Addition of 1,3-Benzoxathiole 3-Oxide Anion to Azomethines under Varying Reaction Conditions[‡]

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The reaction of benzoxathiole 3-oxide with LDA in THF gave an anion which was reacted with azomethines under varying conditions of temperature and solvent. At –78 °C in THF, the two diastereomers resulting from a *trans* addition were mainly obtained, while at temperatures higher than –40 °C, or upon increasing the solvent polarity, only one *trans* and one *cis* diastereomer were obtained.

Introduction

In a previous paper[1] we investigated the reaction between 1,3-benzoxathiole 3-oxide (**1**) and *para*-substituted benzaldehydes under kinetically controlled conditions. With the aim of examining the reactivity of the C=N bond and producing amine derivatives of **1**, we now extend this research to the reaction between the sulfinyl anion and phenyl-, thienyl- or furyl-substituted benzaldimines, with the nitrogen atom protected by PMP.[2] These reactions were carried out under several different reaction conditions in order to increase the diastereoselectivity. Analogous reactions between the methyl tolyl- or -phenylsulfoxide and azomethine derivatives have been reported by other authors.[2–7]

Results and Discussion

This paper describes the reactivity of the sulfinyl anion **2**, obtained from 1,3-benzoxathiole 3-oxide, with aldimines. The formation of **2** is promoted not only by the electron-withdrawing effect of the sulfoxide group but also by the coordination of the metal with the oxygen atom.[8] The use of LDA was necessary due to the reactivity of the sulfoxide heterocyclic ring.[1] The reaction of **2** with 4-substituted aromatic aldimines **3a–g** gave the products **4a–g**, **5a–g**, **6a–e**, **7a–g** (Scheme 1). The relative stereochemistry of the diastereomers was assigned by comparing the NMR spectra with those obtained by reaction of **2** with substituted 4-methoxybenzaldehydes **4–7m** whose structures were determined by X-ray analysis.[1]

The structures of compounds **4a–g**, **5c–d, 6c** and **7a–g** were assigned by comparison of the ^{1}H NMR and ^{13}C NMR spectra with the analogous compounds **4–7m** (Scheme 2). In fact, as summarised in Table 1, the chemical shifts of the protons on the diastereogenic carbons, on the nitrogen atom and C_7 are quite similar because of the equivalent chemical environment. The diastereomers with an arylazomethylenic group *cis* with respect to the sulfoxide oxygen atom have a ^{13}C NMR chemical shift value of $\delta \cdot \approx$ 100 ppm for C_7, compared to a value of $\delta \cdot \approx$ 110 ppm for the *trans* configurations.

When the reaction was carried out at −78 °C in THF and using an LDA/**1** ratio of 2, attack occurred *trans* to the sulfoxide oxygen yielding a product sum (i.e. **4** + **5**) that was greater than 75% (Table 2 entries 7,17,19,22). However, in the absence of the transformation of **5** to **7** (Scheme 3), the *anti* facial diastereoselectivity should be higher than 90%. The reaction of **2** with **3f** resulted in higher selectivity for the adduct **7** (*cis* attack): this can be explained by a greater stabilization of the transition state, due to the simultaneous interaction of the lithium bound to the oxygen of the sulfoxide with the oxygen of the furyl ring and the nitrogen atom. Lower global yields and higher amounts of **7** were obtained when the LDA/**1** ratio was changed to 1.5 and all other conditions remained the same. This can be explained by the fact that adduct **7** is produced not only through the transition state, where anion **2** has reacted with the iminic carbon, but also by the transformation of **5**.

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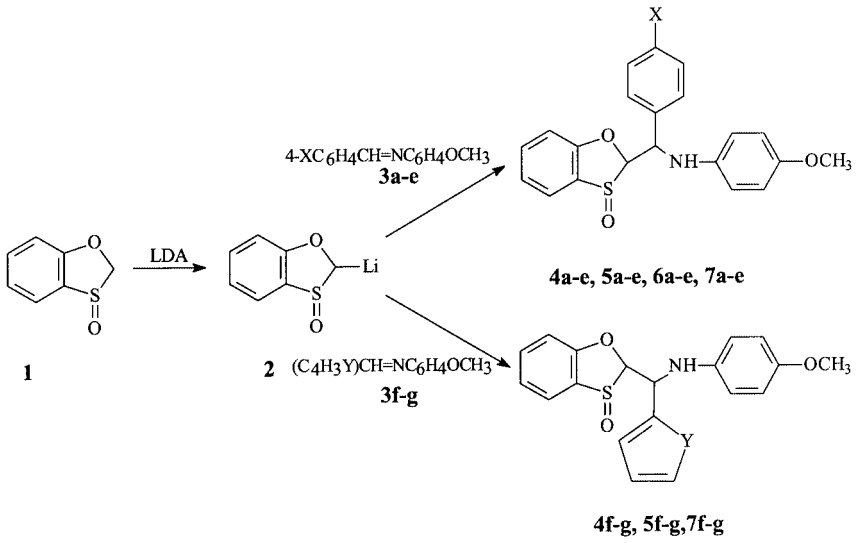
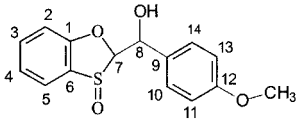


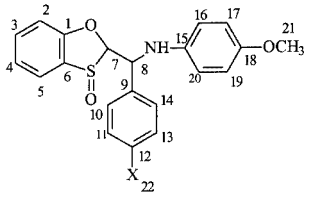
X				
p-OCH_3	**4a**	**5a**	**6a**	**7a**
p-CH_3	**4b**	**5b**	**6b**	**7b**
H	**4c**	**5c**	**6c**	**7c**
p-F	**4d**	**5d**	**6d**	**7d**
p-CF_3	**4e**	**5e**	**6e**	**7e**

Y			
O	**4f**	**5f**	**7f**
S	**4g**	**5g**	**7g**

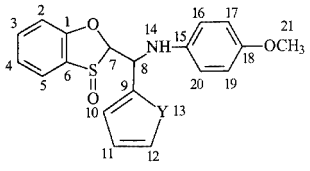
Scheme 1



4m 7S,8R,Ss; **5m** 7S,8S,Ss; **6m** 7R,8R,Ss;**7m** 7R,8S,Ss



X = OCH_3, CH_3, H, F, CF_3



Y = O, S

Scheme 2

When **5** was treated at −78 °C with LDA in THF/HMPA, at −40 °C in THF, or at room temp. with NaOH in DMSO, **5** was completely transformed into **7**, while after the same reaction time with LDA in THF at −78 °C the transformation of **5** to **7** was partial. However, compounds **4**, **6**, and **7** remained unchanged even at room temperature.

The conversion of **5** into **7** occurs by an inversion of configuration at the α carbon, probably by transfer of the aminic proton on the α carbon. This hypothesis is supported by the fact that in the ^{1}H NMR spectra of **5** the coupling constants H_7-H_8 and H_8-H_N are consistent with a conformation in which the NH proton is near to the C-7 carbon but on the opposite side to the C7-bound proton. This conformation was not found for the other adducts. This model would explain the lower molar fraction of **7** observed when the LDA/**1** ratio was increased (Table 2, entries 6, 7, 8, 16, 17, 18, 19) − the higher base concentration should lead to a greater degree of NH proton abstraction making its transfer to the α carbon atom unlikely.

Increasing the temperature made *cis* addition easier, with formation of higher amounts of the thermodynamically favoured adduct **7**. In the case of entry 12 the yield was very low while **7** was formed with high selectivity (93%, see Table 2). This low yield could be due to side reactions leading to decomposition of **2**. The possible transition states leading to **6** and **7**, which were built by molecular models, do not show meaningful steric hindrance differences, therefore we believe that the increased selectivity of **7** is mainly due to an easier transformation of **5** into **7** or to its greater thermodynamic stability. Also, although to a lesser extent, **7** can be derived from the reaction of **2** with the electrophile. In this reaction the solvation of the lithium cation and the formation of a tight ion-pair with the nitrogen anion should not favour a reduction of the steric hindrance on the *cis* side.[6]

The carbocation character of the iminic carbon was evaluated from plots of the differences in carbon chemical shifts versus σ_p (from experiments using $CDCl_3$ and DMSO

Table 1. ^{1}H and ^{13}C NMR chemical shifts of diastereomers **4**−**7**

			(7*S*,8*R*,*S*s + 7*R*,8*S*,*R*s)					(7*S*,8*S*,*S*s + 7*R*,8*R*,*R*s)	
Compound	H8	H7	OH or NH	C7	Compound	H8	H7	OH or NH	C7
4m	5.00	5.71	6.29	110.3	**5m**	5.28	5.74	6.18	109.1
4a	4.61	5.78	6.45	107.8	**5a**	5.13	5.81	6.01	109.3
4c	4.71	5.84	6.54	107.7	**5c**	5.24	5.84	6.03	109.5
4d	4.78	5.82	6.54	107.8	**5d**	5.30	5.85	6.06	109.4
4e	4.82	5.86	6.58	107.8	**5e**	5.34	5.85	6.04	109.6
4f	4.93	5.88	6.19	106.4	**5f**				
4g	5.12	5.81	6.38	107.5	**5g**	5.57	5.89	5.96	108.9
			(7*R*,8*R*,*S*s + 7*S*,8*S*,*R*s)					(7*R*,8*S*,*S*s + 7*S*,8*R*,*R*s)	
6m	5.14	5.41	6.22	101.4	**7m**	5.07	5.39	6.52	100.7
6c	5.08	5.52	6.47	101.0	**7c**	5.04	5.54	6.66	100.8
					7a	4.99	5.44	6.46	100.2
					7b	4.98	5.44	6.48	100.2
					7d	5.08	5.48	6.54	99.9
					7e	5.17	5.53	6.68	99.6
					7f	5.11	5.60	6.28	98.5
					7g	5.30	5.51	6.46	99.7

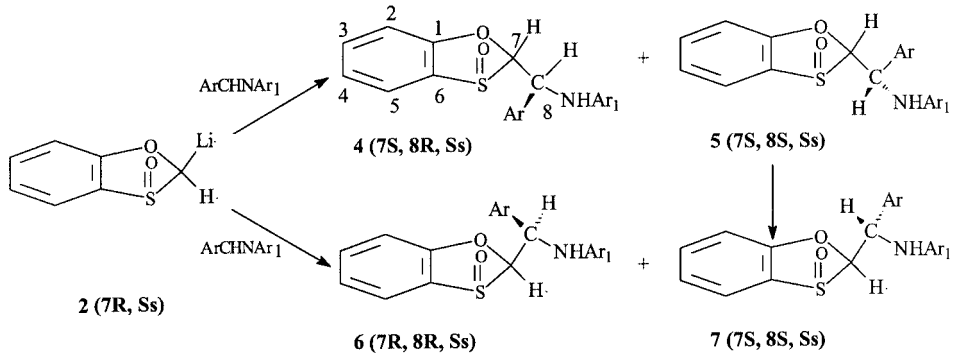
Table 2. Product distribution for the reaction **2** + **3** in neat THF in the range −78 to 0 °C

	X	Entry	*T* (°C) **1**+**LDA**	*T* (°C) **2**+**E**	Unreact. (%) **1**	**LDA/1**	Molar fraction **4**	**5**	**6**	**7**	Yield (%)
3a	4-MeO-Φ	1	−78	−78	52	1.5	51	49	0	0	21
		2	−78	−60	46	2.0	43	31	5	21	24
		3	−78	−40	10	2.0	33	2	8	57	42
3b	4-Me-Φ	4	−78	−78	100	1.5	–	–	–	–	–
		5	−78	−40	67	2.0	46	16	7	31	13
3c	Φ	6	−78	−78	9	2.5	45	39	3	13	68
		7	−78	−78	–	2.0	43	37	4	16	83
		8	−78	−78	16	1.5	47	33	–	20	52
		9[a]	−78	−40	–	2.0	30	3	9	58	80
		10	−78	−40	–	2.0	28	2	12	57	77
		11	−78	−20	–	2.0	18	3	10	70	76
		12	−78	0	–	2.0	3	3	1	93	22
		13	−40	−40	3	2.0	31	2	7	59	74
		14	−40	−20	26	2.0	23	5	15	57	29
		15	−20	−20	8	2.0	24	5	9	62	16
3d	4-F-Φ	16	−78	−78	28	1.5	40	16	2	42	46
		17	−78	−78	–	2.0	39	46	1	15	77
3e	4-CF_3-Φ	18	−78	−78	24	1.5	38	17	2	43	56
		19	−78	−78	15	2.0	34	44	2	20	70
3f	furyl	20	−78	−78	19	1.5	36	10	–	54	42
		21	−78	−40	8	2.0	30	2	–	68	51
3g	thienyl	22	−78	−78	–	2.0	61	36	–	2	47
		23	−78	−40	9	2.0	40	17	–	43	53

[a] Quenching was carried out at the same temperature of the reaction (−40 °C) with pyridinium chloride, in DMF as solvent.

as solvents) in order to explain the low, or lack of, reactivity of the carbocation **2** with the imine **3b** (entries 4,5). The Hammett plots are not linear (see Figure 1 and 2), and although they account for the higher reactivity of the unsubstituted derivative they do not explain the lack of reactivity of **3b** and the much lower reactivity of **3a** when compared with the reactivity of **3d**−**e**.

Also, the IR spectra do not show any difference in the C-N double bond character.[10,11] On the other hand the ^{1}H NMR spectra recorded at −60 °C for the different electrophiles are similar and therefore all the electrophiles have the same configuration of the C=N bond (Table 3). Considering that the steric hindrance difference between the aromatic substituents is very low, we believe that the C-N



Scheme 3

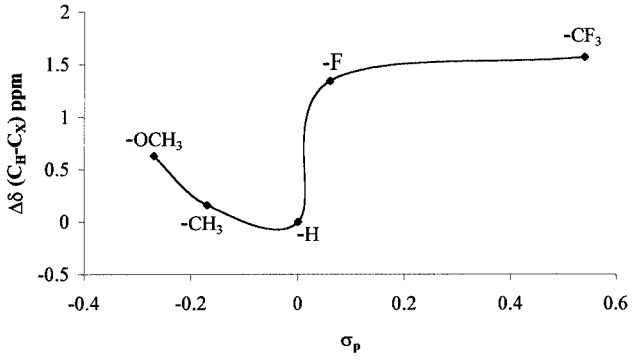


Figure 1. A Hammett plot of the difference in chemical shifts of the iminic carbon with [D_6]DMSO as solvent

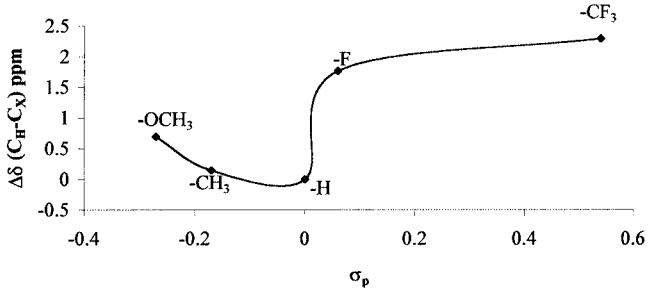


Figure 2. A Hammett plot of the iminic carbon chemical shifts difference in $CDCl_3$ as solvent

Table 3. Absolute and relative ^{13}C chemical shifts of the iminic carbon atom in different solvents and Hammett substituent constants for the substituted azomethines

X	σ_p	^{13}C [D_6]DMSO	Δδ	^{13}C $CDCl_3$	Δδ
OCH_3	−0.27	157.89	0.63	157.68	0.70
CH_3	−0.17	158.36	0.16	158.23	0.14
H	0	158.53	0	158.37	0
F	0.06	157.18	1.34	156.61	1.76
CF_3	0.54	156.96	1.57	156.07	2.29

double bond polarisation in the excited and ground states is very different and that the methyl and methoxy groups can decrease the carbocation character considerably.

An increase of solvent polarity improves the reaction yields and favours the selective production of adduct **4** (Table 4) when X is an electron-withdrawing substituent. In fact a greater solvation of both the lithium and the iminic carbon, increasing the steric hindrance, reduces the already poor *cis* attack and favours the *trans* addition. Electron-withdrawing substituents can lead to a transition state with the iminic carbon more positive and therefore more solvated. This fact does not contradict the results obtained or the reported Hammett plots.[10,11] In fact in the transition state the double bond character of the C=N group should have been lost and therefore electron-withdrawing groups can only increase the positive charge on the iminic carbon. Also the amount of diastereomer **7** is increased because the reaction 5→7 is favoured by the higher polarity. On the other hand, higher reaction yields could be the result of the

Table 4. Product distribution for the reaction **2** + **3(c−e)** in THF/HMPA mixtures in the range −78 to −40 °C

	Entry	Solvent **1** + **LDA**	Solvent **2** + **E**	*T* (°C) **1** + **LDA**	*T* (°C) **2** + **E**	Unreac. (%) **1**	**LDA/1**	Molar fraction **4**	**5**	**6**	**7**	Yield (%)
	24	THF	THF/HMPA	−78	−78	−	2.0	47	2	2	49	91
3c	25	THF	THF/HMPA	−78	−78	−	1.5	46	3	3	48	86
	26	THF	THF/HMPA	−78	−40	−	2.0	31	1	15	54	86
3d	27	THF	THF/HMPA	−78	−78	8	1.5	47	2	1	49	69
3e	28	THF	THF/HMPA	−78	−78	−	2.0	57	3	1	39	87

increased C=N bond polarization and greater carbocation character.

The reported data on open chain or conformationally flexible cyclic sulfoxides[2,4] led to the expectation that the reaction of **2** with benzaldimines should result in the formation of the adducts arising from an attack on the same side of the oxygen atom of the SO group. Instead, analogous to our previous report,[1] we found that when **2** was reacted with **3(a,c-e)** under kinetic control, the attack occurred more favourably on the side opposite the SO group. When the attack occurs on the other side, coordination of the imine nitrogen with the lithium cation is geometrically impossible and the adducts mainly arise from the direct interaction of **2** with the iminic carbon or, presumably, through transition states analogous to those previously reported for the reaction of **2** with the benzaldehydes.[1] Therefore we believe that the transition state proposed by several authors[2,4] is not general, but restricted to conformationally free systems. The substituents on the aromatic moiety of the azomethines have little affect on the *facial* diastereoselectivity both at the methylenic carbon of **1** (α at sulfoxide group) and at the imine carbon atom. The substitution of the aryl by a heterocyclic ring produced a greater influence on the facial diastereoselectivity.

The diastereomers **4−7** were isolated by fractional crystallization or by flash chromatography (see Exp. Sect.). Molar fractions (Table 2 and 3) were determined by HPLC analysis on the basis of calibration plots. Finally, despite the fact that reaction diastereoselectivity was not high, the diastereomer **7** was isolated with a high degree of purity (95−96%) by treating the reaction mixture with diethyl ether or diethyl ether/methanol, which dissolved the other diastereomers.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-300 spectrometer with tetramethylsilane as an internal reference; δ values are given in ppm and *J* values in Hz. MS spectra were recorded at 70 eV with a Hewlett−Packard 5989A mass spectrometer using the direct insertion probe (DIP) method. IR spectra were recorded with a Nicolet FT-IR 210 spectrophotometer. Microanalyses were carried out on a Carlo Erba model 1106 Elemental Analyzer. Analytical TLC plates and silica gel (230−400 mesh) were purchased from Merck. Flash chromatography was performed on silica gel 60, 0.04−0.063 mm (Fluka). Melting points were determined with a Kofler hot stage microscope and are uncorrected.

In order to determine yields and molar fractions HPLC analyses were performed on a machine with a Waters 600 pump connected to a Waters 996 photodiode array detector on a Spherisorb-CN normal phase column of 250 mm length and 4.6 mm i.d., and hexane/2-propanol (75:25) as eluent (1 mL/min). The chromatogram was extracted at λ_{max}. With the exception of compounds **4b**, **6(a,b,d,e)** and **5(b,f)** all determinations were carried out on the basis of calibration plots on the pure compounds. The above-mentioned compounds were produced in very low yields and their isolation and characterisation was difficult and meaningless from a synthetic point of view. Nevertheless, their retention times showed the same sequences for the different electrophiles and their UV spectra overlapped with those of the other diastereomers. Therefore correction factors for the diastereomers were very similar.

Materials: Reagent-grade reagents and solvents were used. All the reagents were purchased from Aldrich Chemical Co. Solutions of butyllithium in hexane were purchased from Aldrich Chemical Co. and were analysed by the Gilman double-titration method.[12] Solutions of LDA in THF were prepared by literature methods.[13] All solvents were dried and purified using standard techniques. Petroleum ether (b.p. 40−60 °C) was used for chromatography.

Imines and (±)-1,3-Benzoxathiole 3(2*H*)-Oxide: The imines **3(a, c-g)** and (±)1,3-benzoxathiole 3(2*H*)-oxide (**1**) were prepared as described in the literature.[9,14−16] The imine **3b** was not yet described in the literature and has been prepared by the same method; its spectroscopic data are reported below.

4-Methoxy-*N*-[(4-methylphenyl)methylidene]aniline (3b): Crystallised from ethanol, m.p. 88−90 °C. IR (KBr. disk): $\tilde{\nu}$ = 1624 cm^{-1}, 1585, 1606, 1569, 1503, 1466, 1440, 1268, 1239, 1109, 1032, 882, 837, 817, 778. ^{1}H NMR ($CDCl_3$): δ = 2.40 (s, 3 H, CH_3), 3.80 (s, 3 H, OCH_3), 6.92 (d, ^3J = 8.1 Hz, 2 H, 10-H, 12-H), 7.25 (d, ^3J = 8.4 Hz, 4 H, 2-H, 3-H, 5-H, 6-H), 7.81 (d, ^3J = 8.1 Hz, 2 H, 9-H, 13-H), 8.43 (s, 1 H, 7-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (q, *C*H$_3$), 55.3 (q, O*C*H$_3$), 114.2 (d, C-3, C-5), 122.1 (d, C-2, C-6), 128.6 (d, C-9, C-13), 129.3 (d, C-10, C-12), 133.4 (s, C-1), 141.5 (s, C-8), 144.4 (s, C-11), 158.1 (s, C-4), 158.2 (d, C-7) ppm. EI-MS (DIP): *m*/*z* (%) = 225 (88) [M$^+$], 224 (15), 210 (100), 181(9), 167 (8), 155 (7), 92 (8), 91 (9), 77 (14). $C_{15}H_{15}NO$ (225.29): calcd. C 79.97, H 6.71, N 6.22; found C 79.90, H 6.65, N 6.25.

General Method for the Condensation between 2-Lithiated 1,3-Benzoxathiole 3(2*H*)-Oxide and Electrophiles: A solution of compound **1** (3.47 mmol) in dry THF (12 mL) was added dropwise to a stirred solution of LDA (8.7 mmol) in dry THF (15 mL) cooled to temperature in between −78 and −20 °C. After stirring for 10 min at the temperatures reported in Table 2 and 4, a solution of the azomethine (4.20 mmol) in dry THF (6 mL) was added. Stirring was continued for a further 15 min and the reaction was quenched with aqueous saturated NH_4Cl, extracted with dichloromethane and dried (Na_2SO_4), filtered and the solvent removed in vacuo. When the addition of diethyl ether or diethyl ether/methanol to the crude reaction mixture residue resulted in a single crystalline compound, this was isolated and identified. If a mixture of the less soluble adducts was obtained, further separation was carried out by flash chromatography. Analogous separations were performed to recover the remaining compounds from their mother liquor. In order to increase the reaction diastereoselectivity different temperatures and solvent mixtures were used. Solvents, yields and molar fractions of the diastereomers from the reactions with **3a−g** are summarised in Table 2 and 3.

In this manner the following compounds, as racemic mixtures, were isolated and characterized.

(2*S*,*S*$_S$)-2-[(1*R*)-1-(4-Methoxyphenyl)-1-(4-methoxyphenylamino)-methyl]-1,3-benzoxathiole 3(2*H*)-Oxide (4a): Flash chromatography (7:3, diethyl ether/petroleum ether), white crystals, yield 13%, m.p. 165−165.5 °C. IR (nujol): $\tilde{\nu}$ = 3313 cm^{-1} (NH), 1611, 1585, 1508, 1306, 1236, 1210, 1176, 1124, 1094, 1061, 1031, 829, 751, 725. ^{1}H NMR ([D$_6$]DMSO): δ = 3.69 (s, 3 H, 21-OCH_3), 3.82 (s, 3 H, 22-OCH_3), 4.64 (t, ^3J = 10.5 Hz, 1 H, 8-H), 5.79 (d, ^3J = 9.6 Hz, 1 H, 7-H), 6.45 (d, ^3J = 10.3 Hz, 1 H, NH), 6.69−6.77 (m, 4 H, 16-H, 17-H, 19-H, 20-H), 6.96 (d, ^3J = 8.4 Hz, 2 H, 11-H, 13-H), 7.26(d, ^3J = 7.4 Hz, 1 H, 2-H), 7.32 (t, ^3J = 7.5 Hz, 1 H, 4-H),

7.46 (d, ^3J = 8.4 Hz, 2 H, 10-H, 14-H), 7.71 (t, ^3J = 7.4 Hz, 1 H, 3-H), 8.10 (d, ^3J = 7.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 55.1 (q, O*C*H$_3$), 55.3 (q, O*C*H$_3$), 55.3 (d, C-8), 107.8 (d, C-7), 113.2 (d, C-2), 113.8 (d, C-16, C-20), 114.5 (d, C-11, C-13), 115.1 (d, C-17, C-19), 123.1 (d, C-4), 128.1 (d, C-5), 128.9 (d, C-10, C-14), 129.1 (s, C-6), 131.2 (s, C-9), 135.0 (d, C-3), 140.5 (s, C-15), 151.6 (s, C-18), 158.8 (d, C-12), 159.6 (s, C-1) ppm. EI-MS (DIP): *m*/*z* (%) = 395 (2) [M$^+$], 255 (10), 243 (18), 242 (100) [CH$_3$OC$_6$H$_4$CHNHC$_6$H$_4$OCH$_3$]$^+$, 240 (10), 227 (4), 226 (3), 198(4), 137 (7), 134 (14), 122 (17), 121 (18), 109 (2), 108 (3), 107 (5), 92 (5), 77 (12). C$_{22}$H$_{21}$NO$_4$S (395.47): calcd. C 66.82, H 5.35, N 3.54, S 8.11; found C 66.92, H 5.22, N 3.49, S 8.05.

(2*S*,*S*$_S$)-2-[(1*S*)-1-(4-Methoxyphenyl)-1-(4-methoxyphenylamino)-methyl]-1,3-benzoxathiole 3(2*H*)-Oxide (5a): Flash chromatography (7:3, diethyl ether/petroleum ether), white crystals, yield 10%, m.p. 141−142 °C. IR (nujol): ṽ = 3324 cm^{-1} (NH), 1612, 1583, 1516, 1312, 1239, 1176, 1138, 1075, 1029, 829, 755, 725. ^{1}H NMR ([D$_6$]DMSO): δ = 3.69 (s, 3 H, 21-OC*H*$_3$), 3.84 (s, 3 H, 22-OC*H*$_3$), 5.13 (dd, ^3J = 5.2, 9.5 Hz, 1 H, 8-H), 5.81 (d, ^3J = 5.2 Hz, 1 H, 7-H), 6.01 (d, ^3J = 9.5 Hz, 1 H, NH), 6.74 (s, 4 H, 16-H, 17-H, 19-H, 20-H), 6.95 (d, ^3J = 8.4 Hz, 2 H, 11-H, 13-H), 7.25 (d, ^3J = 7.4 Hz, 1 H, 2-H), 7.31 (t, ^3J = 7.5 Hz, 1 H, 4-H), 7.56 (d, ^3J = 8.4 Hz, 2 H, 10-H, 14-H), 7.71 (t, ^3J = 7.4 Hz, 1 H, 3-H), 8.99 (d, ^3J = 7.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 55.1 (d, C-8), 55.2 (q, O*C*H$_3$), 55.3 (q, O*C*H$_3$), 109.3 (d, C-7), 113.2 (d, C-2), 113.9 (d, C-16, C-20), 114.4 (d, C-11, C-13), 115.5 (d, C-17, C-19), 123.1 (d, C-4), 128.1 (d, C-5), 129.0 (d, C-10, C-14), 128.9(s, C-6), 131.2 (s, C-9), 134.8 (d, C-3), 140.3 (s, C-15), 151.5 (s, C-18), 158.9 (d, C-12), 159.7 (s, C-1) ppm. EI-MS (DIP): *m*/*z* (%) = 395 (3) [M$^+$], 378 (2), 255 (9), 243 (18), 242 (100) [CH$_3$OC$_6$H$_4$CHNHC$_6$H$_4$OCH$_3$]$^+$, 240 (15), 227 (5), 226 (6), 198(5), 137 (9), 134 (20), 122 (21), 121 (15), 109 (4), 108 (2), 107 (3), 92 (5), 77 (16). C$_{22}$H$_{21}$NO$_4$S (395.47): calcd. C 66.82, H 5.35, N 3.54, S 8.11; found C 66.95, H 5.26, N 3.45, S 8.10.

(2*R*,*S*$_S$)-2-[(1*S*)-1-(4-Methoxyphenyl)-1-(4-methoxyphenylamino)-methyl]-1,3-benzoxathiole 3(2*H*)-Oxide (7a): Flash chromatography (7:3, diethyl ether/petroleum ether), white crystals, yield 24%, m.p. 195.5−196 °C. IR (nujol): ṽ = 3306 cm^{-1} (NH), 1608, 1511, 1231, 1178, 1030, 829, 766, 724. ^{1}H NMR ([D$_6$]DMSO): δ = 3.71 (s, 3 H, 21-OC*H*$_3$), 3.76 (s, 3 H, 22-OC*H*$_3$), 4.99 (t, ^3J = 10.5 Hz, 1 H, 8-H), 5.44 (d, ^3J = 10.5 Hz, 1 H, 7-H), 6.46 (d, ^3J = 10.5 Hz, 1 H, NH), 6.78 (s, 4 H, 16-H, 17-H, 19-H, 20-H), 7.04 (d, ^3J = 7.5 Hz, 2 H, 11-H, 13-H), 7.27 (d, ^3J = 7.8 Hz, 1 H, 2-H), 7.31 (t, ^3J = 7.8 Hz, 1 H, 4-H), 7.63 (d, ^3J = 7.5 Hz, 2 H, 10-H, 14-H), 7.70 (t, ^3J = 7.8 Hz, 1 H, 3-H), 8.18 (d, ^3J = 7.8 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 53.2 (d, C-8), 55.1 (q, O*C*H$_3$), 55.3 (q, O*C*H$_3$), 100.2 (d, C-7), 113.2 (d, C-2), 113.9 (d, C-16, C-20), 114.5 (d, C-11, C-13), 115.6 (d, C-17, C-19), 123.1 (d, C-4), 128.1 (d, C-5), 129.4 (d, C-10, C-14), 130.7 (s, C-6), 130.9 (s, C-9), 134.8 (d, C-3), 140.3 (s, C-15), 151.8 (s, C-18), 158.8 (d, C-12), 159.8 (s, C-1) ppm. EI-MS (DIP): *m*/*z* (%) = 395 (4) [M$^+$], 378 (4), 255 (6), 243 (16), 242 (100) [CH$_3$OC$_6$H$_4$CHNHC$_6$H$_4$OCH$_3$]$^+$, 241 (20), 240 (30) [CH$_3$OC$_6$H$_4$CNC$_6$H$_4$OCH$_3$]$^+$, 227 (12), 226 (20), 199(5), 171 (7), 155 (9), 154 (12), 137 (24), 136 (7), 134 (26), 122 (21), 121 (24), 109 (5), 108 (9), 107 (10), 92 (16), 77 (36). C$_{22}$H$_{21}$NO$_4$S (395.47): calcd. C 66.82, H 5.35, N 3.54, S 8.11; found C 66.92, H 5.22, N 3.49, S 8.05.

(2*R*,*S*$_S$)-2-[(1*S*)-1-(4-Methylphenyl)-1-(4-methoxyphenylamino)-methyl]-1,3-benzoxathiole 3(2*H*)-Oxide (7b): Flash chromatography (7:3, diethyl ether/petroleum ether), white crystals, yield 4%, m.p. 184−185 °C. IR (nujol): ṽ: the NH absorption is of very low intensity and therefore not detectable,[17] 1586 cm^{-1}, 1306, 1274, 1220, 1157, 1125, 1040, 998, 825, 774, 694. ^{1}H NMR ([D$_6$]DMSO): δ = 2.39 (s, 3 H, C*H*$_3$), 3.71 (s, 3 H, OC*H*$_3$), 4.98 (t, ^3J = 10.8 Hz, 1 H, 8-H), 5.44 (d, ^3J = 10.2 Hz, 1 H, 7-H), 6.48 (d, ^3J = 11.1 Hz, 1 H, NH), 6.77 (s, 4 H, 16-H, 17-H, 19-H, 20-H), 7.26−7.31 (m, 3 H, 2-H, 11-H, 13-H), 7.33 (t, ^3J = 7.2 Hz, 1 H, 4-H), 7.58 (d, ^3J = 7.5 Hz, 2 H, 10-H, 14-H), 7.69 (t, ^3J = 8.1 Hz, 1 H, 4-H), 8.18 (d, ^3J = 7.2 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 20.8 (q, *C*H$_3$), 53.5 (d, C-8), 55.3 (q, O*C*H$_3$), 100.2 (d, C-7), 113.2 (d, C-2), 114.5 (d, C-16, C-20), 115.6 (d, C-17, C-19), 123.1 (d, C-4), 128.2 (d, C-5), 128.2 (d, C-11,C-13), 128.6 (d, C-10, C-14), 130.6 (s, C-6), 134.9 (d, C-3), 136.1 (s, C-9), 136.9 (s, C-12), 140.3 (s, C-15), 151.8 (s, C-18), 159.8 (s, C-1) ppm. EI-MS (DIP): *m*/*z* (%) = 379 (23) [M$^+$], 363 (5), 362 (16), 239 (9), 238 (6), 227 (17), 226 (100) [CH$_3$C$_6$H$_4$CHNHC$_6$H$_4$OCH$_3$]$^+$, 225 (11), 224 (35), 137 (57), 134 (14), 122 (12), 121 (11), 109 (8), 108 (10), 107 (6), 105 (10), 97 (15), 96 (22), 95 (9), 92 (12), 91 (2), 77 (25). C$_{22}$H$_{21}$NO$_3$S (379.47): calcd. C 69.63, H 5.58, N 3.69, S 8.45; found C 69.52, H 5.62, N 3.81, S 8.50.

(2*S*,*S*$_S$)-2-[(1*R*)-1-(4-Methoxyphenylamino)-1-phenylmethyl]-1,3-benzoxathiole 3(2*H*)-Oxide (4c): Flash chromatography (7:3, diethyl ether/petroleum ether), white crystals, yield 43%, m.p. 167−168 °C. IR (nujol): ṽ = 3280 cm^{-1} (NH),1585, 1530, 1509, 1236, 1221, 1035, 843, 761, 701. ^{1}H NMR ([D$_6$]DMSO: δ = 3.70 (s, 3 H, OC*H*$_3$), 4.71 (t, ^3J = 9.9 Hz, 1 H, 8-H), 5.84 (d, ^3J = 9.6 Hz, 1 H, 7-H), 6.54 (d, ^3J = 10.5 Hz, 1 H, NH), 6.75 (s, 4 H, 16-H, 17-H, 19-H, 20-H), 7.26 (d, ^3J = 8.7 Hz, 1 H, 2-H), 7.30−7.36 (m, 2 H, 4-H,12-H), 7.41 (t, ^3J = 7.2 Hz, 2 H, 11-H, 13-H), 7.56 (d, ^3J = 7.2 Hz, 2 H, 10-H, 14-H), 7.72 (t, ^3J = 8.7 Hz, 1 H, 3-H), 8.11 (d, ^3J = 7.8 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 55.2 (d, C-8), 55.8 (q, O*C*H$_3$), 107.7 (d, C-7), 113.1 (d, C-2), 114.5 (d, C-16, C-20), 115.0 (d, C-17, C-19), 123.0 (d, C-4), 127.7 (d, C-5), 127.8 (dm, C-11,C-13), 128.1 (d, C-12), 128.3 (d, C-10, C-14), 129.1 (s, C-6), 134.9 (d, C-3), 139.4 (s, C-9), 140.4 (s, C-15), 151.6 (s, C-18), 159.6 (s, C-1) ppm. EI-MS (DIP): *m*/*z* (%) = 365 (5) [M$^+$], 349 (2), 347 (3), 226 (4), 225 (9), 224 (4), 223 (4), 213 (17), 212 (100) [C$_6$H$_5$CHNHC$_6$H$_4$OCH$_3$]$^+$, 211 (16), 210 (28), 197 (6), 196 (14), 180 (4), 168 (7), 167 (7), 137 (7), 134 (9), 123 (5), 122 (5), 108 (10), 92 (9), 91 (11), 77 (20). C$_{21}$H$_{19}$NO$_3$S (365.45): calcd. C 69.02, H 5.24, N 3.83, S 8.77; found C 69.10, H 5.10, N 3.90, S 8.55.

(2*S*,*S*$_S$)-2-[(1*S*)-1-(4-Methoxyphenylamino)-1-phenylmethyl]-1,3-benzoxathiole 3(2*H*)-Oxide (5c): Flash chromatography (7:3, diethyl ether/petroleum ether), white crystals, yield 31%, m.p. 123−124 °C. IR (nujol): ṽ = 3297 cm^{-1} (NH), 1589, 1534, 1509, 1239, 1228, 1034, 825, 763, 75. ^{1}H NMR ([D$_6$]DMSO): δ = 3.73 (s, 3 H, OC*H*$_3$), 5.24 (dd, ^3J = 9.6, 5.4 Hz, 1 H, 8-H), 5.84 (d, ^3J = 5.4 Hz, 1 H, 7-H), 6.03 (d, ^3J = 9.6 Hz, 1 H, NH), 6.75 (s, 4 H, 16-H, 17-H, 19-H, 20-H), 7.26 (t, ^3J = 7.5 Hz, 1 H, 4-H), 7.34−7.38 (m, 2 H, 2-H,12-H), 7.41 (t, ^3J = 7.2 Hz, 2 H, 11-H, 13-H), 7.65 (d, ^3J = 7.2 Hz, 2 H, 10-H, 14-H), 7.70 (t, ^3J = 7.8 Hz, 1 H, 3-H), 7.98 (d, ^3J = 7.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 55.2 (d, C-8), 55.8 (q, O*C*H$_3$), 109.5 (d, C-7), 113.2 (d, C-2), 114.4 (d, C-16, C-20), 115.1 (d, C-17, C-19), 122.6 (d, C-4), 127.4 (d, C-5), 127.7 (d, C-12), 127.8 (dm, C-11,C-13), 128.2 (d, C-10, C-14), 129.0 (s, C-6), 134.7 (d, C-3), 138.4 (s, C-9), 140.9 (s, C-15), 151.6 (s, C-18), 160.2 (s, C-1) ppm. EI-MS (DIP): *m*/*z* (%) = 365 (2) [M$^+$], 349 (10), 348 (31), 347 (100) [M$^+$ − H$_2$O], 332 (6), 243 (13), 229 (7), 223 (18), 213 (7), 212 (42) [C$_6$H$_5$CHNHC$_6$H$_4$OCH$_3$]$^+$, 211 (47), 210 (40), 197 (14), 196 (46), 180 (5), 168 (7), 167 (19), 141 (5), 139 (3),137 (7), 134 (7), 115 (5), 108 (5), 107 (5), 104 (8), 92 (12), 77 (26). C$_{21}$H$_{19}$NO$_3$S (365.45): calcd. C 69.02, H 5.24, N 3.83, S 8.77; found C 69.05, H 5.15, N 3.79, S 8.65.

(2*R*,S_S)-2-[(1*R*)-1-(4-Methoxyphenylamino)-1-phenylmethyl]-1,3-benzoxathiole 3(2*H*)-Oxide (6c): Flash chromatography (7:3, diethyl ether/petroleum ether), white crystals, yield 10%, m.p. 176−177 °C. IR (nujol): $\tilde{\nu}$ = 3295 cm^{-1} (NH),1589, 1529, 1503, 1247, 1221, 1042, 841, 763, 703. ^1H NMR ([D$_6$]DMSO): δ = 3.71 (s, 3 H, OCH_3), 5.07 (br. t, ^3J = 10.2, 8.7 Hz, 1 H, 8-H), 5.52 (d, ^3J = 10.2 Hz, 1 H, 7-H), 6.46 (d, ^3J = 8.7 Hz, 1 H, NH), 6.71−6.80 (m, 4 H, 16-H, 17-H, 19-H, 20-H), 7.34 (t, ^3J = 7.5 Hz, 1 H, 4-H), 7.44−7.54 (m, 4 H, 2-H,11-H,12-H,13-H), 7.74−7.82 (m, 3 H, 10-H, 14-H, 3-H), 8.09 (d, ^3J = 7.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 55.2 (d, C-8), 55.3 (q, OCH_3), 101.0 (d, C-7), 113.2 (d, C-2), 114.2 (d, C-16, C-20), 114.6 (d, C-17, C-19), 123.1 (d, C-4), 127.8 (d, C-5), 128.2 (d, C-12), 128.7 (m, C-11,C-13, C-10, C-14), 130.7 (s, C-6), 135.0 (d, C-3), 139.3 (s, C-9), 141.3 (s, C-15), 151.2 (s, C-18), 159.6 (s, C-1) ppm. EI-MS (DIP): *m*/*z* (%) = 365 (15) [M^+], 349 (7), 348 (22), 347 (25) [$M^+ - H_2O$], 332 (6), 243 (3), 225 (17), 223 (13), 213 (10), 212 (56) [$C_6H_5CHNHC_6H_4OCH_3]^+$, 211 (22), 210 (100), [$C_6H_5CNC_6H_4OCH_3]^+$,197 (5), 196 (5), 180 (6), 168 (6), 167 (13), 137 (24), 134 (6), 122 (9), 109 (6), 108 (6), 107 (6), 104 (7), 92 (16), 77 (34). $C_{21}H_{19}NO_3S$ (365.45): calcd. C 69.02, H 5.24, N 3.83, S 8.77; found C 69.10, H 5.20, N 3.85, S 8.80.

(2*R*,S_S)-2-[(1*S*)-1-(4-Methoxyphenylamino)-1-phenylmethyl]-1,3-benzoxathiole 3(2*H*)-Oxide (7c): Flash chromatography (7:3, diethyl ether/petroleum ether), white crystals, yield 53%, m.p. 223−224 °C. IR (nujol): $\tilde{\nu}$ = 3320 cm^{-1} (NH), 1588, 1531, 1509, 1296, 1249, 1216, 1033, 1010, 819, 763, 698. ^1H NMR ([D$_6$]DMSO): δ = 3.71 (s, 3 H, OCH_3), 5.04 (t, ^3J = 10.9 Hz, 1 H, 8-H), 5.54 (d, ^3J = 10.5 Hz, 1 H, 7-H), 6.66 (d, ^3J = 11.4 Hz, 1 H, NH), 6.77 (s, 4 H, 16-H, 17-H, 19-H, 20-H), 7.27 (d, ^3J = 8.1 Hz, 1 H, 2-H), 7.33 (t, ^3J = 7.5 Hz, 1 H, 4-H), 7.40−7.50 (m, 3 H, 11-H,12-H,13-H), 7.67−7.76 (m, 3 H, 10-H, 14-H, 3-H), 8.19 (d, ^3J = 7.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 53.8 (d, C-8), 55.3 (q, OCH_3), 100.1 (d, C-7), 113.1 (d, C-2), 114.5 (d, C-16, C-20), 115.5 (d, C-17, C-19), 123.1 (d, C-4), 127.7 (d, C-5), 128.1 (d, C-12), 128.3 (dm, C-11, C-13), 128.4 (d, C-10, C-14), 130.6 (s, C-6), 134.8 (d, C-3), 139.2 (s, C-9), 140.3 (s, C-15), 151.7 (s, C-18), 159.8 (s, C-1) ppm. EI-MS (DIP): *m*/*z* (%) = 365 (5) [M^+], 348 (4), 240 (4), 225 (7), 224 (5), 223 (4), 213 (18), 212 (100) [$C_6H_5CHNHC_6H_4OCH_3]^+$, 210 (18), [$C_6H_5CNC_6H_4OCH_3]^+$,197 (5), 193 (4), 183 (4), 180 (5), 168 (9), 167 (7), 165 (4), 152 (4),137 (35), 136 (7), 135 (11), 134 (17), 122 (18), 109 (9), 108 (8), 107 (11), 105 (21), 104 (12), 95 (11), 92 (15), 91 (15), 77 (46). $C_{21}H_{19}NO_3S$ (365.45): calcd. C 69.02, H 5.24, N 3.83, S 8.77; found C 69.12, H 5.22, N 3.81, S 8.73

(2*S*,S_S)-2-[(1*R*)-1-(4-Fluorophenyl)-1-(4-methoxyphenylamino)-methyl]-1,3-benzoxathiole 3(2*H*)-Oxide (4d): Flash chromatography (7:3, diethyl ether/petroleum ether), white crystals, yield 30%, m.p. 175−177 °C. IR (nujol): $\tilde{\nu}$ = 3310 cm^{-1} (NH), 1586, 1509, 1236, 1157, 1123, 1033, 821, 755, 723. ^1H NMR ([D$_6$]DMSO): δ = 3.71 (s, 3 H, OCH_3), 4.75 (t, ^3J = 10.6 Hz, 1 H, 8-H), 5.82 (d, ^3J = 10.2 Hz, 1 H, 7-H), 6.54 (d, ^3J = 10.8 Hz, 1 H, NH), 6.76 (s, 4 H, 16-H, 17-H, 19-H, 20-H), 7.08 (d, ^3J = 8.7 Hz, 1 H, 2-H), 7.20−7.28 (m, 3 H, 4-H, 11-H, 13-H), 7.68−7.75 (m, 3 H, 3-H, 10-H, 14-H), 8.10 (d, ^3J = 7.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 55.1 (d, C-8), 55.2 (q, OCH_3), 107.2 (d, C-7), 113.1 (d, C-2), 114.5 (d, C-16, C-20), 114.7 (dd, $^2J_{C,F}$ = 28.5 Hz, C-11, C-13), 115.0 (d, C-17, C-19), 123.0 (d, C-4), 128.1 (d, C-5), 129.7 (dd, $^3J_{C,F}$ = 7.8 Hz, C-10, C-14), 129.9 (s, C-6), 134.9 (d, C-3), 135.56 (s, C-9), 140.2 (s, C-15), 151.6 (s, C-18), 159.5 (s, C-1), 161.7 (dm, $^1J_{C,F}$ = 242.8 Hz, C-12) ppm. EI-MS (DIP): *m*/*z* (%) = 383 (7) [M^+], 367 (1), 366 (2), 243 (8), 242 (2), 231 (15), 230 (100) [$FC_6H_4CHNHC_6H_4OCH_3]^+$, 228 (9), 215 (4), 214 (2), 186 (5), 185 (2), 137 (7), 134 (5), 122 (8), 109 (6), 108 (3), 107 (4), 92 (4), 77 (5). $C_{21}H_{18}FNO_3S$ (383.43): calcd. C 65.79, H 4.73, F 4.95, N 3.65, S 8.36; found C 65.69, H 4.77, F 4.80, N 3.72, S 8.40.

(2*S*,S_S)-2-[(1*S*)-1-(4-Fluorophenyl)-1-(4-methoxyphenylamino)-methyl]-1,3-benzoxathiole 3(2*H*)-Oxide (5d): Flash chromatography (7:3, diethyl ether/petroleum ether), white crystals, yield 35%, m.p. 172−173 °C. IR (nujol): $\tilde{\nu}$ = 3329 cm^{-1} (NH), 1600, 1583, 1505, 1414, 1308, 1261, 1240, 1217, 1152, 1124, 1065, 1030, 994, 853, 835, 819, 783, 756, 721. ^1H NMR ([D$_6$]DMSO): δ = 3.70 (s, 3 H, OCH_3), 5.30 (dd, ^3J = 5.7, 9.9 Hz, 1 H, 8-H), 5.85 (d, ^3J = 5.7 Hz, 1 H, 7-H), 6.05 (d, ^3J = 9.9 Hz, 1 H, NH), 6.75 (s, 4 H, 16-H, 17-H, 19-H, 20-H), 7.20−7.29 (m, 3 H, 4-H, 11-H, 13-H), 7.35 (d, ^3J = 8.1 Hz, 1 H, 2-H), 7.67−7.73 (m, 3 H, 3-H, 10-H, 14-H), 7.98 (d, ^3J = 7.8 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 55.3 (q, OCH_3), 57.2 (d, C-8), 109.3 (d, C-7), 113.3 (d, C-2), 114.5 (d, C-16, C-20), 115.1 (dd, $^2J_{C,F}$ = 21.8 Hz, C-11, C-13), 115.3 (d, C-17, C-19), 122.77 (d, C-4), 127.5 (d, C-5), 129.0 (s, C-6), 130.0 (dd, $^3J_{C,F}$ = 7.3 Hz, C-10, C-14), 134.7 (s, C-9), 134.9 (d, C-3), 140.8 (s, C-15), 151.8 (s, C-18), 160.3 (s, C-1), 161.7 (dm, $^1J_{C,F}$ = 242.8 Hz, C-12) ppm. EI-MS (DIP): *m*/*z* (%) = 383 (3) [M^+], 367 (1), 366 (1), 365 (2), 243 (10), 242 (5), 231 (16), 230 (100) [$FC_6H_4CHNHC_6H_4OCH_3]^+$, 229 (10), 228 (21), 214 (6), 186 (7), 185 (4), 137 (10), 134 (10), 122 (14), 109 (12), 108 (7), 107 (7), 92 (9), 77 (11). $C_{21}H_{18}FNO_3S$ (383.43): calcd. C 65.79, H 4.73, F 4.95, N 3.65, S 8.36; found C 65.70, H 4.77, F 4.90, N 3.60, S 8.28.

(2*R*,S_S)-2-[(1*S*)-1-(4-Fluorophenyl)-1-(4-methoxyphenylamino)-methyl]-1,3-benzoxathiole 3(2*H*)-Oxide (7d): Flash chromatography (7:3, diethyl ether/petroleum ether), white crystals, yield 34%, m.p. 194−195 °C. IR (nujol): $\tilde{\nu}$ = 3318 cm^{-1} (NH),1605, 1589, 1529, 1510, 1294, 1251, 1237, 1217, 1181, 1125, 1106, 1035, 1019, 830, 797, 762, 724. ^1H NMR ([D$_6$]DMSO): δ = 3.72 (s, 3 H, OCH_3), 5.08 (t, ^3J = 10.2 Hz, 1 H, 8-H), 5.48 (d, ^3J = 9.9 Hz, 1 H, 7-H), 6.54 (d, ^3J = 10.8 Hz, 1 H, NH), 6.80 (s, 4 H, 16-H, 17-H, 19-H, 20-H), 7.27−7.34 (m, 4 H, 2-H, 4-H, 11-H, 13-H), 7.67−7.77 (m, 3 H, 3-H, 10-H, 14-H), 8.19 (d, ^3J = 7.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 53.1 (d, C-8), 55.2 (q, OCH_3), 99.9 (d, C-7), 113.2 (d, C-2), 114.5 (d, C-16, C-20), 115.2 (dd, $^2J_{C,F}$ = 21.3 Hz, C-11, C-13), 115.9 (d, C-17, C-19), 123.1 (d, C-4), 128.1 (d, C-5), 130.2 (dd, $^3J_{C,F}$ = 7.8 Hz, C-10, C-14), 130.6 (s, C-6), 134.8 (d, C-3), 135.3 (s, C-9), 140.1 (s, C-15), 151.9 (s, C-18), 159.7 (s, C-1), 161.7 (dm, $^1J_{C,F}$ = 240.9 Hz, C-12) ppm. EI-MS (DIP): *m*/*z* (%) = 383 (30) [M^+], 367 (7), 366 (28), 365 (4), 243 (12), 242 (8), 231 (16), 230 (100) [$FC_6H_4CHNHC_6H_4OCH_3]^+$, 229 (18), 228 (66), 214 (11), 186 (7), 185 (7), 137 (30), 134 (9), 122 (16), 109 (15), 108 (10), 107 (10), 92 (9), 77 (17). $C_{21}H_{18}FNO_3S$ (383.43): calcd. C 65.79, H 4.73, F 4.95, N 3.65, S 8.36; found C 65.90, H 4.70, F 4.85, N 3.70, S 8.30.

(2*S*,S_S)-2-[(1*R*)-1-(4-Methoxyphenylamino)-1-(4-trifluoromethylphenyl)methyl]-1,3-benzoxathiole 3(2*H*)-Oxide (4e): Flash chromatography (7:3, diethyl ether/petroleum ether), white crystals, yield 49%, m.p. 184−185 °C. IR (nujol): $\tilde{\nu}$ = 3309 cm^{-1} (NH),1619, 1589, 1559, 1511, 1328, 1249, 1216, 1170, 1125, 1067, 1033, 1017, 827, 760. ^1H NMR ([D$_6$]DMSO): δ = 3.69 (s, 3 H, OCH_3), 4.87 (t, ^3J = 10.3 Hz, 1 H, 8-H), 5.85 (d, ^3J = 9.9 Hz, 1 H, 7-H), 6.70 (d, ^3J = 10.8 Hz, 1 H, NH), 6.74 (s, 4 H, 16-H, 17-H, 19-H, 20-H), 7.28 (d, ^3J = 8.4 Hz, 1 H, 2-H), 7.34 (t, ^3J = 7.5 Hz, 1 H, 4-H), 7.73 (t, ^3J = 8.4 Hz, 1 H, 3-H), 7.79 (s, 4 H, 10-H, 11-H, 13-H, 14-H), 8.13 (d, ^3J = 7.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 55.2 (q, OCH_3), 65.4 (d, C-8), 107.1 (d, C-7), 113.3 (d, C-2), 114.6 (d, C-16, C-20), 115.0 (d, C-17, C-19), 123.2 (d, C-4), 124.3 (qt, $^1J_{C,F}$ = 270.7 Hz, CF_3), 125.3 (dq, $^3J_{C,F}$ =

3.7 Hz, C-11, C-13), 128.2 (d, C-5), 128.3 (dq, $^2J_{C,F}$ = 31.6 Hz, C-12), 128.7 (d, C-10, C-14), 129.0 (s, C-6), 135.1 (d, C-3), 140.0 (s, C-15), 144.5 (s, C-9), 151.8 (s, C-18), 159.5 (s, C-1) ppm. EI-MS (DIP): *m*/*z* (%) = 433 (4) [M$^+$], 416(1), 415(2), 293 (5), 292 (2), 291 (1), 281 (17), 280 (100) [$CF_3C_6H_4CHNHC_6H_4OCH_3$]$^+$, 279 (10), 278 (15), 265 (5), 264 (7), 236 (4), 137 (22), 134 (6), 122 (14), 109 (7), 108 (12), 92 (7), 77 (18). $C_{22}H_{18}F_3NO_3S$ (433.44): calcd. C 60.96, H 4.19, F 13.15, N 3.23, S 7.40; found C 61.00, H 4.10, F 13.09, N 3.30, S 7.30.

(2*S*,*S*$_S$)-2-[(1*S*)-1-(4-Methoxyphenylamino)-1-(4-trifluoromethylphenyl)methyl]-1,3-benzoxathiole 3(2*H*)-Oxide (5e): Flash chromatography (7:3, diethyl ether/petroleum ether), white crystals, yield 31%, m.p. 127−128 °C. IR (nujol): $\tilde{\nu}$ = 3307 cm^{-1} (NH), 1587, 1512, 1326, 1238, 1166, 1124, 1067, 1037, 824, 754. ^{1}H NMR ([D$_6$]DMSO): δ = 3.69 (s, 3 H, OC*H*$_3$), 5.52 (dd, ^3J = 5.1, 10.2 Hz, 1 H, 8-H), 5.90 (d, ^3J = 5.1 Hz, 1 H, 7-H), 6.10 (d, ^3J = 10.2 Hz, 1 H, NH), 6.75 (s, 4 H, 16-H, 17-H, 19-H, 20-H), 7.27 (t, ^3J = 7.8 Hz, 1 H, 4-H), 7.37 (d, ^3J = 7.8 Hz, 1 H, 2-H), 7.71 (t, ^3J = 7.8 Hz, 1 H, 3-H), 7.79 (d, ^3J = 8.1 Hz, 2 H, 10-H, 14-H), 7.90 (d, ^3J = 8.1 Hz, 2 H, 11-H, 13-H), 7.99 (d, ^3J = 7.8 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 55.2 (q, O*C*H$_3$), 57.5 (d, C-8), 109.0 (d, C-7), 113.4 (d, C-2), 114.5 (d, C-16, C-20), 115.3 (d, C-17, C-19), 122.8 (d, C-4), 124.2 (qt, $^1J_{C,F}$ = 270.1 Hz, CF_3), 125.2 (dq, $^3J_{C,F}$ = 3.7 Hz, C-11, C-13), 127.5 (d, C-5), 128.4 (dq, $^2J_{C,F}$ = 31.4 Hz, C-12), 128.8 (d, C-10, C-14), 129.1 (s, C-6), 134.8 (d, C-3), 140.6 (s, C-15), 143.6 (s, C-9), 151.8 (s, C-18), 160.3 (s, C-1) ppm. EI-MS (DIP): *m*/*z* (%) = 433 (5) [M$^+$], 416(1), 415(1), 294 (2), 293 (7), 292 (5), 291 (3), 281 (17), 280 (100) [$CF_3C_6H_4CHNHC_6H_4OCH_3$]$^+$, 278 (24), 265 (5), 264 (5), 236 (6), 137 (22), 134 (8), 123 (22), 122 (20), 109 (8), 108 (30), 107 (8), 92 (12), 77 (19). $C_{22}H_{18}F_3NO_3S$ (433.44): calcd. C 60.96, H 4.19, F 13.15, N 3.23, S 7.40; found C 61.10, H 4.12, F 13.17, N 3.26, S 7.35.

(2*R*,*S*$_S$)-2-[(1*S*)-1-(4-Methoxyphenylamino)-1-(4-trifluoromethylphenyl)methyl]-1,3-benzoxathiole 3(2*H*)-Oxide (7e): Flash chromatography (7:3, diethyl ether/petroleum ether), white crystals, yield 34%, m.p. 188−189 °C. IR (nujol): $\tilde{\nu}$ = 3308 cm^{-1} (NH), 1588, 1527, 1511, 1329, 1249, 1215, 1170, 1067, 1033, 1016, 834, 760. ^{1}H NMR ([D$_6$]DMSO): δ = 3.72 (s, 3 H, OC*H*$_3$), 5.16 (t, ^3J = 10.7 Hz, 1 H, 8-H), 5.53 (d, ^3J = 10.2 Hz, 1 H, 7-H), 6.68 (d, ^3J = 11.1 Hz, 1 H, NH), 6.80 (s, 4 H, 16-H, 17-H, 19-H, 20-H), 7.29 (d, ^3J = 8.4 Hz, 1 H, 2-H), 7.35 (t, ^3J = 7.5 Hz, 1 H, 4-H), 7.70 (t, ^3J = 8.4 Hz, 1 H, 3-H), 7.87 (d, ^3J = 8.1 Hz, 2 H, 10-H, 14-H), 7.97 (d, ^3J = 8.1 Hz, 2 H, 11-H, 13-H), 8.20 (d, ^3J = 7.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 53.4 (d, C-8), 55.2 (q, O*C*H$_3$), 99.6 (d, C-7), 113.2 (d, C-2), 114.6 (d, C-16, C-20), 115.5 (d, C-17, C-19), 123.2 (d, C-4),), 125.3 (dq, $^3J_{C,F}$ = 3.7 Hz, C-11, C-13), 127.9 (qt, $^1J_{C,F}$ = 272.5 Hz, CF_3), 128.1 (d, C-5),), 128.4 (dq, $^2J_{C,F}$ = 31.5 Hz, C-12), 129.1 (d, C-10, C-14), 130.5 (s, C-6), 134.9 (d, C-3), 139.8 (s, C-15), 144.1 (s, C-9), 152.0 (s, C-18), 159.7 (s, C-1) ppm. EI-MS (DIP): *m*/*z* (%) = 433 (12) [M$^+$], 416(7), 293 (14), 292 (9), 291 (6), 281 (17), 280 (100) [$CF_3C_6H_4CHNHC_6H_4OCH_3$]$^+$, 278 (31), 265 (5), 264 (5), 236 (5), 137 (17), 122 (7), 109 (3), 108 (4), 92 (6), 77 (13). $C_{22}H_{18}F_3NO_3S$ (433.44): calcd. C 60.96, H 4.19, F 13.15, N 3.23, S 7.40; found C 61.00, H 4.10, F 13.09, N 3.30, S 7.30.

(2*S*,*S*$_S$)-2-[(1*R*)-1-Furyl-1-(4-methoxyphenylamino)methyl]-1,3-benzoxathiole 3(2*H*)-Oxide (4f): Flash chromatography (7:3, diethyl ether/petroleum ether), white crystals, yield 15%, m.p. 109−109.5 °C. IR (nujol): $\tilde{\nu}$ = 3281 cm^{-1} (NH), 1586, 1510, 1281, 1241, 1067, 1030, 820, 746. ^{1}H NMR ([D$_6$]DMSO): δ = 3.73 (s, 3 H, OC*H*$_3$), 4.93 (t, ^3J = 9.6 Hz, 1 H, 8-H), 5.75 (d, ^3J = 8.4 Hz, 1 H, 7-H), 6.19 (d, ^3J = 10.5 Hz, 1 H, NH), 6.46 (br. s, 1 H, 12-H), 6.50 (d, ^3J = 3.0 Hz, 1 H, 11-H), 6.79 (s, 4 H, 16-H, 17-H, 19-H, 20-H), 7.29−7.34 (m, 2 H, 2-H, 4-H), 7.67 (br. s, 1 H, 10-H), 7.70 (t, ^3J = 8.1 Hz, 1 H, 3-H), 8.09 (d, ^3J = 8.1 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 50.9 (d, C-8), 55.3 (q, O*C*H$_3$), 106.4 (d, C-7), 109.6 (s, C-10), 110.5 (s, C-11), 113.1 (d, C-2), 114.5 (d, C-16, C-20), 115.1 (d, C-17, C-19), 123.0 (d, C-4), 127.9 (d, C-5), 128.9 (s, C-6), 134.9 (d, C-3), 140.4 (s, C-15), 142.8 (d, C-12), 151.6 (s, C-18), 151.9 (s, C-9), 159.8 (s, C-1) ppm. EI-MS (DIP): *m*/*z* (%) = 355 (1) [M$^+$], 215 (8), 214 (2), 203 (14), 202 (100) [$(C_4H_3O)CHNHC_6H_4OCH_3$]$^+$, 200 (4), [$C_6H_5CNC_6H_4OCH_3$]$^+$, 186 (5), 186 (7), 137 (9), 134 (11), 122 (23), 109 (5), 108 (4), 107 (5), 96 (5), 95 (7), 92 (7), 77 (14). $C_{19}H_{17}NO_4S$ (355.40): calcd. C 64.21, H 4.82, N 3.94, S 9.02; found C 64.28, H 4.85, N 3.87, S 9.05.

(2*R*,*S*$_S$)-2-[(1*S*)-1-Furyl-1-(4-methoxyphenylamino)methyl]-1,3-benzoxathiole 3(2*H*)-Oxide(7f): Flash chromatography (3:2, diethyl ether/petroleum ether), white crystals, yield 35%, m.p. 183.6−184.5 °C. IR (nujol): $\tilde{\nu}$ = 3277 cm^{-1} (NH), 1586, 1530, 1510, 1301, 1282, 1236, 1220, 1146, 1118, 1081, 1035, 852, 817, 759, 740. ^{1}H NMR ([D$_6$]DMSO): δ = 3.75 (s, 3 H, OC*H*$_3$), 5.14 (t, ^3J = 10.6 Hz, 1 H, 8-H), 5.59 (d, ^3J = 10.2 Hz, 1 H, 7-H), 6.28 (d, ^3J = 11.1 Hz, 1 H, NH), 6.55 (br. s, 1 H, 12-H), 6.70 (d, ^3J = 3.0 Hz, 1 H, 11-H), 6.81- 6.88 (m, 4 H, 16-H, 17-H, 19-H, 20-H), 7.33 −7.37 (m, 2 H, 2-H, 4-H), 7.25 (t, ^3J = 7.2 Hz, 1 H, 3-H), 7.77 (br. s, 1 H, 10-H), 8.19 (d, ^3J = 8.1 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 48.2 (d, C-8), 55.3 (q, O*C*H$_3$), 98.5 (d, C-7), 109.0 (s, C-10), 110.6 (s, C-11), 113.2 (d, C-2), 114.5 (d, C-16, C-20), 115.7 (d, C-17, C-19), 123.1 (d, C-4), 128.0 (d, C-5), 130.5 (s, C-6), 134.9 (d, C-3), 140.1 (s, C-15), 142.8 (d, C-12), 152.0 (s, C-18), 152.2 (s, C-9), 159.8 (s, C-1) ppm. EI-MS (DIP): *m*/*z* (%) = 355 (14) [M$^+$], 338 (18), 215(12), 214 (8), 213 (7), 203 (13), 202 (100) [$(C_4H_3O)CHNHC_6H_4OCH_3$]$^+$, 200 (19), [$C_6H_5CNC_6H_4OCH_3$] $^+$, 186 (7), 137 (23), 134 (12), 122 (23), 109 (7), 108 (6), 107 (6), 96 (8), 95 (9), 92 (9), 77 (17). $C_{19}H_{17}NO_4S$ (355.40): calcd. C 64.21, H 4.82, N 3.94, S 9.02; found C 64.36, H 4.77, N 3.85, S 9.08.

(2*S*,*S*$_S$)-2-[(1*R*)-1-(4-Methoxyphenylamino)-1-thienylmethyl]-1,3-benzoxathiole 3(2*H*)-Oxide (4g): Flash chromatography (7:3, diethyl ether/petroleum ether), white crystals, yield 29%, m.p. 175−177 °C. IR (nujol): $\tilde{\nu}$ = 3287 cm^{-1} (NH), 1584, 1528, 1509, 1280, 1238, 1179, 1124, 1066, 1031, 857, 819, 758, 715. ^{1}H NMR ([D$_6$]DMSO): δ = 3.72 (s, 3 H, OC*H*$_3$), 5.12 (t, ^3J = 9.7 Hz, 1 H, 8-H), 5.81 (d, ^3J = 8.7 Hz, 1 H, 7-H), 6.38 (d, ^3J = 10.5 Hz, 1 H, NH), 6.77 (s, 4 H, 16-H, 17-H, 19-H, 20-H), 7.05 (dd, ^3J = 5.1, 3.6 Hz, 1 H, 11-H), 7.23 (d, ^3J = 3.6 Hz, 1 H, 10-H), 7.29−7.36 (m, 2 H, 2-H, 4-H), 7.50 (d, ^3J = 5.1 Hz, 1 H, 12-H), 7.72 (t, ^3J = 7.8 Hz, 1 H, 3-H), 8.08 (d, ^3J = 7.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 52.3 (d, C-8), 55.3 (q, O*C*H$_3$), 107.5 (d, C-7), 113.2 (d, C-2), 114.5 (d, C-16, C-20), 115.1 (d, C-17, C-19), 123.1 (d, C-4), 125.7 (s, C-12), 126.3 (s, C-10), 126.8 (d, C-11), 128.0 (d, C-5), 129.0 (s, C-6), 135.0 (d, C-3), 140.3 (s, C-15), 142.6 (s, C-9), 151.9 (s, C-18), 159.8 (s, C-1) ppm. EI-MS (DIP): *m*/*z* (%) = 371 (5) [M$^+$], 355 (1), 354 (2), 353 (2), 231 (13), 230 (5), 229 (4), 219 (15), 218 (100) [$(C_4H_3S)CHNHC_6H_4OCH_3$]$^+$, 216 (27), [$(C_4H_3S)CHNHC_6H_4OCH_3$]$^+$, 137 (18), 134 (24), 122 (32), 109 (13), 108 (14), 97 (41), 92 (14), 77 (29). $C_{19}H_{17}NO_3S_2$ (371.46): calcd. C 61.43, H 4.61, N 3.77, S 17.26; found C 61.55, H 4.55, N 3.81, S 17.32.

(2*S*,*S*$_S$)-2-[(1*S*)-1-(4-Methoxyphenylamino)-1-thienylmethyl]-1,3-benzoxathiole 3(2*H*)-Oxide (5g): Flash chromatography (7:3, diethyl ether/petroleum ether), white crystals, yield 17%, m.p. 149−150 °C. IR (nujol): $\tilde{\nu}$ = 3281 cm^{-1} (NH), 1586, 1533, 1520,

1262, 1238, 1168, 1136, 1069, 1054, 847, 835, 772. ^{1}H NMR ([D$_6$]DMSO): δ = 3.72 (s, 3 H, OC*H*$_3$), 5.57 (dd, ^3J = 5.3, 9.4 Hz, 1 H, 8-H), 5.89 (d, ^3J = 5.3 Hz, 1 H, 7-H), 5.96 (d, ^3J = 9.4 Hz, 1 H, NH), 6.76−6.84 (s, 4 H, 16-H, 17-H, 19-H, 20-H), 7.04 (dd, ^3J = 4.8, 3.6 Hz, 1 H, 11-H), 7.29 −7.39 (m, 3 H, 2-H, 4-H, 10-H), 7.45 (d, ^3J = 4.8 Hz, 1 H, 12-H), 7.75 (t, ^3J = 7.2 Hz, 1 H, 3-H), 8.13 (d, ^3J = 7.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 54.3 (d, C-8), 55.3 (q, O*C*H$_3$), 108.9 (d, C-7), 113.2 (d, C-2), 114.4 (d, C-16, C-20), 115.4 (d, C-17, C-19), 123.1 (d, C-4), 125.8 (s, C-12), 126.7 (s, C-10), 126.8 (d, C-11), 128.0 (d, C-5), 130.7 (s, C-6), 134.8 (d, C-3), 141.8 (s, C-15), 142.0 (s, C-9), 151.9 (s, C-18), 159.6 (s, C-1) ppm. EI-MS (DIP): *m*/*z* (%) = 371 (5) [M$^+$], 354 (1), 353 (2), 231 (18), 230 (6), 229 (2), 219 (15), 218 (100) [(C$_4$H$_3$S)CHNHC$_6$H$_4$OCH$_3$]$^+$, 216 (14), [(C$_4$H$_3$S)CHNHC$_6$H$_4$OCH$_3$]$^+$, 137 (9), 134 (18), 122 (19), 109 (5), 108 (6), 97 (6), 97 (19), 92 (6), 77 (10). $C_{19}H_{17}NO_3S_2$ (371.46): calcd. C 61.43, H 4.61, N 3.77, S 17.26; found C 61.51, H 4.58, N 3.75, S 17.30.

(2*R*,*S*$_S$)-2-[(1*S*)-1-(4-Methoxyphenylamino)-1-thienylmethyl]-1,3-benzoxathiole 3(2*H*)-Oxide (7g): Flash chromatography (7:3, diethyl ether/petroleum ether), white crystals, yield 23%, m.p. 187 °C. IR (nujol): $\tilde{\nu}$ = 3287 cm^{-1} (NH), 1585, 1530, 1509, 1289, 1248, 1213, 1173, 1113, 1081, 1030, 851, 821, 797, 760, 722. ^{1}H NMR ([D$_6$]DMSO): δ = 3.73 (s, 3 H, OC*H*$_3$), 5.30 (t, ^3J = 10.2 Hz, 1 H, 8-H), 5.51 (d, ^3J = 9.9 Hz, 1 H, 7-H), 6.46 (d, ^3J = 10.8 Hz, 1 H, NH), 6.82 (s, 4 H, 16-H, 17-H, 19-H, 20-H), 7.13 (dd, ^3J = 7.4, 8.2 Hz, 1 H, 11-H), 7.33 −7.37 (m, 2 H, 2-H, 4-H), 7.41 (d, ^3J = 7.14 Hz, 1 H, 10-H), 7.57 (d, ^3J = 8.2 Hz, 1 H, 12-H), 7.73 (t, ^3J = 8.1 Hz, 1 H, 3-H), 8.19 (d, ^3J = 7.8 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 50.1 (d, C-8), 55.3 (q, O*C*H$_3$), 99.7 (d, C-7), 113.3 (d, C-2), 114.6 (d, C-16, C-20), 115.8 (d, C-17, C-19), 123.3 (d, C-4), 125.8 (s, C-12), 127.0 (s, C-10), 127.0 (d, C-11), 128.2 (d, C-5), 130.6 (s, C-6), 135.1 (d, C-3), 140.1 (s, C-15), 142.7 (s, C-9), 152.2 (s, C-18), 159.9 (s, C-1) ppm. EI-MS (DIP): *m*/*z* (%) = 371 (46) [M$^+$], 355 (17), 354 (70), 353 (8), 231 (14), 230 (9), 229 (12), 219 (15), 218 (100) [(C$_4$H$_3$S)CHNHC$_6$H$_4$OCH$_3$]$^+$, 216 (74), [(C$_4$H$_3$S)CHNHC$_6$H$_4$OCH$_3$]$^+$, 137 (22), 134 (13), 122 (12), 109 (9), 108 (8), 97 (17), 92 (13), 77 (26). $C_{19}H_{17}NO_3S_2$ (371.46): calcd. C 61.43, H 4.61, N 3.77, S 17.26; found C 61.65, H 4.58, N 3.70, S 17.37.

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