Synthesis and Antimicrobial Study of New 8-bromo-1,3-diaryl-2,3-dihydro-1H-naphtho[1,2e][1,3]oxazines

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Abstract

A series of new 8-Bromo-1,3-bis(aryl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazines **2a–n** have been synthesized, in which 6-bromonaphthol undergoes a ring closure reaction with substituted aryl and heteroarylaldehydes to give naphthoxazine derivatives. Some of these were hydrolyzed to obtain the aminobenzylnaphthols **3c** and **3l** which are further condensed with different aryl/heteroarylaldehydes to yield **4a–e.** The structures were confirmed through elemental analysis, spectral studies and single crystal X-ray study. The compounds were screened for their antibacterial and antifungal activity and some of them exhibited promising activity.

Keywords: 8-Bromo-1,3-diaryl-2,3-dihydro-1*H*-naphtho[1,2e][1,3]oxazine, Ring-closure reaction, Aryl/heteroarylaldehydes, Single crystal X-ray, Antimicrobial activities

1. Introduction

Heterocycles containing the oxazine nucleus are found to possess a wide range of biological applications (Takimoto & Calvo, 2008; Ohnacker, & Scheffler, H. 1960). Efavirenz, a trifluoromethyl-1,3-oxazin-2-one, is a non-nucleoside reverse transcriptase inhibitor which shows high activity against a variety of HIV-1 mutant strains (Young *et al*., 1995). 1,3-Oxazine derivatives are also known as progesterone receptor agonists (Zhang *et al*., 2003). Oxazine derivatives have shown analgesic, antipyretic anticonvulsant and antimicrobial activity (Clauson-Kaas *et al.*, 1968; Singh *et al.,* 1995; Latif et al., 1982). Oxazine with naphthalene ring, called naphthoxazine are used in the treatment of Parkinson's disease (Millan *et al*., 2004; Joyce *et al*., 2003). Naphthoxazines are also known for their psycho stimulating and antidepressant activity (Nozulak & Giger, 1987). Dihydrofuronaphth[1,3]oxazines have shown anti-tumor activity (Benameur *et al*., 1996). The stereoelectronic effects in ring-chain tautomerism of 1,3-diarylnaphth[1,2-*e*][1,3]oxazines and 3-alkyl-1-arylnaphth[1,2-*e*][1,3]oxazines is reported (Szatmari *et al*., 2004). The studies on the synthesis of 1,3-diarylnaphthoxazines (Turgut *et al.,* 2007) and substituent effects in the ring-chain tautomerism are reported (Szatmari *et al*., 2003). The synthesis and conformational analysis of naphth[1',2':5,6][1,3]oxazino[3,2-c][1,3]benzoxazine and naphtha[1'2':5,6][1,3]oxazino[3,4-c][1,3] benzoxazine derivatives have been reported (Heydenreich *et al*., 2006). Only few reports are available regarding their biological activity. Hence, there is enough scope to explore new oxazine derivatives for biological activities. In this connection, the present paper describes the synthesis and antimicrobial study of new 8-bromo-1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2e][1,3]oxazines.

2. Experimental

TLC was run on a Merck silica gel 60 F254 coated aluminum plates and melting points were taken in open capillary tubes and are uncorrected. Elemental analysis was carried out using Flash EA 1112 Series, CHNSO Analyzer (Thermo). IR spectra in KBr pellets were recorded on Jasco FT/IR-4100 FTIR spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ and in DMSO-d6 on a Bruker DRX-300 (300 MHz) spectrometer using TMS as internal standard and Mass spectra were recorded on a Jeol SX 102/Da-600 mass spectrometer/data system using Argon/Xenon (6kv,10mA) as FAB gas.

2.1 General procedure for the synthesis of 8-bromo-1,3-bis(aryl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazines (2a-n)

To 6-bromo-2-naphthol (2.23 g, 0.01 mol) in methanol (10 ml) was added aryl or heteroarylaldehyde (0.02 mol; freshly distilled if a liquid) and 10 ml of 25-30% methanolic ammonia. The mixture was left to stand at ambient temperature for 2-3 days, during which the crystalline products separated out. The crude product were filtered off, washed with cold methanol and purified by recrystallization.

8-Bromo-1,3-bis(phenyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (2a)

^{1}H NMR ($CDCl_3$, δ ppm): 5.52 (s, 1H, CH), 5.64 (s, 1H, CH), 7.21-8.1(m, 15H, ArH), 8.14 (s, 1H, naphthalene ring proton). ^{13}C-NMR ($CDCl_3$, δ ppm): 53.49, 79.09, 113.68, 114.31, 114.80, 115.75, 116.03, 116.93, 120.31, 124.19, 125.78, 127.78, 128.20, 128.56, 129.74, 130.12, 130.29, 134.01. MS FAB: 416 M^+, 418 $[M+2]^+$.

8-Bromo-1,3-bis(2-chlorophenyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (2b)

^{1}H NMR ($CDCl_3$, δ ppm): 5.97 (s ,1H , CH), 6.05 (s,1H, CH), 6.85-7.92 (m, 13H, ArH), 8.95 (s, 1H, naphthalene ring proton), 11.85 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$, δ ppm): 53.55, 80.01, 113.68, 114.31, 114.80, 115.75, 116.03, 116.93, 120.31, 124.19,124.89, 125.78, 127.78, 128.20, 128.56, 129.74, 130.12, 130.29, 134.01,136.10, 136.44, 136.52, 146.23. MS FAB: 452 M^+, 454 $[M+2]^+$.

8-Bromo-1,3-bis(3-methoxyphenyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (2c)

^{1}H NMR ($CDCl_3$, δ ppm): 3.53 (s, 3H, OCH3), 3.69 (s, 3H, OCH3), 5.96 (s, 1H, CH), 6.02 (s, 1H, CH), 6.81-7.90 (m, 12H, ArH), 9.06 (s, 1H, naphthalene ring proton), 12.60 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$, δ ppm): 53.49, 55.57, 67.76, 80.57,110.51, 110.74, 111.23, 114.46, 116.03, 116.72, 119.95, 120.43, 120.85, 121.19, 121.43,123.22, 123.67, 127.96, 128.50,128.72, 129.08, 129.49, 130.48, 133.02 156.74, 159.27. MS FAB: 476 M^+, 478 $[M+2]^+$.

8-Bromo-1,3-bis(4-methoxyphenyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (2d)

^{1}H NMR ($CDCl_3$, δ ppm): 3.46 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 5.96 (s, 1H, CH), 6.06 (s, 1H, CH), 6.74-7.89(m, 12H, ArH), 9.07 (s, 1H, naphthalene ring proton), 12.61 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$, δ ppm): 53.49, 55.46, 55.57, 80.27, 110.74, 111.23, 114.46, 116.72, 119.95, 120.43, 120.85, 121.19, 121.43,123.22, 123.67, 127.96,128.72, 129.49, 130.48, 133.02 156.77, 159.28. MS FAB: 476 M^+, 478 $[M+2]^+$.

8-Bromo-1,3-bis(3-bromophenyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (2e)

^{1}H NMR ($CDCl_3$, δ ppm): 5.51 (s, 1H, CH), 5.67 (s, 1H, CH), 7.16-8.16(m, 13H, ArH).

^{13}C-NMR ($CDCl_3$, δ ppm): 53.49, 79.09, 113.68, 114.31, 114.80, 115.75, 116.03, 116.93,

199.86,120.31, 123.6,124.19, 125.78, 127.24,127.78, 128.20, 128.56, 129.74,130.06, 130.12, 130.29, 130.68, 131.68,134.01. MS FAB: 574 M^+, 576 $[M+2]^+$.

8-Bromo-1,3-bis(2-furyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (2f)

^{1}H NMR ($CDCl_3$, δ ppm): 5.96 (s, 1H, CH), 6.06 (s, 1H, CH), 6.74-7.89 (m, 11H, ArH).

^{13}C-NMR ($CDCl_3$, δ ppm): 53.49, 79.09, 105.68, 105.81, 114.80, 115.75, 120.31, 124.19, 125.78, 127.78, 128.20, 128.56, 129.74, 130.12, 130.29, 134.01, 141.58, 141.62, 153.6, 155.2. MS FAB: 396 M^+, 398 $[M+2]^+$.

8-Bromo-1,3-bis(3,4-dimethoxyphenyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (2g)

^{1}H NMR ($CDCl_3$, δ ppm): 3.62-3.91 (m, 12H, OCH_3), 5.42 (s ,1H , CH), 5.65 (s, 1H, CH), 6.51-7.89 (m, 11H, ArH). ^{13}C-NMR(CDCl3, δ ppm): 53.49, 55.61, 80.09, 110.74, 114.46, 116.03, 116.72, 119.95, 120.43, 120.85, 121.19, 121.43,123.22, 123.67, 127.96, 128.50,128.72, 129.08, 129.49, 130.48, 133.02, 156.30, 156.32. MS FAB: 536 M^+, 538 $[M+2]^+$.

8-Bromo-1,3-bis(2-methoxyphenyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (2i)

^{1}H NMR (CDCl3, δ ppm): 3.62 (s, 3H, OCH3), 3.68 (s, 3H, OCH3), 5.96 (s, 1H, CH), 6.06 (s,1H, CH), 6.74-7.89(m, 12H, ArH), 9.07(s, 1H, ArH). ^{13}C-NMR ($CDCl_3$, δ ppm): 53.49, 55.57, 67.76, 80.57,110.51, 110.74, 111.23, 114.46, 116.03, 116.72, 119.95, 120.43, 120.85, 121.19, 121.43, 123.22, 123.67, 127.96, 128.50, 128.72, 129.08, 129.49, 130.48, 133.02 156.74, 159.27. MS FAB: 476 M^+, 478 $[M+2]^+$.

8-Bromo-1,3-bis(4-chlorophenyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (2j)

^{1}H NMR ($CDCl_3$, δ ppm): 5.55 (s ,1H , CH), 5.59 (s, 1H, CH), 7.21-7.94 (m, 12H, ArH),

8.61(s,1H,ArH). ^{13}C-NMR ($CDCl_3$, δ ppm): 53.49, 79.09, 113.68, 114.31, 114.80, 115.75, 116.03, 116.93, 120.31, 124.19, 125.78, 127.32, 127.78, 128.20, 128.56, 129.74, 130.12, 130.29, 134.01, 134.12. MS FAB: 485 M^+, 487 $[M+2]^+$.

8-Bromo-1,3-bis[4-(methylthio)phenyl]-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (2k)

^{1}H NMR ($CDCl_3$, δ ppm): 2.47 (s, 3H, SCH_3), 2.50 (s, 3H, SCH3), 5.55 (s ,1H , CH), 5.61 (s, 1H, CH), 7.11-7.62 (m, 4H, ArH), 7.62-7.67 (m, 6H, ArH), 7.9 (d, 2H, J=8.7, ArH), 8.15 (s, 1H, ArH). ^{13}C-NMR ($CDCl_3$, δ ppm): 13.8, 55.36, 79.26, 113.68, 114.31, 114.80, 115.75, 116.03, 116.93, 120.31, 124.19, 125.78,126.35,127.12, 127.78, 128.20, 128.56, 129.74, 130.29, 136.18. MS FAB: 508 M^+, 510 $[M+2]^+$.

8-Bromo-1,3-bis(3-methylphenyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (2l)

^{1}H NMR ($CDCl_3$, δ ppm): 2.35 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 5.96 (s ,1H , CH), 6.06 (s, 1H, CH), 6.74-7.89(m, 12H, ArH), 9.07 (s, 1H, naphthalene ring proton), 12.61 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$, δ ppm): 21.20, 55.49, 79.09, 110.68, 114.31, 114.80, 115.75, 116.03, 116.93, 120.31, 124.19, 125.78, 126.32, 126.98, 127.22, 127.78, 128.20, 128.56, 129.74, 130.12, 130.29, 134.01, 138.23. MS FAB: 444 M^+, 446 $[M+2]^+$.

8-Bromo-1,3-bis(3-pyridinyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (2m)

^{1}H NMR ($CDCl_3$, δ ppm): 5.66 (s ,1H , CH), 5.68 (s, 1H, CH), 7.18-7.97(m, 9H, ArH), 8.52 (t, 1H, J=8.0 Hz, py proton), 8.64 (t, 1H, J=7.9 Hz, py proton), 8.70 (d, 1H, J=7.2 Hz, py proton), 8.82 (d, 1H, J=7.2 Hz, py proton). ^{13}C-NMR ($CDCl_3$, δ ppm): 51.67, 84.55, 113.06, 117.37, 120.36, 123.11, 124.15, 125.14, 128.72,128.91, 129.74, 130.16, 130.20, 130.67, 133.87, 136.67, 137.42, 147.81, 148.90, 149.82, 150.78, 152.42.MS FAB: 418 M^+, 420 $[M+2]^+$.

2.2 General procedure for the synthesis of 1-(aminosubstituted methyl)-2-naphthols 3c and 3l

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

1-[Amino(3-methoxyphenyl)methyl]-6-bromo-2-naphthol (3c)

^{1}H NMR ($CDCl_3$, δ ppm): 1.58 (bs, 2H, NH_2), 3.73 (s, 1H, OCH_3), 6.05 (s, 1H, CH), 6.79 (d, 1H, J=8.1 Hz, ArH), 6.96-7.02 (m, 2H, ArH), 7.14-7.25 (m, 2H, ArH), 7.38 (d, 2H, J=9.3 Hz, ArH), 7.58 (t, 1H, J=9.3 Hz, ArH), 7.85 (s, 1H, ArH).MS FAB: 358 M^+, 360 $[M+2]^+$.

IR (KBr, γ_{max} cm^{-1}): 3358, 3187, 1508. Elemental analysis % Calculated (Found) for $C_{18}H_{16}BrNO_2$: C- 60.35(60.33), H- 4.50(4.49) and N-3.91(3.89). m.p:138-140 °C

1-[Amino(3-methylphenyl)methyl]-6-bromo-2-naphthol (3l)

^{1}H NMR ($CDCl_3$, δ ppm): 1.58 (bs, 2H, NH_2), 2.39 (s, 1H, CH_3), 6.01 (s, 1H, CH), 7.06-7.25 (m, 5H, ArH), 7.37 (d, 1H, J=9 Hz, ArH), 7.55 (d, 1H, J=9 Hz, ArH), 7.60 (d, 1H, J=9 Hz, ArH), 7.93 (s, 1H, ArH) MS FAB: 342 M^+, 346 $[M+2]^+$.

IR (KBr, γ_{max} cm^{-1}): 3356, 3329, 1511. Elemental analysis % Calculated (Found) for $C_{18}H_{16}BrNO$: C- 63.17(63.16), H- 4.71(4.69) and N-4.09(4.07). m.p.:118-120 °C.

2.3 General procedure for the synthesis of 8-bromo-1,3-diaryl-2,3-dihydro-1H-naphtho[1,2e][1,3]oxazines (4a-e)

To a solution of the appropriate aminonaphthol **3c** or **3l (**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 product separated were filtered off and then recrystallized in methanol.

8-Bromo-1-(3-methoxyphenyl)-3-(4-chlorophenyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (4a)

^{1}H NMR ($CDCl_3$, δ ppm): 3.76 (s, 3H, OCH_3), 5.61 (s ,1H , CH), 5.89 (s, 1H, CH), 6.81- 6.86(m, 4H, ArH),7.05-7.69(m, 6H, ArH), 7.90(d, 1H, J=6.9Hz, ArH), 7.95(d, 1H, J=7.8Hz, ArH), 8.90 (s, 1H, naphthalene ring proton). ^{13}C-NMR ($CDCl_3$, δ ppm): 53.49, 55.15, 79.09, 113.68, 114.31, 114.80, 115.75, 116.03, 116.93, 120.31, 124.19, 124.67,125.78, 127.78, 128.20, 128.56, 129.74, 130.12, 130.29, 134.01, 152.63, 158.93. MS FAB: 480 M^+, 482 $[M+2]^+$.

8-Bromo-1-(3-methoxyphenyl)-3-(3-methylphenyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (4b)

^{1}H NMR ($CDCl_3$, δ ppm): 2.37 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 5.59 (s ,1H , CH), 5.70 (s, 1H, CH), 6.77-7.91(m, 12H, ArH), 8.6 (s, 1H, naphthalene ring proton). ^{13}C-NMR ($CDCl_3$, δ ppm): 20.12, 53.97, 55.22, 81.95, 113.68, 114.31, 114.80, 115.75, 116.03, 116.93, 117.06, 119.65, 120.31,121.42, 121.42,123.31, 124.70, 125.78, 127.78, 128.20, 128.56, 129.74, 130.12, 130.29, 134.01, 158.63. MS FAB: 460 M^+, 462 $[M+2]^+$.

8-Bromo-1-(3-methoxyphenyl)-3-pyridin-3-yl-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (4c)

^{1}H NMR ($CDCl_3$, δ ppm): 3.79 (s, 3H, OCH_3), 5.61 (s ,1H , CH), 5.74 (s, 1H, CH), 6.83(d, 2H, J=9.9Hz, ArH),7.24-7.40(m, 6H, ArH), 7.69(d, 1H, J=6.7Hz, ArH), 7.92-7.95(m, 2H, ArH), 8.61(s, 1H, ArH), 8.85 (s, 1H, ArH). ^{13}C-NMR($CDCl_3$, δ ppm): 51.67, 54.43, 80.58, 114.31, 115.75, 116.03, 116.93,117.42, 120.31, 123.11, 124.19, 125.18, 127.78, 128.20, 128.91, 129.74, 130.12, 130.29, 130.67, 134.01,136.67,137.89,149.30, 149.82. MS FAB: 447 M^+, 449 $[M+2]^+$.

8-Bromo-1-(3-methylphenyl)-3-pyridin-3-yl-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (4d)

^{1}H NMR ($CDCl_3$, δ ppm): 2.37 (s, 3H, CH_3), 5.61 (s, 1H, CH), 5.74 (s, 1H, CH), 6.83(d, 2H, J=8.9Hz, ArH), 7.24-7.40(m, 6H, ArH), 7.86-7.95(m, 3H, ArH), 8.61(s, 1H, ArH), 8.85 (s, 1H, ArH). ^{13}C-NMR($CDCl_3$, δ ppm): 20.23, 54.33, 80.18, 114.21, 115.65, 116.01, 116.84, 117.39, 120.31, 123.21, 124.17, 125.09, 127.76, 128.18, 128.91, 129.69, 130.12, 130.27, 130.65, 134.12, 136.77, 137.91, 149.28, 149.82. MS FAB: 431 M^+, 433 $[M+2]^+$.

8-Bromo-1-(3-methylphenyl)-3-(4-chlorophenyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (4e)

^{1}H NMR ($CDCl_3$, δ ppm): 2.39 (s, 3H, CH_3), 5.55 (s, 1H, CH), 5.59 (s, 1H, CH), 7.20-7.92(m, 12H, ArH), 8.3 (s, 1H, ArH). ^{13}C-NMR ($CDCl_3$, δ ppm): 20.22, 53.49, 79.09, 113.68, 114.31, 114.80, 115.75, 116.03, 116.93, 120.31, 124.19, 124.67,125.78, 127.78, 128.20, 128.56, 129.74, 130.12, 130.29, 134.01, 152.63, 158.93. MS FAB: 464 M^+, 466 $[M+2]^+$.

2.4 Pharmacology

2.4.1 Antibacterial studies

The newly synthesized compounds were screened for their antibacterial activity against *Escherichia coli* (ATTC-25922), *Staphylococcus aureus* (ATTC-25923), *Pseudomonas aeruginosa* (ATCC-27853) and *Klebsiella pneumoniae* (recultured) bacterial strains by serial plate dilution method (Barry, 1991; James *et al.,* 1991). Serial dilutions of the drug in Mueller Hinton broth were taken in tubes and their pH was adjusted to 5.0 using phosphate buffer. A standardized suspension of the test bacterium was inoculated and incubated for 16-18 h at 37°C.

A number of antimicrobial discs are placed on the agar for the sole purpose of producing zones of inhibition in the bacterial lawn. Twenty milliliters of agar media was poured into each Petri dish. Excess of suspension was decanted and plates were dried by placing in an incubator at 37°C for an hour. Using a punch, wells were made on these seeded agar plates and minimum inhibitory concentrations of the test compounds in dimethylsulfoxide (DMSO) were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The Petri dishes were prepared in triplicate and maintained at 37°C for 3-4 days. Antibacterial activity was determined by measuring the diameter of inhibition zone. Activity of each compound was compared with ciprofloxacin as standard (Fenlon, & Cynamon, 1986). Zone of inhibition was determined for newly synthesized compounds at 10 μg/ml concentration and the results are presented in **Table 4**.

2.4.2 Antifungal studies

Newly prepared compounds were also screened for their antifungal activity against *Aspergilus flavus* (NCIM No.524), *Aspergilus fumigates* (NCIM No. 902), *Penicillium* (*S.aurus*) (recultured) and *Trichophyton mentagrophytes* (recultured) in DMSO by serial plate dilution method (Arthington-Skaggs *et al*., 2000; Verma *et al*., 1998). Sabourands agar media was prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 ml) and adjusting the pH to 5.7. Normal saline was used to make a suspension of spore of fungal strains for lawning. A loopful of particular fungal strain was transferred to 3 ml saline to get a suspension of corresponding species. Twenty milliliters of agar media was poured into each Petri dish. Excess of suspension was decanted and plates were dried by placing in incubator at 37°C for 1 h. Using a punch, wells were made on these seeded agar plates minimum inhibitory concentrations of the test compounds in DMSO were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The Petri dishes were prepared in triplicate and maintained at 37°C for 3-4 days. Antifungal activity was determined by measuring the diameter of inhibition zone at 10 μg/ml concentration. Activity of each compound was compared with Fluconazole as standard. Zone of inhibitions were determined and the results are given in **Table 5**.

3. Results and discussion

The reaction sequence employed for synthesis of the title compounds are shown in **scheme 1** and **scheme 2**. 8-Bromo-1,3-bis(aryl)-2,3-dihydro-1*H*-naphtho[1,2e][1,3]oxazines **(2a-n)** were obtained by treating 6-bromonaphthol with aryl aldehydes in presence of methanolic ammonia at room temperature for 2-3 days. The reaction leads to the generation of two chiral centers in the structure which would result in a mixture of diastereomers. The newly synthesized compounds were characterized based on their elemental analysis and spectral (^{1}H NMR, ^{13}C NMR and FAB mass) data. The characterization data of all the new compounds are presented in **Table 1.** The formation of 8-Bromo-1,3-bis(phenyl)-2,3-dihydro-1H-naphtho[1,2-e] [1,3]oxazine **(2a)** and 8-bromo-1,3-bis(3-methoxyphenyl)-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine **(2c)** was confirmed through elemental analysis, spectral data and single crystal X-ray studies (Jasinsik *et al*., 2010; Sarojini *et al*., 2007). In ^{1}H NMR, the peaks due to two OCH_3 groups appeared as singlet at δ 3.53 and 3.69. Two singlets were observed at δ 5.96 and δ 6.02 representing N-CH- and O-CH- protons of oxazine ring respectively. The aromatic protons resonated as multiplet at δ 6.81-7.90 accounting for 12 protons. A singlet was observed at δ 9.06 representing naphthalene ring proton and a broad singlet at δ 12.06 accounted for NH proton. While ^{13}C NMR showed signals at 53.49 and 55.57 due to two OCH_3. The other signals at 67.76 and 80.57 were due to C-atoms of N-CH- and O-CH-. The aromatic carbon signals appeared at 110.51, 110.74, 111.23, 114.46, 116.03, 116.72, 119.95, 120.43, 120.85, 121.19, 121.43,123.22, 123.67, 127.96, 128.50,128.72, 129.08, 129.49, 130.48, 133.02 156.74, 159.27 accounting for 22 carbon atoms. The structure of this compound was also confirmed through single crystal X-ray studies (Sarojini *et al.,* 2007).

The naphthoxazine **2c** and **2l** were subjected to acid hydrolysis to get Betti bases (Betti, 1941). [1-*α*-aminobenzyl]-6-bromo-2-naphthols **3c**, **3l** in good yield. In the ^{1}H NMR spectrum of **3c**, the NH_2 protons resonated at δ 1.58 as a broad singlet and methoxy protons resonated as a singlet at δ 3.73 integrating for three protons while the singlet due to -N-CH- appeared at δ 6.05. The signal for naphthalene ring proton appeared as follows; C4-H appeared at δ 6.79 as doublet J=8.1Hz and C5-H as singlet at δ 7.85. The C7-H proton resonated at δ 7.38 as doublet with J=9.3 Hz. The C5 –H phenyl ring proton resonated at δ 7.58 J=9.3 Hz as triplet. The FAB mass of this compound showed the molecular ion peak at m/z = 358 and the other peak was observed at 360 (M+2) indicating the presence of bromine. The reactions of the Betti bases **3c, 3l** with equivalent amounts of arylaldehydes/heteroaldehydes afforded the corresponding 8-bromo-1,3-diaryl-2,3-dihydro-1*H*-naphtho[1,2e][1,3]oxazines **(4a-e) (Table 2).** The characterization data of all the compounds are given in **Table 3.** In a typical example, the ^{1}H NMR of **4d** showed a singlet at δ 2.37 accounting for three protons, indicating the presence of CH_3. The N-CH- and O-CH- protons resonated as singlets at δ 5.61 and 5.74 respectively. The C5-H proton appeared as a singlet at δ 8.61 and a singlet was observed at δ 8.85 representing

the pyridine ring proton. In ^{13}C-NMR the signal at δ 20.23 accounting for CH_3 and at δ 54.33 and 80.18 for N-CH- and O-CH- were observed. The FAB mass of this compound showed the molecular ion peak at m/z = 431.

Compound *8-Bromo-1,3-bis(4-fluorophenyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (***2h)** was obtained as colourless blocks by recrystallization from acetonitrile solution and characterized through single crystal X-ray study, which reveals the following: $C_{24}H_{16}BrF_2NO$, M_r = 452.28, triclinic, $P\overline{1}$ (No. 2), a = 8.7436 (8) Å, b = 10.7804 (10) Å, c = 11.6475 (13) Å, α = 102.536 (5)°, β = 109.154 (6)°, γ = 104.135 (6)°, V = 951.31 (18) Å^3, Z = 2, ρ_{calc} = 1.579 g cm^{-3}, μ = 2.195 mm^{-1}, F(000) = 456, Nonius Kappa CCD diffractometer, Mo Kα radiation, λ = 0.71073 Å, T = 120 K, $R(F)$ = 0.033, $wR(F^2)$ = 0.082, S = 1.04. All the bond lengths and bond angles fall within their expected ranges of values (Allen *et al.,* 1987). The molecular structure of **2h** is shown in **Fig. 1** and intermolecular N–H···π interactions are shown in **Fig. 2**. The conformation of the six-membered C1/C10/C11/N1/C12/O1 oxazine ring approximates to a half-chair, with C1/C10/C11/O1 roughly coplanar (r.m.s. deviation = 0.021 Å) and C12 and N1 displaced from their mean plane by +0.384 (6) Å and –0.328 (6) Å, respectively. The C11–N1–C12 bond angle of 110.9 (3)° and the bond angle sum of 331° for N1 are strongly indicative of sp^3 hybridization for the nitrogen atom and its attached H atom (coordinates freely refined) occupies a *pseudo* axial site. The dihedral angles between the C1–C10 naphthalene ring system and the pendant C13–C18 and C19–C24 fluorobenzene rings were 20.50 (17) and 74.05 (16)°, respectively. In the crystal, inversion dimers arise, being linked by pairs of N–H···π (Page & Rzepa, 1996) interactions [N–H = 0.85 (4) Å, H···π = 2.49 (4) Å, N–H···π = 166 (3)°, where π is the centroid of the C4–C9 ring at the symmetry position [1–x, –y, 1–z], as shown in **Fig. 2**. Any aromatic π–π stacking effects in the crystal of **2h** must be very weak, with a minimum centroid–centroid separation of 3.926 (2) Å. All the H atoms were located in difference maps and their positions and U_{iso} values were freely refined. [X-ray crystallographic files, in Cif format, for the structure determinations of **2h** (**CCDC 760555**) has been deposited with the Cambridge Crystallographic Data Center, CCDC: 26091. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ (fax: ? 44-1223-336033; email: deposit@ccdc.cam.uk or http://www.ccdc.cam.ac.uk.].

Compounds were also screened for their antibacterial and antifungal activity. Almost all the compounds tested showed moderate to good activity against the bacterial and fungal strains. Compounds **2h, 2j, 2l** and **4e** showed promising results. The good activity could be attributed to the presence of phenyl ring substituted with fluoro, chloro and methyl groups attached to the oxazine ring. Replacing one of the aryl substituent with a different aryl/heteroaryl group showed increase in the activity of **4a, 4b, 4c, 4d** and **4e**.

In the antifungal activity study, compound **4e** emerged with good activity against fungal strains, particularly against *Aspergilus flavus.* This may be due to the presence of 3-methylphenyl and 4-chlorophenyl groups attached to the naphthoxazine ring.

4. Conclusions

The present study reports the synthesis of series of new naphthoxazine derivative. Structure of compound **2h** was elucidated through single crystal X-ray diffraction. The newly synthesized compounds were screened for their biological activity. Some of the new compounds found to exhibit good activity against tested bacterial and fungal strains. Compounds having fluoro, chloro and methyl substituted phenyl group attached to naphthoxazine showed promising activity. However it is a preliminary study and these newly synthesized compounds should be subjected to detailed pharmacological and toxicological evaluation for their application in clinical use.

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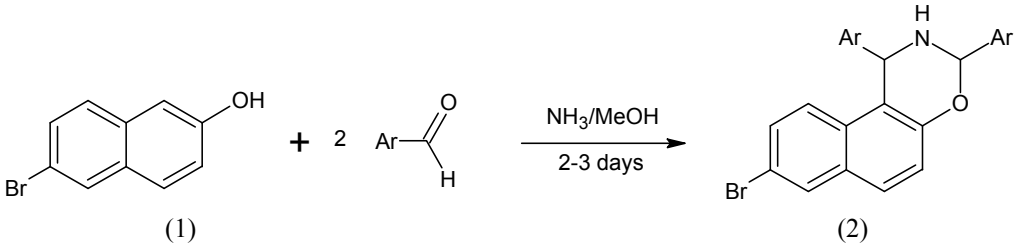
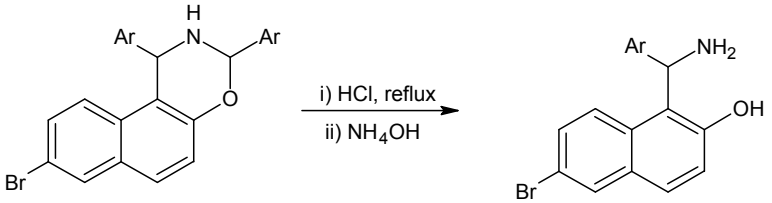
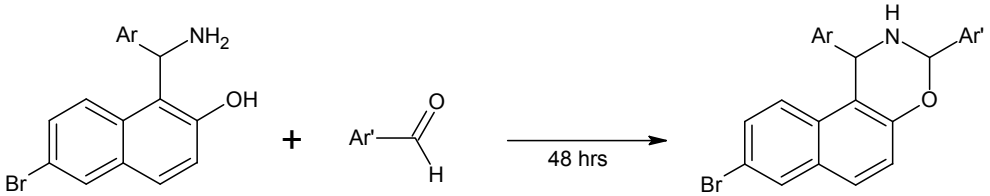


(1) (2)

Scheme 1



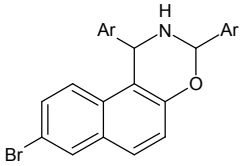
(2) (3)

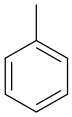
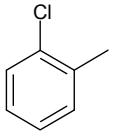
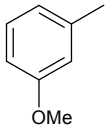
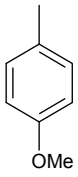
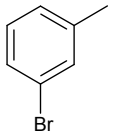
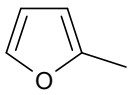
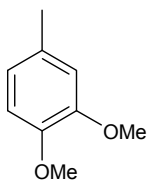


(3) (4)

Scheme 2

Table 1. Characterization data of compounds 2a-n



Compd.	Ar	m. p. (°C)	Yield %	Mol. formula	Elemental analysis % found (calculated)		
					C	H	N
2a		150-152	51	$C_{24}H_{18}BrNO$	69.19 (69.24)	4.31 (4.35)	3.34 (3.36)
2b		106-108	46	$C_{24}H_{16}BrCl_2NO$	59.39 (59.41)	3.31 (3.32)	2.89 (2.88)
2c		88-90	52	$C_{26}H_{22}BrNO_3$	65.48 (65.55)	4.61 (4.66)	2.90 (2.94)
2d		162-164	56	$C_{26}H_{22}BrNO_3$	65.50 (65.55)	4.60 (4.66)	2.92 (2.94)
2e		148-150	40	$C_{24}H_{16}Br_3NO$	50.20 (50.21)	2.79 (2.80)	2.43 (2.43)
2f		118-120	65	$C_{20}H_{14}BrNO_3$	60.61 (60.62)	3.52 (3.56)	3.51 (3.53)
2g		132-134	48	$C_{28}H_{26}BrNO_5$	62.65 (62.69)	4.88 (4.88)	2.59 (2.61)

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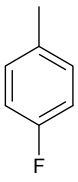
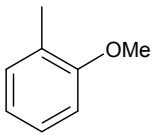
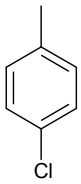
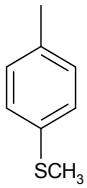
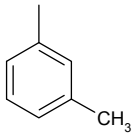
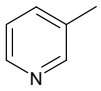
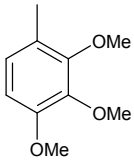
2h		162-164	50	$C_{24}H_{16}BrF_2NO$	63.70 (63.73)	3.55 (3.56)	3.01 (3.09)
2i		130-132	49	$C_{26}H_{22}BrNO_3$	65.51 (65.55)	4.60 (4.66)	2.93 (2.94)
2j		172-174	60	$C_{24}H_{16}BrCl_2NO$	59.38 (59.41)	3.31 (3.32)	2.85 (2.88)
2k		156-158	41	$C_{26}H_{22}BrNOS_2$	61.39 (61.41)	4.33 (4.36)	2.71 (2.75)
2l		124-126	49	$C_{26}H_{22}BrNO$	70.26 (70.27)	4.96 (4.99)	3.11 (3.15)
2m		118-120	40	$C_{22}H_{16}BrN_3O$	63.15 (63.17)	3.84 (3.85)	10.01 (10.04)
2n		138-140	48	$C_{30}H_{30}BrNO_7$	60.39 (60.41)	5.03 (5.06)	2.31 (2.34)

Table 2. Substituents Ar and Ar' of compounds 4a-e

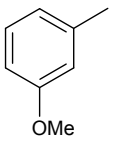
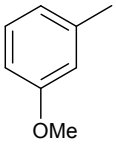
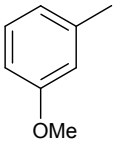
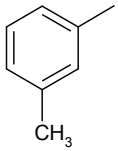
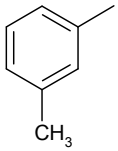
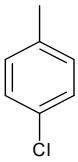
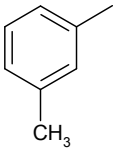
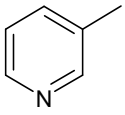
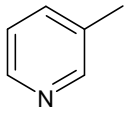
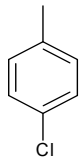
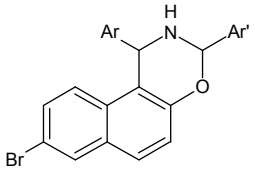
Compound	4a	4b	4c	4d	4e
Ar					
Ar'					

Table 3. Characterization data of compounds 4a-e



Compound	m.p. (°C)	Yield %	Mol. formula	Elemental analysis % found (calculated)		
				C	H	N
4a	152-154	68	$C_{25}H_{19}BrClNO_2$	62.44 (62.45)	3.96 (3.98)	2.90 (2.91)
4b	114-116	69	$C_{26}H_{22}BrNO_2$	67.81 (67.83)	4.79 (4.81)	3.01 (3.04)
4c	134-136	52	$C_{24}H_{19}BrN_2O_2$	64.42 (64.42)	4.27 (4.28)	6.24 (6.26)
4d	120-122	60	$C_{24}H_{19}BrN_2O$	66.81 (66.83)	4.42 (4.44)	6.48 (6.49)
4e	156-158	65	$C_{25}H_{19}BrClNO$	64.59 (64.60)	4.10 (4.12)	3.02 (3.01)

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Table 4. Antibacterial activity of the compounds 2a-n and 4a-e at 10 µg/ml concentration. (Diameter of zone of inhibition in mm)

Compound	*E.coli*	*S.aureus*	*K.pneumoniae*	*P.aeruginosa*
2a	-	-	-	-
2b	11	9	10	11
2c	6	9	10	10
2d	12	13	9	13
2e	-	-	-	-
2f	9	8	8	6
2g	12	11	11	10
2h	18	15	16	12
2i	12	13	9	11
2j	16	19	11	18
2k	-	-	-	-
2l	16	15	16	16
2m	11	10	10	10
2n	13	15	11	12
4a	14	14	12	10
4b	16	14	11	12
4c	14	12	14	14
4d	12	15	14	14
4e	18	12	18	16
Ciprofloxacin	24	27	24	20

Table 5. Antifungal activity of the compounds 2a-n and 4a-e at 10 µg/ml concentration. (Diameter of zone of inhibition in mm)

Compound	*Penicillium*	*Trichophton*	*Aspergilus Flavus*	*Aspergilus Fumigatus*
2a	-	-	-	-
2b	11	9	10	11
2c	6	9	10	10
2d	12	13	9	13
2e	-	-	-	-
2f	9	8	8	6
2g	12	11	11	10
2h	19	15	18	12
2i	15	13	9	11
2j	16	12	18	12
2k	-	-	-	-
2l	16	15	16	16
2m	11	10	10	10
2n	13	15	11	12
4a	14	14	12	14
4b	16	14	11	12
4c	14	12	14	14
4d	10	15	14	14
4e	16	15	18	18
Fluconazole	21	18	21	20

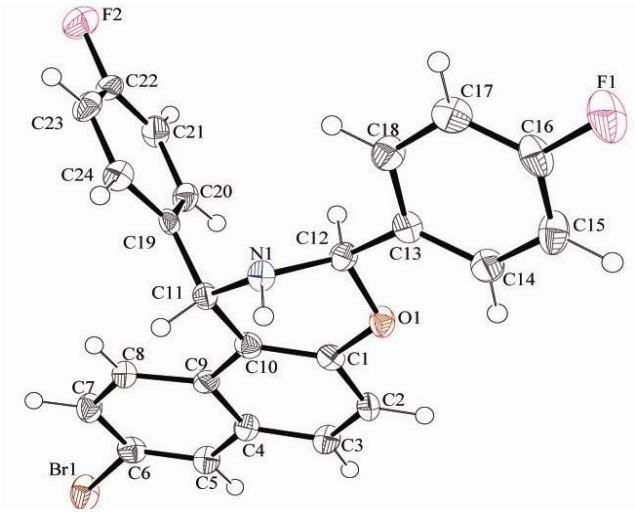

Figure 1. Molecular structure of 2h showing 50% displacement ellipsoids for the non-hydrogen atoms

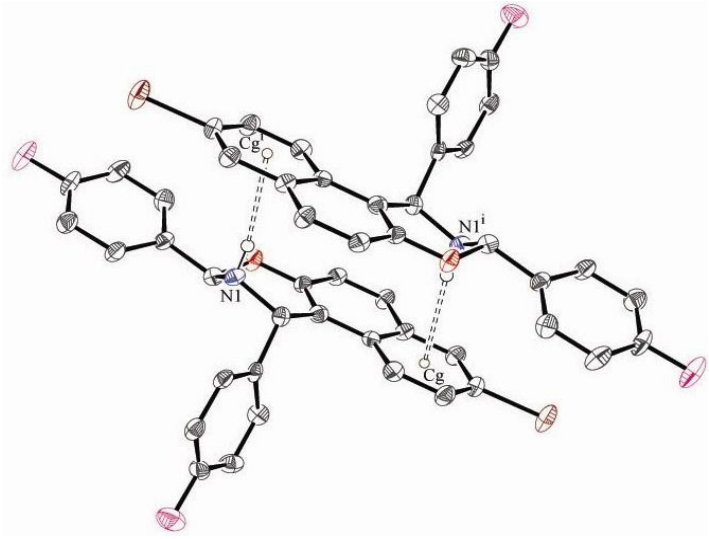

Figure 2. N–H···π interactions in the crystal of 2h

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