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Rapid and efficient synthesis of 2-substituted-tetrahydropyrido[3,4-*b*] quinoxalines using TDAE strategy

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ABSTRACT

We report herein an original and rapid synthesis of substituted 2-tosyl-1,2,3,4-tetrahydropyrido[3,4-*b*]quinoxaline derivatives by TDAE strategy from 2,3-bis(bromomethyl)quinoxaline and *N*-(toluenesulfonyl)benzylimines.

The quinoxaline derivatives show very interesting biological properties,[1] such as antibacterial,[1b] antiviral,[2] anticancer,[3] antifungal, antihelmintic, antileishmanial,[4] anti-HIV,[4] insecticidal, and anti-inflammatory activites,[5] and their interest in medicinal chemistry is far from coming to an end.[6] Many drug candidates bearing quinoxaline core structures are in clinical trials in antiviral,[7] anticancer, antibacterial,[1d] and CNS (central nervous system) therapeutic areas. Among them, the XK469 ((±)-2-[4-(7-chloro-2-quinoxaliny)oxy]phenoxy propionic acid) (Fig. 1) was known as anti neoplastic quinoxaline topoisomerase II inhibitor and possesses antitumor activity especially against murine and human solid tumors.[8–10]

On the other hand, the tetra- and dihydropyrido[3,4-*b*]pyrazine derivatives exhibited interesting biological activity as anticancer agents.[11] In spite of the great interest that could represent combined structures presenting the quinoxaline and the tetrahydropyridine nucleus, few synthesis of tetra-hydropyrido[3,4-*b*] quinoxaline derivatives have been reported.[12]

Since 2003, we have shown that from *o*- and *p*-nitrobenzyl chloride, tetrakis(dimethylamino)ethylene (TDAE)[13] could generate a nitrobenzyl carbanion which is able to react with various electrophiles as aromatic aldehydes, α-ketoester, ketomalonate, α-ketolactam and sulfonimine derivatives.[14] In quinoxaline series, we have reported the reaction of 2-(dibromomethyl)quinoxaline with aromatic aldehydes in the presence of TDAE furnished a mixture of cis/trans isomers of oxiranes[14] and the synthesis of new α-chloroketones based on TDAE strategy from the reaction between 2-(trichloromethyl)-quinoxaline and aromatic aldehydes.[15]

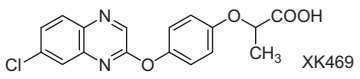

Figure 1. Structure of XK469.

In continuation of our program directed toward the study of single electron transfer reactions of bioreductive alkylating agents[16] and the preparation of new potentially bioactive compounds as anticancer agents,[17] we report herein an original and efficient synthesis of new substituted 2-tosyl-1,2,3,4-tetrahydropyrido[3,4-*b*]quinoxalines based on the TDAE strategy from the reaction between 2,3-bis(bromomethyl)quinoxaline and sulfonimine.

The reaction of 2,3-bis(bromomethyl)quinoxaline **1** with 3 equiv of sulfonimine **2a** in the presence of TDAE at −20 °C for 1 h, led to the 2-tosyl-1,2,3,4-tetrahydropyrido[3,4-*b*]quinoxaline **3a**. The reaction of 2,3-bis(bromomethyl)quinoxaline **1** with sulfonimine **2a** was studied (Scheme 1) under various conditions (Table 1). The best yield in product **3a** (60%) is obtained using 1 equiv of TDAE in THF at −20 °C for 1 h.

We have generalized this reaction with other sulfonimines **2b–k** to prepare a new series of 2-tosyl-1,2,3,4-tetrahydropyrido[3,4-*b*]quinoxalines **3b–k**[18] in moderate to good yields (56–67%) as shown in Scheme 2 and reported in Table 2.

The formation of these pyrido[3,4-*b*]quinoxaline derivatives **3a–k** could be explained by two mechanisms, the first one would

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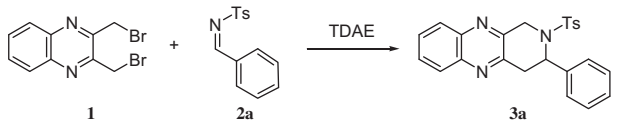
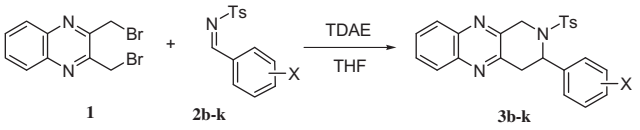


Scheme 1. Reaction of 2,3-bis(bromomethyl)quinoxaline **1** with *N*-(toluenesulfonyl)benzylimine **2a**.

Table 1
Optimization of the reaction of 2,3-bis(bromomethyl)quinoxaline **1** with *N*-(toluenesulfonyl)benzylimine **2a** using TDAE strategy[a]

Entry	Solvent	Equiv of TDAE	Yield[b] (%)
1	THF	1.05	46[c]
2	THF	1.05	60
3	THF	1.5	29
4	DMF	1.05	41

[a] All the reactions are performed using 3 equiv of *N*-(toluenesulfonyl)benzylimine **2a**, 1 equiv of 2,3-bis(bromomethyl)quinoxaline **1** and 1 equiv of TDAE in anhydrous THF stirred at −20 °C for 1 h.
[b] All yields refer to chromatographically isolated pure products and are relative to 2,3-bis(bromomethyl)quinoxaline **1**.
[c] The reaction mixture was stirred at −20 °C for 1 h and then warmed up to room temperature for 0.5 h.



Scheme 2. Reaction of 2,3-bis(bromomethyl)quinoxaline **1** with substituted *N*-(toluenesulfonyl)benzylimine **2b**–**k**.

occur by a nucleophilic addition of carbanion formed by the action of TDAE with 2,3-bis(bromomethyl)quinoxaline, on the imine group of sulfonimine **2a–k** followed by an intramolecular nucleophilic substitution with the second bromomethyl group. The second pathway would envisage the formation of the biradical of 2,3-bis(bromomethyl)quinoxaline which reacts with imine as suggested by Nishiyama in benzene series.[19]

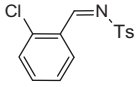
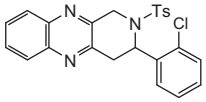
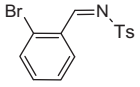
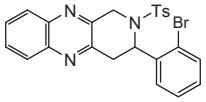
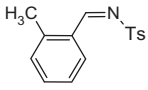
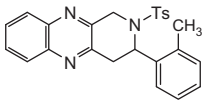
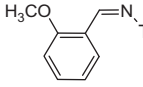
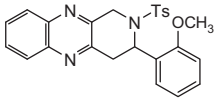
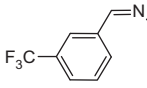
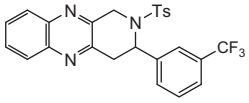
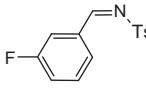
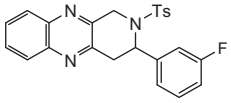
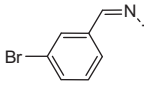
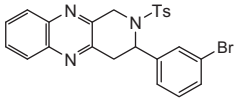
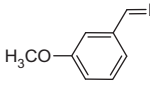
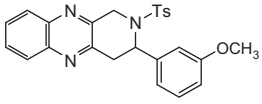
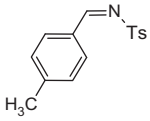
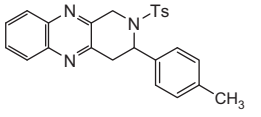
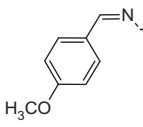
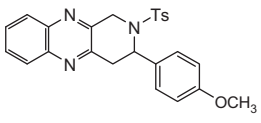
In the absence of intermediates or by-products in this reaction and in order to clarify this mechanism, we envisage the reaction of 2,3-bis(bromomethyl)quinoxaline **1** with another kind of unsaturated compound such as benzaldehyde **4** under the optimal conditions (Scheme 3).

This reaction has not furnished the expected 3-phenyl-3,4-dihydro-1*H*-pyrano[3,4-*b*]quinoxaline, but traces of 2-[3-(bromomethyl)quinoxalin-2-yl]-1-phenylethanol **5** have been identified. The formation of this product may be explained by an ionic addition of carbanion, formed by the action of TDAE with 2,3-bis(bromomethyl)quinoxaline, on the carbonyl group of benzaldehyde. However, the alcoholate intermediate is not enough nucleophile to cyclize by an intramolecular nucleophilic substitution explaining the absence of the formation of 3-phenyl-3,4-dihydro-1*H*-pyrano[3,4-*b*]quinoxaline.

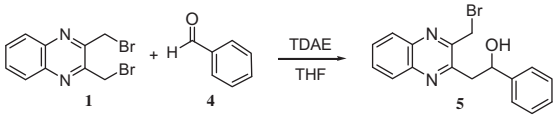
These results with benzaldehyde would seem to confirm an ionic pathway for the formation of these pyrido[3,4-*b*] quinoxaline derivatives **3a–k**.

In conclusion, we have developed in this work the synthesis of new substituted pyrido[3,4-*b*]quinoxalines by an easy, original, and mild procedure using TDAE methodology from 2,3-bis(bromomethyl)quinoxaline **1** and sulfonimines **2a–k**. The anti-plasmodial and cytotoxic activities of all synthesized compounds are under active investigation.

Table 2
Reaction of 2,3-bis(bromomethyl)quinoxaline **1** with substituted *N*-(toluenesulfonyl)benzylimine **2b–k** using TDAE strategy[a]

	Sulfonimine	Product	Yield[b] (%)
1		**3b** 	59
2		**3c** 	65
3		**3d** 	56
4		**3e** 	66
5		**3f** 	61
6		**3g** 	58
7		**3h** 	64
8		**3i** 	63
9		**3j** 	67
10		**3k** 	64

[a] All the reactions are performed using 3 equiv of substituted *N*-(toluenesulfonyl)benzylimines **2b–k**, 1 equiv of 2,3-bis(bromomethyl)quinoxaline **1** and 1 equiv of TDAE in anhydrous THF stirred at −20 °C for 1 h.
[b] All yields refer to chromatographically isolated pure products and are relative to 2,3-bis(bromomethyl)quinoxaline **1**.



Scheme 3. Reaction of **1** with benzaldehyde **4**.

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18. *General procedure for TDAE reaction of* ***1*** *with* ***2a–k***. Into a two-necked flask equipped with a drying tube (silica gel) and a nitrogen inlet was added 100 mL of anhydrous THF solution of 2,3-bis(bromomethyl)quinoxaline (**1**) (0.3 g, 0.95 mmol) and corresponding *N*-(benzenesulfonyl)benzylimine **2a–k** (3 equiv). The solution was stirred and maintained at this temperature for 30 min and then was added dropwise (via a syringe) the TDAE (0.28 g, 1.42 mmol). The solution was vigorously stirred at −20 °C for 1 h. After this time, TLC analysis (CH_2Cl_2) clearly showed that compound **1** was totally consumed. The solution was filtered (to remove the octamethyl-oxamidinium dibromide). The filtrate was concentrated in vacuo, diluted with dichloromethane, washed with H_2O (3 × 40 mL) and dried over $MgSO_4$. After evaporation, the crude product was purified by silica gel chromatography (CH_2Cl_2) and recrystallized from isopropanol, gave corresponding 2-substituted-tetrahydropyrido[3,4-*b*]quinoxaline derivatives (**3a–k**). New products: **3a**: white solid; mp 182 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.30 (s, 3H, CH_3); 3.44 (dd, 1H, J = 17.5 Hz, J = 6.1 Hz, CH_2); 3.63 (dd, 1H, J = 17.5 Hz, J = 5.2 Hz, CH_2); 4.31 (d, 1H, J = 18.4 Hz, CH_2); 5.80 (d, 1H, J = 18.4 Hz, CH_2); 5.75 (dd, 1H, J = 6.1 Hz, J = 5.2 Hz, CH); 7.14–7.35 (m, 7H, Ar); 7.72 (d, 4H, J = 7.1 Hz, Ar); 7.92–8.00 (m, 2H, Ar). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4 (CH_3); 34.7 (CH_2); 46.0 (CH_2); 54.3 (CH); 127.0 (2 × CH); 127.1 (2 × CH); 127.9 (CH); 128.5 CH); 128.6 (CH); 128.8 (2 × CH); 129.7 (CH); 129.8 (2 × CH); 129.9 (CH); 136.9 (C); 137.6 (C); 141.1 (C); 141.7 (C); 143.7 (C); 148.4 (C); 149.5 (C). Anal. Calcd for $C_{24}H_{21}N_3O_2S$: C, 69.37; H, 5.09; N, 10.11; S, 7.72. Found: C, 69.31; H, 5.21; N, 10.18; S, 7.61. Compound **3b**: white solid; mp 200 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.18 (s, 3H, CH_3); 3.34 (dd, 1H, J = 16.6 Hz, J = 5.3 Hz, CH_2); 3.70 (dd, 1H, J = 16.6 Hz, J = 6.7 Hz, CH_2); 4.68 (d, 1H, J = 17.1 Hz, CH_2); 4.98 (d, 1H, J = 17.1 Hz, CH_2); 5.87 (dd, 1H, J = 6.7 Hz, J = 5.3 Hz, CH); 7.06 (d, 3H, J = 8.2 Hz, Ar); 7.10–7.22 (m, 2H, Ar); 7.31–7.40 (m, 1H, Ar); 7.63 (m, 2H, Ar); 7.70–7.75 (m, 2H, Ar); 7.93–8.02 (m, 2H, Ar). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.2 (CH_3); 36.6 (CH_2); 48.3 (CH_2); 53.9 (CH); 127.0 (CH); 127.6 (2 × CH); 127.7 (CH); 128.6 (CH); 128.7 (CH); 129.1 (CH); 129.4 (2 × CH); 129.8 (CH); 129.9 (CH); 130.2 (CH); 132.6 (C); 135.1 (C); 138.1 (C); 141.1 (C); 141.9 (C); 143.7 (C); 149.1 (C); 150.0 (C). Anal. Calcd for $C_{24}H_{20}ClN_3O_2S$: C, 64.06; H, 4.48; Cl, 7.88; N, 9.34; S, 7.13. Found: C, 63.85; H, 4.59; N, 9.33; S, 7.03. Compound **3c**: white solid; mp 201 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.15 (s, 3H, CH_3); 3.30 (dd, 1H, J = 16.4 Hz, J = 5.7 Hz, CH_2); 3.67 (dd, 1H, J = 16.4 Hz, J = 6.6 Hz, CH_2); 4.74 (d, 1H, J = 16.9 Hz, CH_2); 4.99 (d, 1H, J = 16.9 Hz, CH_2); 5.70 (dd, 1H, J = 6.6 Hz, J = 5.7 Hz, CH); 7.01 (d, 2H, J = 8.2 Hz, Ar); 7.05–7.07 (m, 3H, Ar); 7.52–7.56 (m, 1H, Ar); 7.62 (d, 2H, J = 8.2 Hz, Ar); 7.68–7.76 (m, 2H, Ar); 7.91–8.01 (m, 2H, Ar). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.2 (CH_3); 37.0 (CH_2); 48.6 (CH_2); 56.3 (CH); 122.4 (C); 127.5 (2 × CH); 127.6 (CH); 127.7 (CH); 128.6 (CH); 128.7 (CH); 129.2 (CH); 129.3 (2 × CH); 129.7 (CH); 129.8 (CH); 133.3 (CH); 134.8 (C); 140.0 (C); 141.1 (C); 141.9 (C); 143.7 (C); 149.1 (C); 149.9 (C). Anal. Calcd for $C_{24}H_{20}BrN_3O_2S$: C, 58.30; H, 4.08; N, 8.50; S, 6.49. Found: C, 58.11; H, 4.07; N, 8.41; S, 6.25. Compound **3d**: white solid; mp 186 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.17 (s, 3H, CH_3); 2.60 (s, 3H, CH_3); 3.41 (dd, 1H, J = 18.0 Hz, J = 2.6 Hz, CH_2); 3.59 (dd, 1H, J = 18.0 Hz, J = 6.9 Hz, CH_2); 4.28 (d, 1H, J = 18.3 Hz, CH_2); 4.94 (d, 1H, J = 18.3 Hz, CH_2); 5.85 (dd, 1H, J = 6.9 Hz, J = 2.6 Hz, CH); 6.76–6.94 (m, 2H, Ar); 7.00 (d, 2H, J = 8.2 Hz, Ar); 7.11–7.24 (m, 2H, Ar); 7.62 (d, 2H, J = 8.2 Hz, Ar); 7.71–7.76 (m, 2H, Ar); 7.93–8.01 (m, 2H, Ar). ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.6 (CH_3); 21.2 (CH_3); 34.7 (CH_2); 46.7 (CH_2); 52.6 (CH); 125.9 (CH); 126.2 (CH); 127.5 (2 × CH); 128.3 (CH); 128.4 (CH); 128.6 (CH); 129.4 (2 × CH); 129.7 (CH); 129.8 (CH); 131.4 (CH); 136.0 (C); 136.6 (C); 137.3 (C); 141.1 (C); 141.7 (C); 143.8 (C); 148.9 (C); 150.2 (C). Anal. Calcd for $C_{25}H_{23}N_3O_2S$: C, 69.91; H, 5.40; N, 9.78; S, 7.47. Found: C, 69.56; H, 5.49; N, 9.78; S, 7.33. Compound **3e**: white solid; mp 184 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.19 (s, 3H, CH_3); 3.39 (dd, 1H, J = 16.4 Hz, J = 4.8 Hz, CH_2); 3.67 (dd, 1H, J = 16.4 Hz, J = 6.9 Hz, CH_2); 3.77 (s, 3H, OCH_3); 4.64 (d, 1H, J = 17.3 Hz, CH_2); 5.03 (d, 1H, J = 17.3 Hz, CH_2); 5.86 (dd, 1H, J = 6.9 Hz, J = 4.8 Hz, CH); 6.70–6.86 (m, 2H, Ar); 7.02 (d, 2H, J = 8.2 Hz, Ar); 7.16–7.27 (m, 2H, Ar); 7.59 (d, 2H, J = 8.2 Hz, Ar); 7.68–7.75 (m, 2H, Ar); 7.93–8.00 (m, 2H, Ar). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.2 (CH_3); 36.5 (CH_2); 47.7 (CH_2); 52.1 (CH); 55.1 (OCH_3); 110.7 (CH); 120.4 (CH); 127.2 (2 × CH); 127.6 (CH); 128.1 (C); 128.5 (CH); 128.7 (CH); 129.1 (CH); 129.2 (2 × CH); 129.5 (CH); 129.6 (CH); 136.2 (C); 140.9 (C); 141.7 (C); 143.2 (C); 149.4 (C); 151.0 (C); 156.4 (C). Anal. Calcd for $C_{25}H_{23}N_3O_3S$: C, 67.40; H, 5.20; N, 9.43; S, 7.20. Found: C, 66.86; H, 5.24; N, 9.37; S, 7.02. Compound **3f**: white solid; mp 136 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.30 (s, 3H, CH_3); 3.51 (dd, 1H, J = 17.4 Hz, J = 5.6 Hz, CH_2); 3.61 (dd, 1H, J = 17.4 Hz, J = 3.3 Hz, CH_2); 4.35 (d, 1H, J = 18.2 Hz, CH_2); 5.15 (d, 1H, J = 18.2 Hz, CH_2); 5.74 (dd, 1H, J = 5.6 Hz, J = 3.3 Hz, CH); 7.17 (d, 2H, J = 7.9 Hz, Ar); 7.33–7.48 (m, 4H, Ar); 7.68–7.75 (m, 4H, Ar); 7.93–8.00 (m, 2H, Ar). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4 (CH_3); 35.3 (CH_2); 46.3 (CH_2); 54.4 (CH); 123.6 (q, J = 272.6 Hz, CF_3); 124.0 (q, J = 4.0 Hz, CH); 124.9 (q, J = 3.6 Hz, CH); 127.0 (2 × CH); 128.6 (CH); 128.7 (CH); 129.4 (CH); 129.9 (2 × CH); 130.0 (CH); 130.1 (CH); 131.0 (CH); 131.6 (q, J = 3.6 Hz, C); 136.5 (C); 139.2 (C); 141.3 (C); 141.8 (C); 144.1 (C); 148.0 (C); 148.9 (C). Anal. Calcd for $C_{25}H_{20}F_3N_3O_2S$: C, 62.10; H, 4.17; N, 8.69; S, 6.63. Found: C, 61.87; H, 4.36; N, 8.62; S, 6.42. Compound **3g**: white solid; mp 184 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.30 (s, 3H, CH_3); 3.44 (dd, 1H, J = 17.6 Hz, J = 5.8 Hz, CH_2); 3.57 (dd, 1H, J = 17.6 Hz, J = 2.6 Hz, H_2); 4.35 (d, 1H, J = 18.3 Hz, CH_2); 5.09 (d, 1H, J = 18.3 Hz, CH_2); 5.71 (dd, 1H, J = 5.8 Hz, J = 2.6 Hz, CH); 6.80–7.04 (m, 3H, Ar); 7.15–7.21 (m, 3H, Ar); 7.69–7.75 (m, 4H, Ar); 7.93–8.00 (m, 2H, Ar). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.3 (CH_3); 34.9 (CH_2); 46.1 (CH_2); 54.1 (CH); 114.3 (d, J = 22.3 Hz, CH); 114.9 (d, J = 20.8 Hz, CH); 122.6 (d, J = 2.9 Hz, CH); 127.0 (2 × CH); 128.5 (CH); 128.6 (CH); 129.8 (3 × CH); 129.9 (CH); 130.4 (d,

J = 8.0 Hz, CH); 136.6 (C); 140.5 (d, *J* = 6.6 Hz, C); 141.2 (C); 141.7 (C); 143.9 (C); 148.1 (C); 149.0 (C); 162.6 (d, *J* = 247.4 Hz, C). Anal. Calcd for $C_{24}H_{20}FN_3O_2S$: C, 66.50; H, 4.65; N, 9.69; S, 7.40. Found: C, 66.69; H, 4.79; N, 9.75; S, 7.36. Compound **3h**: white solid; mp 162 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.30 (s, 3H, CH_3); 3.43 (dd, 1H, *J* = 17.5 Hz, *J* = 6.1 Hz, CH_2); 3.60 (dd, 1H, *J* = 17.5 Hz, *J* = 2.9 Hz, CH_2); 4.36 (d, 1H, *J* = 18.2 Hz, CH_2); 5.12 (d, 1H, *J* = 18.2 Hz, CH_2); 5.67 (dd, 1H, *J* = 6.1 Hz, *J* = 2.9 Hz, CH); 7.02–7.19 (m, 4H, Ar); 7.27–7.50 (m, 4H, Ar); 7.68–7.77 (m, 2H, Ar); 7.93–8.00 (m, 2H, Ar). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4 (CH_3); 35.0 (CH_2); 46.2 (CH_2); 54.1 (CH); 123.1 (C); 125.5 (CH); 127.0 (2 × CH); 128.5 (CH); 128.7 (CH); 129.9 (3 × CH); 130.0 (CH); 130.3 (CH); 130.4 (CH); 131.2 (CH); 136.6 (C); 140.3 (C); 141.2 (C); 141.7 (C); 144.0 (C); 148.1 (C); 149.0 (C). Anal. Calcd for $C_{24}H_{20}BrN_3O_2S$: C, 58.30; H, 4.08; N, 8.50; S, 6.49. Found: C, 58.29; H, 4.08; N, 8.50; S, 6.41. Compound **3i**: white solid; mp 174 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.30 (s, 3H, CH_3); 3.43 (dd, 1H, *J* = 17.7 Hz, *J* = 6.4 Hz, CH_2); 3.59 (dd, 1H, *J* = 17.7 Hz, *J* = 2.3 Hz, CH_2); 3.67 (s, 3H, OCH_3); 4.32 (d, 1H, *J* = 18.3 Hz, CH_2); 5.07 (d, 1H, *J* = 18.3 Hz, CH_2); 5.71 (dd, 1H, *J* = 6.4 Hz, *J* = 2.3 Hz, CH); 6.70–6.78 (m, 3H, Ar); 7.07–7.18 (m, 3H, Ar); 7.68–7.74 (m, 4H, Ar); 7.92–7.99 (m, 2H, Ar). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4 (CH_3); 34.8 (CH_2); 46.0 (CH_2); 54.3 (CH); 55.1 (OCH_3); 113.0 (CH); 113.4 (CH); 119.2 (CH); 126.4 (CH); 127.1 (2 × CH); 128.5 (CH); 128.6 (CH); 129.7 (CH); 129.8 (3 × CH); 136.9 (C); 139.3 (C); 141.1 (C); 141.6 (C); 143.7 (C); 148.4 (C); 149.5 (C); 159.9 (C). Anal. Calcd for $C_{25}H_{23}N_3O_3S$: C, 67.40; H, 5.20; N, 9.43; S, 7.20. Found: C, 67.26; H, 5.27; N, 9.43; S, 7.14. Compound **3j**: white solid; mp 158 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.24 (s, 3H, CH_3); 2.30 (s, 3H, CH_3); 3.42 (dd, 1H, *J* = 17.7 Hz, *J* = 6.4 Hz, CH_2); 3.61 (dd, 1H, *J* = 17.7 Hz, *J* = 2.0 Hz, CH_2); 4.29 (d, 1H, *J* = 18.5 Hz, CH_2); 5.06 (d, 1H, *J* = 18.5 Hz, CH_2); 5.71 (dd, 1H, *J* = 6.4 Hz, *J* = 2.0 Hz, CH); 6.99–7.18 (m, 6H, Ar); 7.69–7.74 (m, 4H, Ar); 7.92–7.98 (m, 2H, Ar). ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.9 (CH_3); 21.4 (CH_3); 34.7 (CH_2); 45.8 (CH_2); 54.1 (CH); 127.0 (2 × CH); 127.1 (2 × CH); 128.4 (CH); 128.6 (CH); 129.4 (CH); 129.5 (2 × CH); 129.7 (CH); 129.8 (2 × CH); 134.5 (C); 137.0 (C); 137.7 (C); 141.1 (C); 141.6 (C); 143.7 (C); 148.5 (C); 149.7 (C). Anal. Calcd for $C_{25}H_{23}N_3O_2S$: C, 69.91; H, 5.40; N, 9.78; S, 7.47. Found: C, 69.69; H, 5.49; N, 9.79; S, 7.25. Compound **3k**: white solid; mp 160 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.31 (s, 3H, CH_3); 3.42 (dd, 1H, *J* = 17.7 Hz, *J* = 5.5 Hz, CH_2); 3.59 (dd, 1H, *J* = 17.7 Hz, *J* = 2.0 Hz, CH_2); 3.71 (s, 3H, OCH_3); 4.28 (d, 1H, *J* = 18.5 Hz, CH_2); 5.06 (d, 1H, *J* = 18.5 Hz, CH_2); 5.72 (dd, 1H, *J* = 6.5 Hz, *J* = 2.0 Hz, CH); 6.73 (d, 2H, *J* = 8.7 Hz, Ar); 7.13 (d, 2H, *J* = 8.4 Hz, Ar); 7.17 (d, 2H, *J* = 8.0 Hz, Ar); 7.70–7.74 (m, 4H, Ar); 7.93–8.01 (m, 2H, Ar). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4 (CH_3); 34.8 (CH_2); 45.8 (CH_2); 53.8 (CH); 55.2 (OCH_3); 114.1 (2 × CH); 127.0 (2 × CH); 128.4 (CH); 128.5 (2 × CH); 128.6 (CH); 129.4 (CH); 129.7 (CH); 129.8 (2 × CH); 130.0 (C); 137.0 (C); 141.1 (C); 141.6 (C); 143.7 (C); 148.5 (C); 149.7 (C); 159.1 (C). Anal. Calcd for $C_{25}H_{23}N_3O_3S$: C, 67.40; H, 5.20; N, 9.43; S, 7.20. Found: C, 67.54; H, 5.30; N, 9.47; S, 7.13.

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