**), ion channels and other G-protein-coupled receptors (e.g., compound **4**).[4] Consequently, several synthetic strategies for 1-benzazepines have been developed.[5] 1-Benzazepine derivatives are most commonly accessed through Beckmann[6] or Schmidt[7] ring expansion of derivatives of 1-tetralone or intramolecular Claisen-type condensation.[8] Some recent methods involve metal-catalyzed oxidative cyclization of amino alcohols,[9] intramolecular Heck-type arylation,[10] metal-catalyzed intramolecular amination,[11] and ring-closing metathesis[12,13] of appropriate dienes. However, a simple and general entry to this pharmaceutically important scaffold is desirable. We have recently reported[14] the synthesis of various benz- and heteroannulated oxepin and oxocin derivatives involving tandem application of Claisen rearrangement and ring-closing diene/enyne metathesis as key steps. Herein, we report a synthetic strategy to N-substituted 1-benzazepine derivatives using similar application.

The thermal rearrangement of *N*-allylanilines require drastic conditions compared to corresponding aryl allyl ethers.[15] However, such rearrangements usually proceed with significant rate enhancement under protic or Lewis acid catalysis.[16] It has further been observed that the presence of an additional *N*-alkyl group in the *N*-allylaniline moiety greatly enhances the rate of an aromatic aza-Claisen rearrangement.[17] This led us to consider selective monorearrangement of a *N*,*N*-diallylaniline derivative as a possible mean for the direct preparation of a *C*,*N*-diallyl aniline derivative to be used as a diene precursor of a RCM reaction for the ultimate preparation of the corresponding 1-benzazepine derivative.

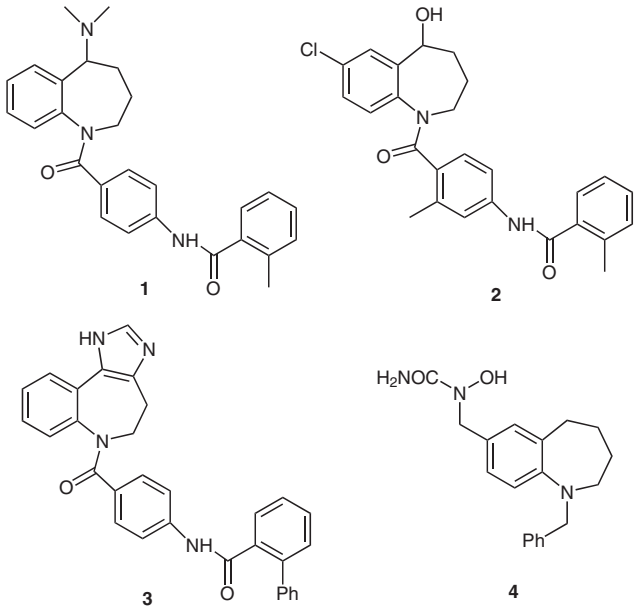

Figure 1 Pharmaceutically important 1-benzazepine derivatives

Accordingly, we first prepared *N*,*N*-diallylaniline **6a** (Scheme 1) by straightforward allylation of aniline with allyl bromide for studying its selective monorearrangement. After considerable experimentation, it was found that the desired monorearrangement of **6a** proceeds best in refluxing chlorobenzene in the presence of $BF_3{\cdot}OEt_2$ (1.5 equiv) within a reasonably short period of time (5–6 h) to provide *N*,2-diallylaniline (**7a**, 64%) as the only product, no double rearrangement being observed. Attempted optimization of the reaction using other high-boiling solvents or by changing the nature/amount of the Lewis acid or prolonging the reaction time, either singly or in combination, had deleterious effects on the outcome of the reaction since varied amount (up to ca. 40%) of 2,6-diallylaniline formed along with some unidentified products at the expense of the desired monorearrangement product **7a**. Similarly, the rearrangement of each of the diallylanilines

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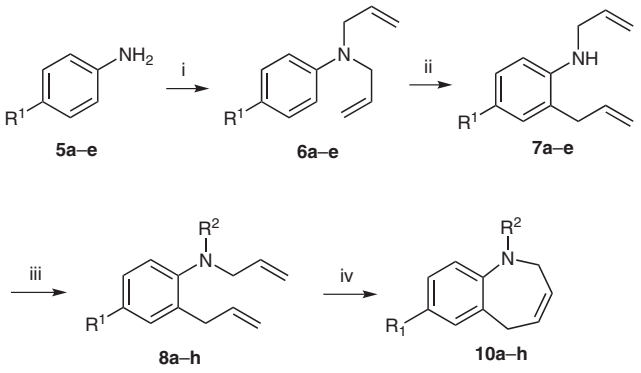


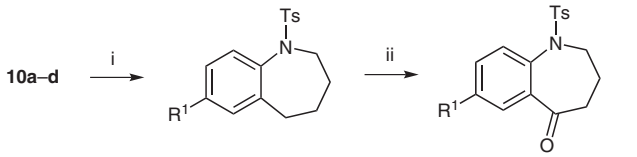
R^1, R^2	Compound (yield, %)
R^1 = H, R^2 = Ts	**5a**, **6a** (66), **7a** (64), **8a** (87), **10a** (91)
R^1 = Me, R^2 = Ts	**5b**, **6b** (71), **7b** (69), **8b** (85), **10b** (83)
R^1 = OMe, R^2 = Ts	**5c**, **6c** (79), **7c** (66), **8c** (83), **10c** (88)
R^1 = Cl, R^2 = Ts	**5d**, **6d** (70), **7d** (62), **8d** (81), **10d** (81)
R^1 = Me, R^2 = COC_6H_4	**8e** (73), **10e** (87)
R^1 = OMe, R^2 = COC_6H_4	**8f** (78), **10f** (80)
R^1 = Cl, R^2 = COC_6H_4	**8g** (81), **10g** (88)
R^1 = NO_2, R^2 = $COCF_3$	**5e**, **6e** (64), **7e** (59), **8h** (67), **10h** (78)

Scheme 1 *Reagents and conditions*: (i) allyl bromide, Et_3N, MeCN, reflux, 18 h; (ii) $BF_3{\cdot}OEt_2$ (1.5 equiv), PhCl, reflux, 5–6 h; (iii) TsCl, Et_3N, CH_2Cl_2, r.t., 24 h, or $(CF_3CO)_2O$, DMAP, Et_3N, CH_2Cl_2, r.t., 24 h, or benzoyl chloride, Et_3N, CH_2Cl_2, 12 h; (iv) **9** (5 mol%), CH_2Cl_2 (0.01 M), r.t., 2–3 h.

6b–e under the developed conditions led to the corresponding rearranged products **7b–e** in acceptable yields. In each of the rearrangement reactions, minor amount (ca. 10%) of the unreacted starting material was also recovered. The electronic nature of the substituents in the starting anilines **6b–e** was found to have little effect on the outcome of the reaction as would be consistent with the concerted nature of the reaction.

Having access to the required aniline derivatives **7a–e**, we then focused on their RCM reaction. To this end, the corresponding *N*-tosyl derivatives **8a–d** and the *N*-benzoyl derivatives **8e–g** were prepared under conventional conditions. The nitroaniline derivative **7e**, however, did not undergo clean N-tosylation or N-benzoylation under some of the attempted conditions. Consequently, it was converted to the corresponding trifluoroacetamide derivative **8h**. Ring-closing metathesis of the diene **8a** proved to be extremely facile with Grubbs first-generation catalyst benzylidene bistricyclohexylphosphinoruthenium(IV) dichloride (**9**) at room temperature, and a high-yield conversion to the azepine derivative **10a** was realized. Similarly, the dienes **8b–h** all underwent smooth RCM to provide the corresponding tetrahydrobenzazepine derivatives **10b–h** in very good to excellent yields.

We next considered incorporation of functionalities in the 5-position of the prepared benzazepine derivatives as relevant to compounds **1** and **2**. Attempted benzylic oxidation of compound **10a** under a range of conditions proved to be unsuccessful. However, the corresponding saturated derivative **11a** underwent oxidation with pyridinium chlorochromate[18] in refluxing benzene leading to the corresponding ketone derivative **12a** in moderate yield. Similarly, the keto derivatives **12b–d** were prepared (Scheme 2).[19]



11a R^1 = H
11b R^1 = Me
11c R^1 = OMe
11d R^1 = Cl

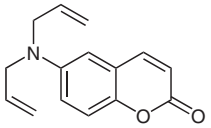
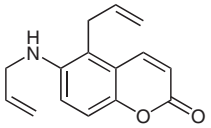
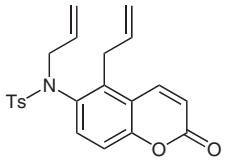
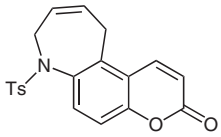
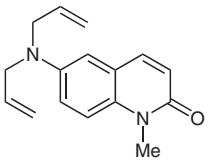
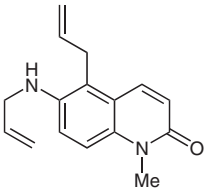
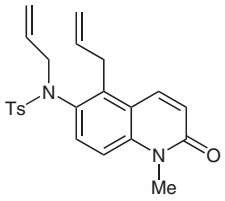
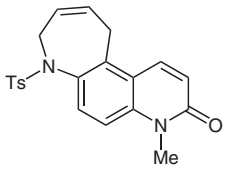
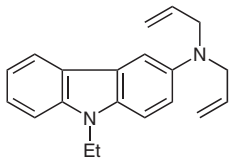
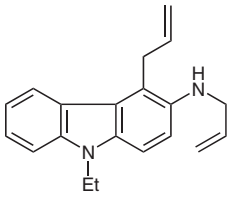
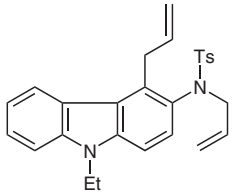
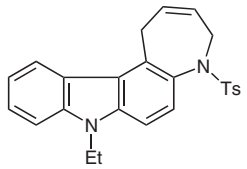
12a R^1 = H, 62%
12b R^1 = Me, 64%
12c R^1 = OMe, 72%
12d R^1 = Cl, 59%

Scheme 2 *Reagents and conditions*: (i) H_2, Pd/C (10%), EtOAc, r.t., 6 h, quant.; (ii) PCC, Celite, benzene, reflux, 24 h, 59–72%.

While several 1-benzazepine derivatives have been prepared and evaluated, little is known about heteroannulated azepine derivatives. Various common ring-sized azacycle-annulated coumarin,[20] 2-quinolone[21] and carbazole[22] derivatives display interesting biological properties. We thus considered extending the present study to 6-aminocoumarin, 6-amino-1-methyl-2-quinolone, and 3-aminocarbazole with a view to prepare corresponding azepine-annulated constructs. Thus, *N*,*N*-diallyl-6-aminocoumarin (**13**, Table 1) was prepared by allylation of 6-aminocoumarin. Pleasingly, compound **13** underwent smooth monorearrangement under the developed conditions to provide the corresponding rearrangement product **14** as the only regioisomer in good yield. Similarly, the *N*,*N*-diallylquinolone derivative **17** and the diallylaminocarbazole derivative **21** also underwent selective monorearrangement to the corresponding angularly allylated compounds **18** and **22**, respectively, in good yields. The regioselectivity observed in the rearrangement of each of the compounds **13**, **17**, and **21** is in line with our earlier results on the rearrangement of corresponding allyl ethers.[14a–d] The bias for an angular rearrangement against a linear rearrangement of allyl ethers accommodated in an appropriate coumarin, quinolone, or carbazole scaffold is well documented. However, it is interesting to note that such a bias in aza-Claisen rearrangement in these systems is also operative. The rearranged products **14**, **18**, and **22** were then converted to the corresponding *N*-tosyl derivatives **15**, **19**, and **23**, respectively. Ring-closing metathesis of each of these dienes separately under the developed conditions then led to the corresponding tetrahydroazepine derivatives **16**, **20**, and **24**, respectively, in very good yields.

In summary, we have developed a suitable protocol for the selective monorearrangement of a *N*,*N*-diallylaniline derivative for the preparation of a N-tethered diene as precursor of the corresponding 1-benzazepine derivative having three points of diversity relevant to drug design. The methodology is simple, general in nature, and it involves the use of easily available starting materials and reagents. The predetermined mode of ring closure and its tolerance to electron-withdrawing groups may make the process complementary to those existing in the literature,

Table 1 Formation of Hetero-Annulated Azepine Derivatives

Entry	Diallylaniline (yield)[a]	Rearranged amine (time, yield)[b]	Precursor diene (yield)[c]	RCM Product (yield)[d]
1	 **13** (78%)	 **14** (4 h, 72%)	 **15** (77%)	 **16** (79%)
2	 **17** (82%)	 **18** (2 h, 85%)	 **19** (69%)	 **20** (82%)
3	 **21** (73%)	 **22** (6 h, 61%)	 **23** (71%)	 **24** (82%)

[a] Appropriate amine, allyl bromide, Et_3N, MeCN, reflux, 18 h.
[b] $BF_3{\cdot}OEt_2$ (1.5 equiv), ClPh, reflux, 2–6 h.
[c] TsCl (1.5 equiv), Et_3N (2 equiv), CH_2Cl_2, r.t., 24 h.
[d] Grubbs catalyst **9** (5 mol%), CH_2Cl_2 (0.01 M), r.t., 2–3 h.

in particular, for the preparation of substituted 1-benzazepines, which are otherwise difficult to access. It may also find application in the synthesis of other medium-sized azacycle-annulated aromatic compounds of interest. Work will be continued along these directions.

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(19) **Representative Procedure for the Sequence of Reactions in Scheme 1: *N*,*N*-Diallyl-4-methylaniline (6b)**
Allyl bromide (2.7 mL, 31.4 mmol) was added dropwise to a solution of **5b** (1.7 g, 15.7 mmol) and Et_3N (4.4 mL, 31.4 mmol) in dry MeCN (25 mL), and the mixture was heated to reflux for 18 h. It was then allowed to come to r.t., concentrated under reduced pressure, and the residual mass was extracted with EtOAc (50 mL). The extract was washed successively with H_2O (25 mL), brine (25 mL), and then dried (Na_2SO_4). It was filtered, concentrated under reduced pressure, and the residue was purified by chromatography over SiO_2 using PE as eluent to afford **6b** as a pale yellow viscous liquid (2.09 g, 71%). IR(neat): 1642, 1619, 1521, 1235, 1182 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.01 (d, 2 H, *J* = 8.2 Hz), 6.62 (d, 2 H, *J* = 7.8 Hz), 5.89–5.80 (m, 2 H), 5.20–5.12 (m, 4 H), 3.88 (d, 4 H, *J* = 4.8 Hz), 2.23 (s, 3 H). Anal. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48. Found: C, 83.34; H, 9.28; N, 7.39.
***N*,2-Diallyl-4-methylaniline (7b)**
Boron trifluoride etherate (1.8 mL, 15 mmol) was slowly added to a solution of **6b** (1.9 g, 10 mmol) in PhCl (15 mL) under nitrogen, and the mixture was heated to reflux for 5 h. It was then allowed to come to r.t., quenched with sat. aq $NaHCO_3$ solution (20 mL), and the aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic mixture was washed successively with H_2O (25 mL), brine (25 mL), and then dried (Na_2SO_4). It was filtered, concentrated under reduced pressure, and the residue was purified by chromatography over SiO_2 using PE as eluent to give starting **6b** (0.17g, 9%) followed by the product **7b** (1.31g, 69%) as a pale yellow viscous liquid. IR(neat): 3442, 3387, 1636, 1618, 1515, 1313 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.94 (d, 1 H, *J* = 8.1 Hz), 6.87 (s, 1 H), 6.55 (d, 1 H, *J* = 8.1 Hz), 5.98–5.92 (m, 2 H), 5.28–5.06 (m, 5 H), 3.76 (dt, 2 H, *J* = 5.4, 1.5 Hz), 3.28 (d, 2 H, *J* = 6.2 Hz), 2.24 (s, 3 H). Anal. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48. Found: C, 83.40; H, 9.26; N, 7.43.
***N*-Allyl-*N*-(2-allyl-4-methylphenyl)-4-methylbenzenesulfonamide (8b)**
p-Toluenesulfonyl chloride (1.71 g, 9 mmol) was added to a solution of **7b** (1.1g, 5.9 mmol) and Et_3N (1.7 mL, 12 mmol) in dry CH_2Cl_2 (20 mL), and the reaction mixture was stirred at r.t. for 12 h. It was then diluted with CH_2Cl_2 (20 mL), and the solution was washed successively with HCl (1 N, 2 × 25 mL), H_2O (25 mL), brine (25 mL), and then dried (Na_2SO_4). It was filtered, concentrated under reduced pressure, and the residue was purified by chromatography over SiO_2 using EtOAc–PE (1:19) as eluent to give the product as a colorless viscous liquid (1.7 g, 85%). IR ($CHCl_3$): 1638, 1598, 1497, 1349, 1219, 1164, 1062 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.58 (d, 2 H, *J* = 8.2 Hz), 7.26 (d, 2 H, *J* = 8.1 Hz), 7.09 (s, 1 H), 6.85 (d, 1 H, *J* = 7.9 Hz), 6.46 (d, 1 H, *J* = 8.0 Hz), 5.97–5.84 (m, 1 H), 5.80–5.68 (m, 1 H), 5.14–5.08 (m, 2 H), 5.01–4.93 (m, 2 H), 4.30 (dd, 1 H, *J* = 14.0, 5.6 Hz), 3.85 (dd, 1 H, *J* = 14.0, 7.6 Hz), 3.55 (dd, 1 H, *J* = 15.5, 6.5 Hz), 3.45 (dd, 1 H, *J* = 15.4, 6.5 Hz), 2.44 (s, 3 H), 2.30 (s, 3 H). Anal. Calcd for $C_{20}H_{23}NO_2S$: C, 70.35; H, 6.79; N, 4.10. Found: C, 70.48; H, 6.88; N, 4.29.
7-Methyl-1-tosyl-2,5-dihydro-1*H*-benzo[*b*]azepine (10b)
Catalyst **9** (14 mg, 5 mol%) was added to a solution of **8b** (0.11g, 0.32 mmol) in dry, degassed CH_2Cl_2 (30 mL) under nitrogen, and the reaction mixture was stirred at r.t. for 2 h. It was then concentrated under reduced pressure and the residue was chromatographed over SiO_2 using EtOAc–PE (1:13) as eluent to give the product **10b** (83 mg, 83%) as a colorless solid; mp 114 °C. IR ($CHCl_3$): 1598, 1496, 1343, 1157 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, 2 H, *J* = 8.2 Hz), 7.24 (d, 2 H, *J* = 8.5 Hz), 7.16 (d, 1 H, *J* = 8.0 Hz), 7.00 (d, 1 H, *J* = 7.9 Hz), 6.87 (s, 1 H), 5.66–5.60 (m, 1 H), 5.45–5.41 (m, 1 H), 4.35 (br s, 2 H), 2.92 (br s, 2 H), 2.42 (s, 3 H), 2.29 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.1, 140.8, 138.7, 138.3, 136.0, 129.9, 129.7, 129.4, 128.0, 127.0, 125.8, 125.3, 49.1, 32.2, 21.5, 21.0. Anal. Calcd for $C_{18}H_{19}NO_2S$: C, 68.98; H, 6.11; N, 4.47. Found: C, 69.13; H, 6.18; N, 4.58. MS (TOFMS ES$^+$): *m/z* = 336 [M^+ + Na].
Selected Data
Compound **10c**: Mp 128 °C. IR (KBr): 1602, 1500, 1341, 1159 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.63 (d, 2 H, *J* = 8.2 Hz), 7.24 (d, 2 H, *J* = 8.1 Hz), 7.19 (d, 1 H, *J* = 8.8 Hz), 6.71 (dd, 1 H, *J* = 8.6, 2.9 Hz), 6.58 (d, 1 H, *J* = 2.7 Hz), 5.65–5.59 (m, 1 H), 5.45–5.41 (m, 1 H), 4.35 (br s, 2 H), 3.78 (s, 3 H), 2.88 (br s, 2 H), 2.42 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2, 143.1, 142.5, 138.6, 131.2, 131.1, 129.4, 127.0, 125.9, 124.9, 114.6, 112.1, 55.3, 49.2, 32.4, 21.5. Anal. Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.80; H, 5.98; N, 4.43. MS (TOFMS ES$^+$): *m/z* = 352 [M^+ + Na].
Compound **12b**: Mp 135 °C. IR (KBr): 1715, 1596, 1491, 1352, 1168 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, 2 H, *J* = 8.3 Hz), 7.41 (d, 1 H, *J* = 8.0 Hz), 7.32 (d, 2 H, *J* = 8.1 Hz), 7.18 (d, 1 H, *J* = 8.1 Hz), 7.03 (s, 1 H), 2.48–2.44 (m, 2 H), 2.38 (s, 3 H), 2.23 (s, 3 H), 2.10–2.04 (m, 3 H), 1.79–1.77 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7, 144.8, 139.4, 136.6, 135.8, 133.4, 129.7, 129.3, 129.1, 128.8, 127.9, 34.4, 29.1, 27.3, 21.7, 21.1. Anal. Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.78; H, 6.04; N, 4.48. MS (TOFMS ES$^+$): *m/z* = 352 [M^+ + Na].
Compound **16**: IR ($CHCl_3$): 1735, 1597, 1342, 1160, 1109 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, 1 H, *J* = 10.0 Hz), 7.68 (d, 2 H, *J* = 8.2 Hz), 7.35 (d, 1 H, *J* = 8.8 Hz), 7.30 (d, 2 H, *J* = 8.1 Hz), 7.17 (d, 1 H, *J* = 8.7 Hz), 6.43 (d, 1 H, *J* = 9.9 Hz), 5.79–5.71 (m, 1 H), 5.54–5.50 (m, 1 H), 4.37 (br s, 2 H), 3.34 (d, 2 H, *J* = 4.0 Hz), 2.45 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.7, 153.7, 143.6, 140.3, 139.6, 138.0, 135.2, 132.6, 129.7, 126.9, 126.7, 123.5, 116.5, 116.3, 115.5, 48.7, 24.6, 21.4. Anal. Calcd for $C_{20}H_{17}NO_4S$: C, 65.38; H, 4.66; N, 3.81. Found: C, 65.66; H, 4.83; N, 3.96. MS (TOFMS ES$^+$): *m/z* (%) = 390(100) [M + Na], 368(41) [M + H].
Compound **20**: mp 224 °C IR (KBr): 1654, 1578, 1455, 1333, 1158, 1123 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, 1 H, *J* = 10.0 Hz), 7.68 (d, 2 H, *J* = 8.2 Hz), 7.47 (d, 1 H, *J* = 9.0 Hz), 7.30–7.22 (m, 3 H), 6.72 (d, 1 H,

J = 10.0 Hz), 5.80–5.73 (m, 1 H), 5.52–5.48 (m, 1 H), 4.13 (br s, 2 H), 3.71 (s, 3 H), 3.35 (d, 2 H, J = 4.3 Hz), 2.44 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.6, 143.5, 140.2, 140.1, 138.4, 134.5, 133.4, 131.6, 129.7, 126.9, 124.1, 121.7, 118.1, 113.2, 49.0, 29.8, 24.6, 21.5. Anal. Calcd for $C_{21}H_{20}N_2O_3S$: C, 66.29; H, 5.30; N, 7.36. Found: C, 66.36; H, 5.41; N, 7.24. MS (TOFMS ES$^+$): m/z = 403 [M + Na].

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