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Synthesis of New 1,3-Disubstituted-2,3-dihydro-1*H*-naphth-[1,2e][1,3]oxazines

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Abstract: 1,3-Disubstituted-2,3-dihydro-1*H*-naphth[1,2-e][1,3]oxazines were prepared through the ring-closure reactions of the aminobenzylnaphthols with substituted aryl- and heteroarylaldehydes.

Keywords: Biological activity, ring-closure reactions, naphth-1,3-oxazines, amino-benzylnaphthols

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Introduction

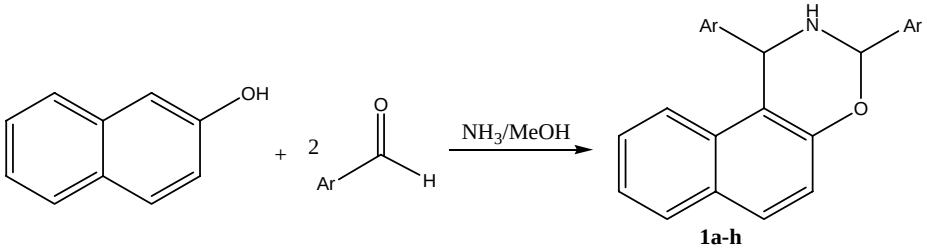
The development of simple synthetic routes to widely used organic compounds using readily available reagents is one of the main objectives of organic synthesis. Nitrogen heterocycles are of special interest because they constitute an important class of natural and nonnatural products, many of which exhibite useful biological activities. Investigation of the 1,3-oxazine heterocycles has shown that they possess varied biological properties such as analgesic, anticonvulsant, antitubercular, antibacterial and anticancer activity [1-4]. Particular attention has been paid to these compounds since the discovery of the non-nucleoside reverse transcriptase inhibitor trifluoromethyl-1,3-oxazine-2-one, which shows high activity against a variety of HIV-1 mutant strains [5]. In addition, naphthoxazine derivatives have exhibited therapeutic potential for the treatment of Parkinson's disease [6,7]. Furthermore, they can be used as intermediates in the synthesis of *N*-substituted aminoalcohols or in

enantioselective syntheses of chiral amines. The tautomeric character of 1,3-*O*,*N*-heterocycles offers a great number of synthetic possibilities [8-10]. Previously, naphth-1,3-oxazine derivatives have been prepared using 2-naphthol and various substituted aryl- and heteroarylaldehydes in the presence of dry methanolic ammonia [11-13]. Our present aim was to extend the synthetic utility of aminobenzylnaphthol by examining its use in the preparation of new heterocyclic 1,3-oxazine compounds.

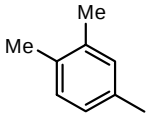
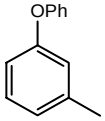
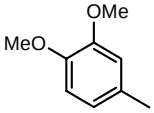
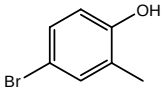
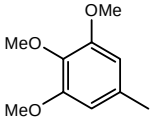
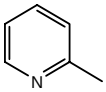
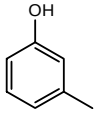
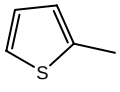
Results and Discussion

Condensation of 2-naphthol with two equivalents of heteroarylaldehydes or substituted benzaldehydes in the presence of ammonia at room temperature (rt) gave compounds **1a-h**. The structures of the aldehyde components, reaction conditions and yields are summarized in Table 1

Table 1. Synthesis of 1,3-oxazines **1a-h**.

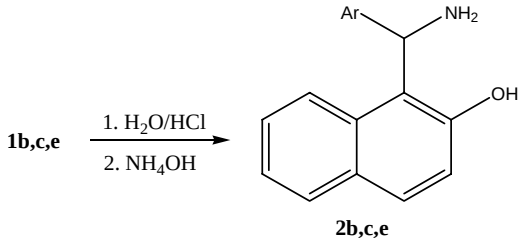


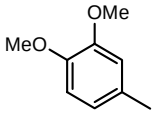
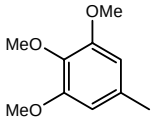
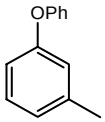
1a-h

Compound	Ar (Yield, %)	Conditions	Compound	Ar (Yield, %)	Conditions
1a	 (45)	48 h, rt	**1e**	 (52)	48 h, rt
1b	 (71)	24 h, rt	**1f**	 (61)	48 h, rt
1c	 (51)	48 h, rt	**1g**	 (59)	24 h, rt
1d	 (49)	48 h, rt	**1h**	 (56)	24 h, rt

Then, compounds **1b**,**c** and **e** were hydrolysed under acidic conditions to give aminobenzyl-naphthols (Betti bases) **2b**,**c** and **e**, respectively. Results are given in Table 2.

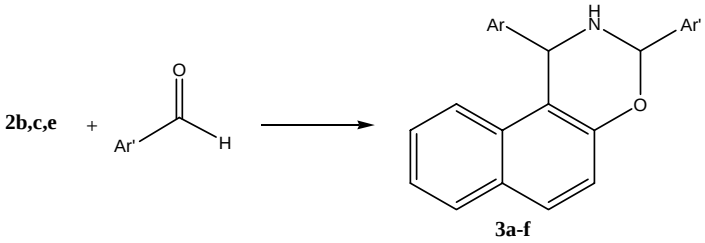
Table 2. Synthesis of aminobenzylnaphthols **2b,c,e**.

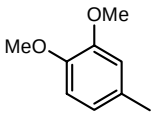
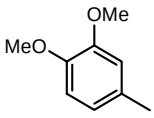
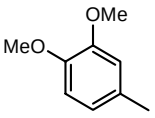
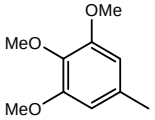
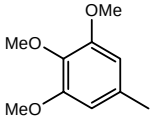
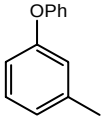
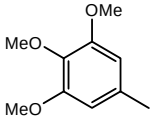
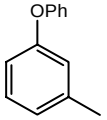
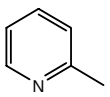
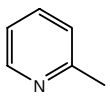
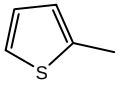
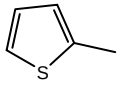


Compound	Ar	Yield, %	Conditions
2b		73	6 h, reflux
2c		69	6 h, reflux
2e		72	6 h, reflux

Finally, the reactions of the Betti bases **2b**,**c**,**e** with equivalent amounts of aldehydes/heteroaldehydes afforded the corresponding 1,3-disubstituted-2,3-dihydro-1*H*-naphth[1,2-e][1,3]oxazines **3a-f** (Table 3).

Table 3. Synthesis of 1,3-oxazines **3a-f**.



Compound	3a	3b	3c	3d	3e	3f
Ar						
Ar′						
Yield, %	46	43	51	50	42	53
Conditions	48 h, rt	48 h, rt	48 h, rt	48 h, rt	48 h, rt	48 h, rt

The Betti reaction, a Mannich-type aminoalkylation, offers a convenient route for preparing 1-(aminosubstituted methyl)-2-naphthols **2** under mild (rt) conditions. Access to these Mannich–type phenolic bases make the aminoalkylation reaction of naphthol derivatives a subject of current chemical interest [5-7]. Subsequent reaction of the aminobenzylnaphthtols with an equivalent amount of a substituted aldehyde in absolute MeOH at ambient temperature gave 1,3-naphthoxazines **3**.

The structures of all the new compounds were confirmed by FTIR, mass spectrometry, NMR and elemental analysis results. Thus, for example, the characteristic C=O bands of the aldehydes disappeared and absorption bands corresponding to NH groups were observed at 3320-3357 cm^{-1} in the IR spectra of the 1,3-oxazines, while NCH proton singlets at 5.47 and 5.78 ppm and NH proton singlets at 2.8-3.00 were observed in the ^{1}H-NMR spectra.

Conclusions

Substituted aminobenzylnaphthols were synthesized in moderate to good yields by the reactions of 2-naphthols with appropriate aldehydes. Some new 1,3-disubstituted-2,3-dihydro-1*H*-naphth[1,2-e]-[1,3]oxazines **1** and **3**, that are expected to show biological activities, were obtained by the ring-closure reactions of these aminobenzylnaphthols and various aldehydes. In addition, if substituted-1,3-amino-alcohols **2** were to be prepared in enantiopure form, they could be useful in the synthesis of chiral ligands.

Experimental

General

NMR spectra were recorded on Bruker Digital FT-NMR 'Avance 400' spectrometer ($CDCl_3$ solvent) with TMS as internal reference. Results are expressed in ppm. IR spectra were recorded on Perkin Elmer FT-IR spectrometer (KBr). GC-EIMS spectra were measured on a Varian SAT2100T mit GC3900 spectrometer using FAB ionization. Melting points were measured on a Gallenkamp melting point apparatus. Silica gel 60 (Merck) was used for column separations. TLC was conducted on standard aluminium sheets precoated with a 0.2 mm layer of silica gel. Elemental analysis were performed using a Flash EA 1112 series apparatus.

General procedure for the synthesis of [1,3]oxazines **1a-h**.

The aryl- or heteroarylaldehyde (2 mmol; freshly distilled if a liquid) and 25 % methanolic ammonia solution (0.5 mL) were added to a solution of 2-naphthol (1 mmol) in absolute MeOH (0.5 mL). The mixture was left to stand at ambient temperature for 2 days, during which the crystalline products **1a-h** separated out. The crude crystals were filtered off, washed with cold MeOH (2 x 2mL) and purified by recrystallization from bp. 40-60°C petroleum ether or by column chromatography (CC), eluting with the indicated solvents.

1,3-Di(3,4-dimethylphenyl)-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine (**1a**): Colorless crystals; yield 45 %; mp. 110 ^{o}C (recrystallized); ^{1}H-NMR ($CDCl_3$): δ = 2.27 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 5.41 (s, 1H, CH), 6.10 (s,1H, CH), 6.72-7.81 (m,12H, ArH); ^{13}C-NMR ($CDCl_3$): δ = 20.77, 21.56, 55.26, 82.44, 112.33, 125.83, 127.54, 130.28, 154.21; Anal. Calcd. for $C_{28}H_{27}NO$: C: 85.46; H: 6.92, N: 3.56. Found: C: 85.21, H: 6.93, N: 3.68; MS: m/z 393.

1,3-Di(3,4-dimethoxyphenyl)-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine (**1b**): Colorless crystals; yield 71 %; mp. 122.5 ^{o}C (CC, 3:1 ethyl acetate/*n*-hexane) ^{1}H- NMR ($CDCl_3$): δ = 3.70 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 5.63 (s, 1H, NCH), 6,12 (s, 1H, CH), 6.69-7.92 (m, 12H, ArH); ^{13}C-NMR ($CDCl_3$): δ = 53.91, 55.25, 82.22, 111.52, 112.20, 120.15, 121.85, 126.85, 129.25, 130.12, 152.63; Anal. Calcd. for $C_{28}H_{27}NO_5$: C: 73.51, H: 5.95, N: 3.06. Found: C: 73.53, H: 5.93, N: 3.08; MS: m/z 457.

1,3-Di(3,4,5-trimethoxyphenyl)-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine (**1c**): Colorless crystals; yield 51 %; mp. 137.4^{o}C (CC, 1:2 ethyl acetate/*n*-hexane); ^{1}H-NMR ($CDCl_3$): δ = 3.71(s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 5.61 (s, 1H, CH), 6,10 (s, 1H, CH), 6.69-7.88 (m, 10H, ArH); ^{13}C-NMR ($CDCl_3$): δ = 54.5, 55.36, 81.20, 112.03, 120.78, 127.38, 128.32, 129.45, 130.11, 148.57, 153.40; Anal. Calcd. for $C_{30}H_{31}NO_7$: C: 69.62, H: 6.04, N: 2.71. Found: C: 69.68, H: 5.99, N: 2.73; MS: m/z 517.

1,3-Di(3-hydroxyphenyl)-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine (**1d**): Pale yellow crystals; yield 49 %; mp. 101.2^{o}C (CC, 1:5 ethyl acetate/chloroform); ^{1}H-NMR ($CDCl_3$): δ = 5.58 (s, 1H, CH), 5.98 (s, 1H, CH), 6.73-7.82 (m, 14H, ArH); ^{13}C-NMR ($CDCl_3$): δ= 56.20, 81.60, 112.84, 114.92, 117.36, 128.65, 130.38, 143.87, 157.10, 160.44; Anal. Calcd. for $C_{24}H_{19}NO_3$: C: 78.03, H: 5.18, N: 3.79. Found: C: 77.99, H: 5.21, N: 3.66; MS: m/z 369.

1,3-Di(3-phenoxyphenyl)-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine (**1e**): Reddish crystals; yield 52 %; mp. 106.1^{o}C (CC, 3:1 ethyl acetate/*n*-hexane); ^{1}H-NMR ($CDCl_3$): δ = 5.51 (s, 1H, CH), 6.12 (s, 1H, CH), 6.92-7.91 (m, 24H, ArH); ^{13}C-NMR ($CDCl_3$): δ = 54.80, 81.50, 117.31, 121.23, 126.80, 129.50, 130.21, 144.90, 152.61, 162.10; Anal. Calcd. for $C_{36}H_{27}NO_3$: C: 82.90, H: 5.22, N: 2.69. Found: C: 82.87, H: 5.23, N: 2.71; MS: m/z 521.

1,3-Di(5-bromo-2-hydroxyphenyl)-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine (**1f**): Pale yellow crystals; yield 61 %; mp. 197.8^{o}C (CC, 3:1 ethyl acetate/*n*-hexane); ^{1}H-NMR ($CDCl_3$): δ = 5.21 (s, 1H, CH), 5.72 (s, 1H, CH), 6.75-7.67 (m, 12H, ArH); ^{13}C-NMR ($CDCl_3$): δ = 56.44, 81.73, 112.56, 114.76, 117.46, 127.75, 130.10, 143.87, 158.24, 159.81; Anal. Calcd. for $C_{24}H_{17}Br_2NO_3$ C: 57.67, H: 3.25, N: 2.65. Found: C: 57.61, H: 3.23, N: 2.63; MS: m/z 527.

1,3-Di(2-pyridinyl)-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine (**1g**): Pale yellow crystals; yield 59 %; mp. 159.4 ^{o}C (CC, 3:1 ethyl acetate/*n*-hexane); ^{1}H-NMR ($CDCl_3$): δ = 5.24 (s, 1H, CH), 5.86 (s, 1H, CH), 7.12-7.89 (m, 10H, ArH), 8.50-8.89 (m, 4H, pyridine); ^{13}C-NMR ($CDCl_3$): δ = 56.23, 81.69, 124.33, 133.67, 139.76, 148.27, 150.52, 154.3; Anal. Calcd. for $C_{22}H_{17}N_3O$: C: 77.86, H: 5.05, N: 12.38. Found: C: 77.89, H: 5.05, N: 12.40; MS: m/z 339.

1,3-Di(2-thienyl)-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine (**1h**): Colorless crystals; yield 56 %; mp. 171 ^{o}C (recrystallized); ^{1}H-NMR ($CDCl_3$): δ = 5.45 (s, 1H, CH), 5.68 (s, 1H, CH), 6.72-7.91 (m, 12H, ArH); ^{13}C-NMR ($CDCl_3$): δ = 53.12, 78.80, 111.56, 120.45, 127.65, 128.53, 129.46, 146.34, 151.57;

Anal. Calcd. for $C_{20}H_{15}NOS_2$: C: 68.74, H: 4.33, N: 4.01. Found: C: 68.77, H: 4.31, N: 3.91; MS: m/z 349.

General procedure for the synthesis of 1-(aminosubstituted methyl)-2-naphthols **2b**,**c** and **e**.

1b, **c** or **e** (1 mmol) were suspended in 20 % HCl (20 mL) and the mixture was stirred and refluxed for 6 h, whereby the crystalline hydrochloride of **2b**,**c**,**e** separated out and was filtered off and washed with EtOAc. The hydrochloride was suspended in H_2O and the mixture was treated with conc. NH_4OH (3 mL) and extracted with EtOAc (3 x 5mL). After drying (Na_2SO_4) and evaporation of the EtOAc phase, crude crystalline compounds **2b**,**c**,**e** were obtained, which were further purified by column chromatography, eluting with the indicated solvents.

1-[Amino-(3,4-dimethoxyphenyl)methyl]-2-naphthol (**2b**): Colorless crystals; yield 73 %; mp. 126 ^oC (3:1 ethyl acetate/*n*-hexane); ^1H-NMR ($CDCl_3$): δ = 3.72 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 5.97 (s,1H, CH), 6.97-7.64 (m, 9H, ArH); ^{13}C-NMR($CDCl_3$): δ = 54.20, 55.25, 113.23, 114.43, 122.38, 124.18, 126.56, 127.10, 129.34, 134.46, 152.10, 153.13; Anal. Calcd. for $C_{19}H_{19}NO_3$: C:73.76, H: 6.19, N: 4.53. Found: C: 73.74, H: 6.20, N: 4.54; MS: m/z 309.

1-[Amino-(3,4,5-trimethoxyphenyl)methyl]-2-naphthol (**2c**): Colorless crystals; yield 69 %; mp. 119 ^oC (3:1 ethyl acetate/*n*-hexane); ^1H-NMR ($CDCl_3$): δ = 3.72 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 5.97 (s, 1H, CH), 6.97-7.64 (m, 8H, ArH); ^{13}C-NMR ($CDCl_3$): δ= 54.34, 55.88, 59.24, 107.23, 115.43, 124.38, 126.58, 127.10, 129.74, 137.46, 152.10, 156.13; Anal. Calcd. for $C_{20}H_{21}NO_4$: C: 70.78, H: 6.23, N: 4.13. Found: C: 70.79, H: 6.23, N: 4.14; MS: m/z 339.

1-[Amino-(3-phenoxyphenyl)methyl]-2-naphthol (**2e**): Colorless crystals; yield 72 %; mp. 114 ^oC (4:1 ethyl acetate/*n*-hexane); ^1H-NMR ($CDCl_3$): δ = 5.99 (s, 1H, CH), 6.85-7.64 (m, 15H, ArH); ^{13}C- NMR ($CDCl_3$): δ = 54.34, 55.88, 115.43, 116.43, 122.38, 123.58, 127.10, 129.74, 131.46, 145.33, 152.10, 155.13; Anal. Calcd. for $C_{20}H_{21}NO_4$: C:80.91, H: 5.61, N: 4.10, Found: C: 80.92, H: 5.63, N: 4.11; MS: m/z 341.

General procedure for the synthesis of 1,3-naphthoxazines **3a-f**.

To a solution of the appropriate aminonaphthol **2b,c** or **e (**1 mmol) in absolute MeOH (20 mL), an equivalent amount of aryl- or heteroarylaldehyde was added, and the mixture was left to stand at ambient temperature for 48h. The crystalline products were filtered off and then purified by column chromatography, eluting with the indicated solvents.

1-(3,4-Dimethoxyphenyl)-3-(3,4,5-trimethoxhyphenyl)-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine (**3a**): Pale yellow crystals; yield 46 %; mp. 133 ^oC (3:1 ethyl acetate/*n*-hexane); ^1H-NMR ($CDCl_3$): δ = 3.73 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.921 (s, 3H, OCH_3), 5.47 (s, 1H, CH), 5.61 (s, 1H, CH), 7.2-8.8 (m, 11H, ArH); ^{13}C-NMR ($CDCl_3$): δ = 54.20, 56.25,

81.70, 112.23, 121.38, 123.18, 126.86, 129.10, 130.14, 156.78, 160.03; Anal. Calcd. for $C_{29}H_{29}NO_6$: C: 71.44, H: 5.99, N: 2.87. Found: C: 71.39, H: 5.97, N: 2.86; MS: m/z 487.

1-(3,4-Dimethoxyphenyl)-3-(3-phenoxyphenyl)-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine (**3b**): Pale yellow crystals; yield 43 %; mp. 127 ^{o}C (3:1 ethyl acetate/*n*-hexane); ^{1}H-NMR ($CDCl_3$): δ = 3.86 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.52 (s, 1H, CH), 5.71 (s, 1H, CH), 7.24-8.82 (m, 18H, ArH); ^{13}C-NMR ($CDCl_3$): δ = 55.20, 55.68, 81.45, 112.12, 120.20, 121.56 123.65, 126.80, 129.54, 152.67, 162.12; Anal. Calcd. for $C_{32}H_{27}NO_4$: C: 78.50, H: 5.55, N: 2.86. Found: C: 78.47, H: 5.57, N: 2.87; MS: m/z 489.

1-(3,4-Dimethoxyphenyl)-3-(2-pyridinyl)-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine (**3c**): Pale yellow crystals; yield 51 %; mp. 143 ^{o}C (4:1 ethyl acetate/*n*-hexane); ^{1}H-NMR ($CDCl_3$): δ = 3.69 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 5.50 (s, 1H, CH), 6.40 (s, 1H, CH), 7.2-8.8 (m, 13H, ArH); ^{13}C- NMR ($CDCl_3$): δ = 55.21, 55.43, 79.80, 112.66, 123.34, 126.93, 128.80, 129.72, 130.23, 148.27, 153.88; Anal. Calcd. for $C_{25}H_{23}N_2O_3$: C:75.36, H: 5.56, N:7.03. Found: C: 75.22, H: 5.57, N: 7.04; MS: m/z 398.

1-(3,4,5-Trimethoxyphenyl)-3-(2-pridinyl)-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine (**3d**): Pale yellow crystals; yield 50 %; mp. 112 ^{o}C (4:1 ethyl acetate/*n*-hexane); ^{1}H-NMR ($CDCl_3$): δ = 3.75 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.52 (s, 1H, CH), 5.87 (s, 1H, CH), 7.22-8.81 (m, 12H, ArH); ^{13}C-NMR ($CDCl_3$): δ = 53.25, 54.01, 81.23, 112.34, 121.45, 126.67, 127.34, 130.78, 157.20; Anal. Calcd. for $C_{26}H_{24}N_2O_4$: C: 72.88, H: 5.64, N: 6.53. Found: C: 72.90, H: 5.62, N: 6.56; MS: m/z 428.

1-(3,4,5-Trimethoxyphenyl)-3-(2-thienyl)-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine (**3e**): Pale yellow crystals; yield 42 %; mp. 148 ^{o}C (5:1 ethyl acetate/*n*-hexane); ^{1}H-NMR ($CDCl_3$): δ = 3.74 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.52 (s, 1H, CH), 5.81 (s, 1H, CH), 7.25-8.88 (m, 11H, ArH); ^{13}C-NMR ($CDCl_3$): δ = 56.4, 80.79, 111.80, 120.32, 123.65, 126.34, 128.23, 133.67, 147.23, 152.78; Anal. Calcd. for $C_{25}H_{22}NO_4S$: C: 69.42, H: 5.13, N: 3.23, S: 7.41 Found: C: 69.41, H: 5.17, N: 3.19, S: 7.33; MS: m/z 432.

1-(3-Phenoxyphenyl)-3-(2-thienyl)-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine (**3f**): Pale yellow crystals; yield 53 %; mp. 153^{o}C (4:1 ethyl acetate/*n*-hexane); ^{1}H-NMR ($CDCl_3$): δ = 5.53 (s, 1H, CH), 6.11 (s, 1H, CH), 7.27-8.89 (m, 18H, ArH); ^{13}C-NMR ($CDCl_3$): δ= 54.40, 81.10, 112.45, 120.89, 123.47, 126.67, 128.48, 133.85, 145.98, 154.65; Anal. Calcd. for $C_{28}H_{21}NO_2S$: C: 77.22, H: 4.97, N: 3.22, S: 7.34. Found: C: 77.36, H: 4.81, N: 3.19, S: 7.33; MS: m/z 435.

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Sample Availability: Samples of the compounds are available from authors.