Chemoselective Reaction of Formalin with 2-(5-Substituted-2-hydroxybenzylamino)phenols: Synthesis of 6-Substituted 3-(2-hydroxyphenyl)-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazines

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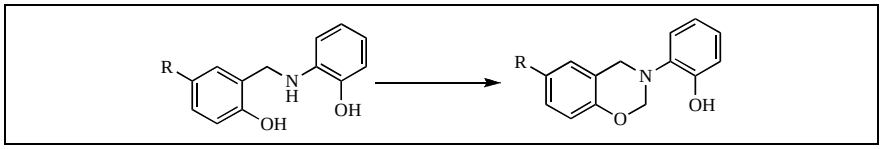

Reaction of 2-(5-substituted-2-hydroxybenzylamino)phenols (**2**) with formalin in ethanol under reflux has chemoselectively led to 2-(6-substituted-2*H*–benzo[*e*][1,3]oxazin-3(4*H*)-yl)phenols (**3**) in good yield involving the ring closure of the hydroxyl group of the C-aryl ring and not that of the N-aryl ring.

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INTRODUCTION

Substituted 1,3-benzoxazines have been found to possess a wide range of biological activities like antimicrobial [1-3], antitumour [4-5], antituberculosis [6-7], anthelmintic [8] *etc*. They are also capable of acting as tranquilizing and sedating agents [9]. In view of this, it has been planned to synthesize a new set of heterocyclic compounds with benzoxazine unit. Accordingly, the ring closure of *N*-phenyl-*N*-benzyl amines with *ortho* hydroxyl groups in both the aromatic rings has been effected by the reaction with formalin leading to a set of hitherto unknown *N*-(2-hydroxphenyl)-3,4-dihydro-benzo[*e*][1,3]-oxazines.

RESULTS AND DISCUSSION

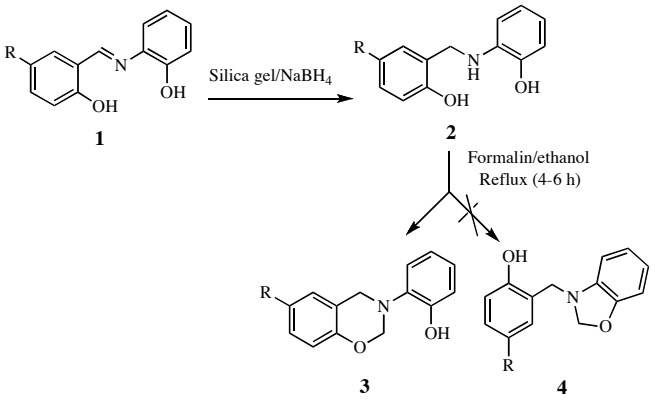
3,4-Dihydro-1,3-benzoxazine can be easily obtained by the reaction of *C*-(2-hydroxybenzyl)-*N*-arylamine with formalin. The *N*-aryl-3,4-dihydro-1,3-benzoxazines are well known to undergo polymerization upon heating [10]. With unsubstituted phenol, formaldehyde and primary aromatic amines as the starting materials, a series of monofunctional benzoxazine resins with low viscosities have been developed at room temperature [11]. However, monomeric *N*-aryl-1,3-benzoxazines have also been prepared. Condensation of 2-hydroxybenzyl alcohol with primary aromatic amines gave *N*-aryl benzoxazines, among other products [12]. Benzoxazines derived from aniline and 4-hydroxybenzoic acid and from phenol and 4-aminobenzoic acid were prepared with two different synthetic approaches [13]. Different *N*-(4-substituted phenyl) benzoxazines were prepared by the reaction of formaldehyde with the reduction product of 2-(imino-methyl)phenols [14].

Though there are several reports on the formation of monomeric benzoxazines, no attempt has been made so far to analyse the course of the reaction of formalin with *N*-benzylaniline with hydroxyl groups in the *ortho* position of both the aromatic rings. The cyclisation by formalin can occur at the C-aryl ring to give 3,4-dihydro-benzo[*e*][1,3]oxazine derivative, but there is a possibility for the cyclisation involving the *ortho* hydroxyl group of the N-aryl ring forming a five membered heterocyclic compound **4**. In the present work, it has been planned to investigate the course of the above reaction.

The substituted *N*-benzylanilines, the precursors for the investigation, 2-(5-substituted-2-hydroxybenzylamino)-phenols (**2**), have been prepared by the sodium borohydride reduction of the respective imines (**1**) [15] by an eco-friendly path using silica gel without solvent following a reported procedure [16]. All the synthesized compounds **2** are new and are fully characterized by nmr. Amines **2** on treatment with formalin under reflux in ethanol has led to the formation of a single product **3** identified as 6-substituted 3-(2-hydroxyphenyl)-3,4-di-hydrobenzoxazine in very good yield (Scheme 1). All compounds were characterized by nmr spectral data. The ^{1}H nmr spectrum of **3a** exhibits two sharp singlets at 4.34 and 5.00 ppm each accounting for two hydrogens for the methylene protons of the oxazine ring indicating that the oxazine ring is not rigid [17]. In the ^{13}C nmr spectrum, the respective carbons appear at 51.6 and 81.0 ppm. It can be noted that polymerization, which is common for N-aryl benzoxazines, did not take place under the reaction conditions. The reaction has taken place chemoselectively with the hydroxyl group in the aryl ring of the benzyl group and not that of the N-phenyl group.

The analytical and nmr data are not sufficient to conclude that the compound formed in Scheme 1 is not 3-benzyl-2,3-dihydrobenzo[*d*]oxazole **4**. Even different two dimensional nmr spectra reveal same type of connectivity for both the structures **3** and **4**. However, the

Scheme 1



Compound **1, 2** and **3**	R
a	$C(CH_3)_3$
b	$CH(CH_3)_2$
c	C_6H_5
d	Cl
e	OCH_3
f	$C(C_2H_5)(CH_3)_2$
g	$C(C_6H_5)(CH_3)_2$
h	Br
i	C_2H_5

fact that the hydroxyl group of the C-aryl ring is involved in ring closure and not that of the N-aryl ring is proved by carrying out the reaction under identical condition on simple 2-(benzylamino)phenol without success in the expected ring closure. The mass spectra of **3b** and **3h** have been recorded under EI mode. Both the compounds do not exhibit molecular ion peak. However, both compounds show peaks due to the fragments X-C_8H_7O (m/e = 162.10, X = $CH(CH_3)_2$, m/e = 197.97, X = Br) which can result only from structure **3** and not **4**, supporting the assignment.

A multi-component approach by irradiating a mixture of 4-substituted phenol, 2-aminophenol and formaldehyde has led to the formation of the target compound **3** with poor yield, the rest of the reaction mixture being polymeric in nature. Thus, it is clear that an approach involving the initial formation of the secondary amine followed by the formalin treatment seems more beneficial than the single pot approach wherein the polymerization dominates over the formation of the monomeric benzoxazine. Blocking the *ortho* positions of the aryl rings would have probably prevented the polymerization in the former approach. It is also observed that the reaction of **2** with formalin proceeds smoothly under microwave irradiation without any solvent giving **3** in comparable yield with reduced reaction time. Reaction gets completed in less than five minutes under microwave radiation suggesting this method to be more advantageous than the conventional one.

The antibacterial activity of the synthesized 6-substituted 3-(2-hydroxyphenyl)-3,4-dihydrobenzoxazines **3** have been studied against Gram positive (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram negative (*Escherichia coli, Klebsiella pneumoniae* and *Pseudomonas aeruginosa*) bacteria by dilution method. Unfortunately, all the compounds (**3**) do not show any significant activity *in vitro* against the tested organisms.

EXPERIMENTAL

All chemicals were of reagent grade quality and used without further purification. All melting points were recorded in open capillaries and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz spectrometer at 300 MHz and 75 MHz respectively in $CDCl_3$/DMSO-d_6 using TMS as internal standard. The signals due to NH and OH are so broad that in many cases they are not all visible at all, but exchange with D_2O. Microanalyses were carried out on a Perkin-Elmer instrument. GC-MS spectra were record on Thermo Finnigan spectrophotometer. All chromatographic separations were performed on 60-120 mesh silica gel using petroleum ether-ethyl acetate as eluent.

General procedure for preparation of the 2-(5-substituted-2-hydroxylbelzylamino)phenols (2) [16]. To a ground mixture of 2-(2-hydroxy-5-substituted benzylideneamino)phenol (3 mmoles), sodium borohydride (12 mmoles) and 2 g of silica gel (60 - 120 mesh) a few drops of chloroform followed by a few drops of water were added. After vigorous stirring for ten minutes, the reduction product (**2**) was extracted with hot chloroform and recrystallised from ethyl acetate.

2-(5-*tert*-Butyl-2-hydroxybenzylamino)pheno1 (2a). This compound was obtained as brown crystals (Ethyl acetate), yield 95%, mp 119-120 °C; ^1H nmr (300 MHz, $CDCl_3$): δ 1.31 (s, 9H), 4.40 (s, 2H), 6.77-6.91, (m, 5H), 7.16 (d, J = 2.4 Hz, 1H), 7.23 (dd, J = 8.4, 2.4 Hz, 1H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 31.5, 34.0, 49.0, 114.7, 115.2, 116.0, 120.6, 121.5, 122.3, 125.6, 125.9, 135.9, 142.8, 144.9, 154.2. *Anal.* calcd. for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16%. Found: C, 75.21; H, 7.83; N, 5.13%.

2-(5-*iso*-Propyl-2-hydroxybenzylamino)pheno1 (2b). This compound was obtained as brown crystals (Ethyl acetate), yield 85%, mp 110-112 °C; ^1H nmr (300 MHz, $CDCl_3$): δ 1.23 (d, J = 6.9 Hz, 6H), 2.84 (m, J = 6.9 Hz, 1H), 4.38 (s, 2H), 6.76-7.20 (m, 7H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 24.3, 33.3, 48.9, 114.7, 115.2, 116.4, 120.6, 121.6, 122.8, 126.6, 126.9, 136.0, 140.5, 144.8, 154.6. *Anal.* calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44%. Found: C, 74.64; H, 7.40; N, 5.39%.

2-(5-Phenyl-2-hydroxybenzylamino)pheno1 (2c). This compound was obtained as brown crystals (Ethyl acetate), yield 90%, mp 105-107 °C; ^1H nmr (300 MHz, $CDCl_3$): δ 4.41 (s, 2H), 6.71-7.56 (m, 12H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 49.0, 114.9, 115.5, 117.0, 120.9, 121.5, 123.5, 126.6, 127.3, 127.6*, 128.7, 133.3, 135.8, 140.7, 145.1, 156.2. [*one aromatic carbon was merged with other]. *Anal.* calcd. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81%. Found: C, 78.29; H, 5.85; N, 4.78%.

2-(5-Chloro-2-hydroxybenzylamino)pheno1 (2d). This compound was obtained as brown crystals (Ethyl acetate), yield 88%, mp 113-115 °C; ^1H nmr (300 MHz, $CDCl_3$): δ 4.39 (s, 2H), 6.72-7.45 (m, 7H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 48.6, 114.8, 115.5, 117.9, 121.1, 121.6, 124.6, 128.1, 128.7, 129.3, 135.4, 144.9, 155.3. *Anal.* calcd. for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.84; N, 5.61%. Found: C, 62.50; H, 4.80; N, 5.57%.

2-(2-Hydroxy-5-methoxybenzylamino)pheno1 (2e). This compound was obtained as brown crystals (Ethyl acetate), yield 91%, mp 166-167 °C; ^{1}H nmr (300 MHz, DMSO-d_6): δ 3.67 (s, 3H), 4.08 (s, 2H), 6.58-6.90 (m, 5H), 7.14 (d, J = 7.8 Hz, 1H), 7.69 (d, J = 2.5 Hz, 1H); ^{13}C nmr (75 MHz, DMSO-d_6): δ 53.2, 54.5, 112.5, 114.9, 115.0, 115.1, 118.4, 120.7, 122.9, 124.3, 135.0, 148.7, 151.1, 151.4. *Anal.* calcd. for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71%. Found: C, 68.52; H, 6.13; N, 5.67%.

2-(5-*tert*-Pentyl-2-hydroxybenzylamino)pheno1 (2f). This compound was obtained as yellow crystals (Ethyl acetate), yield 93%, mp 105-106 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 0.69 (t, J = 7.5 Hz, 3H), 1.26 (s, 6H), 1.61 (q, J = 7.5 Hz, 2H), 4.39 (s, 2H), 6.71-6.99 (m, 5H), 7.08 (d, J = 2.4 Hz, 1H), 7.17 (dd, J = 8.4, 2.4 Hz, 1H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 9.2, 28.6, 37.0, 37.2, 49.1, 114.7, 115.2, 116.0, 120.5, 121.5, 122.3, 126.3, 126.6, 136.0, 141.1, 144.9, 154.1. *Anal.* calcd. for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91%. Found: C, 75.73; H, 8.09; N, 4.87%.

2-(2-Hydroxy-5-(2-phenylpropan-2-yl)benzylamino)phen-o1 (2g). This compound was obtained as brown crystals (Ethyl acetate), yield 82%, mp 101-102 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.76 (s, 6H), 4.38 (s, 2H), 6.71-7.45 (m, 12H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 30.8, 42.1, 48.7, 114.6, 115.0, 115.8, 120.5, 120.8, 122.6, 125.4, 126.6, 127.2, 127.9*, 135.8, 142.2, 145.3, 150.8, 154.1. [*one aromatic carbon was merged with other]. *Anal.* calcd. for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20%. Found: C, 79.21; H, 6.90; N, 4.17%.

2-(5-Bromo-2-hydroxybenzylamino)pheno1 (2h). This compound was obtained as brown crystals (Ethyl acetate), yield 85%, mp 115-117 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 4.38 (s, 2H), 6.75-7.57 (m, 7H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 48.5, 110.9, 112.1, 116.2, 118.4, 119.4, 120.6, 121.1, 129.2, 134.5, 136.3, 149.9, 161.9. *Anal.* calcd. for $C_{13}H_{12}BrNO_2$: C, 53.08; H, 4.11; N, 4.76%. Found: C, 53.05; H, 4.08; N, 4.73%.

2-(5-Ethyl-2-hydroxybenzylamino)pheno1 (2i). This compound was obtained as brown crystals (Ethyl acetate), yield 95%, mp 106-108 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.21 (t, J = 7.5 Hz, 3H), 2.58 (q, J = 7.5 Hz, 2H), 4.37 (s, 2H), 6.74-7.16 (m, 2H), 6.81 (d, J = 8.1 Hz, 1H), 6.84-6.89 (m, 2H), 6.98 (d, J = 2.1 Hz, 1H), 7.04 (dd, J = 8.1, 2.1 Hz, 1H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 16.0, 28.1, 48.9, 114.8, 115.3, 116.5, 120.7, 121.5, 123.0, 128.1, 128.4, 135.9, 136.1, 145.0, 154.5. *Anal.* calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76%. Found: C, 74.01; H, 7.00; N, 5.72%.

General procedure for the synthesis of 2-(6-substituted-2*H*-benzo[*e*][1,3]oxazin-3(4*H*)-yl)phenols (3). A mixture of 2-(2-hydroxy-5-substituted belzylamino)phenol **2**, (3 mmoles) and formalin (35%, w/v, 6 mmoles) in ethanol (50 mL) was refluxed for 5 h. The progress of the reaction was monitored on tlc. After completion, ice-cold water (50 mL) was added to the reaction mixture and extracted with chloroform, the combined organic layers were dried over anhydrous sodium sulphate and the solvent evaporated. The crude mixture was purified by column chromatography using petroleum ether-ethyl acetate (99:1 v/v mixture) as eluent to afford pure benzoxazines (**3**). The products were recrystallised from ethanol.

2-(6-*tert*-Butyl-2*H*–benzo[*e*][1,3]oxazin-3(4*H*)-yl)phenol (3a). This compound was obtained as brown crystals (Ethanol), yield 95%, mp 133-135 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.29 (s, 9H), 4.34 (s, 2H), 5.00 (s, 2H), 6.77 (td, J = 7.5, 1.5 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.94-6.99 (m, 2H), 7.10 (td, J = 7.5, 1.5 Hz, 1H), 7.17 (dd, J = 7.5, 1.5 Hz, 1H), 7.22 (dd, J = 8.4, 2.4 Hz, 1H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 31.5, 34.1, 51.6, 81.0, 114.6, 116.5, 119.8, 120.4, 123.4, 124.3, 125.1, 127.2, 136.0, 144.0, 151.3, 151.5. *Anal.* calcd. for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94%. Found: C, 76.24; H, 7.43; N, 4.90%.

2-(6-iso-Propyl-2*H*–benzo[*e*][1,3]oxazin-3(4*H*)-yl)phenol (3b). This compound was obtained as brown crystals (Ethanol), yield 89%, mp 103-105 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.22 (d, J = 6.9 Hz, 6H), 2.83 (m, J = 6.9 Hz, 1H), 4.32 (s, 2H), 4.98 (s, 2H), 6.65-7.22 (m, 7H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 24.1, 33.3, 51.4, 81.0, 114.6, 116.8, 120.2, 120.4, 124.3, 124.4, 126.0, 127.2, 136.0, 141.6, 151.3, 151.8. *Anal.* calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20%. Found: C, 75.77; H, 7.07; N, 5.17%.

2-(6-Phenyl-2*H*–benzo[*e*][1,3]oxazin-3(4*H*)-yl)phenol (3c). This compound was obtained as brown crystals (Ethanol), yield 90%, mp 87-88 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 4.42 (s, 2H), 5.07 (s, 2H), 6.79 (td, J = 7.5, 1.5 Hz, 1H), 6.97-7.00 (m, 2H), 7.12 (td, J = 7.5, 1.5 Hz, 1H), 7.19 (dd, J = 7.5, 1.5 Hz, 1H), 7.22 (d, J = 2.1 Hz, 1H), 7.27-7.55 (m, 6H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 51.4, 81.2, 114.7, 117.4, 120.5, 120.8, 124.3, 125.4*, 126.7, 126.9, 127.4, 128.8, 134.4, 135.8, 140.5, 151.3, 153.5 [*one aromatic carbon was merged with other]. *Anal.* calcd. for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62%. Found: C, 79.23; H, 5.61; N, 4.65%.

2-(6-Chloro-2*H*-benzo[*e*][1,3]oxazin-3(4*H*)-yl)phenol (3d). This compound was obtained as brown crystals (Ethanol), yield 92%, mp 72-74 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 4.33 (s, 2H), 5.03 (s, 2H), 6.76 (td, J = 7.5, 1.5 Hz, 1H), 6.85 (d, J = 8.7 Hz, 1H), 6.95-7.17 (m, 5H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 51.0, 81.1, 114.9, 118.4, 120.5, 122.0, 124.1, 125.9, 126.5, 127.4, 128.1, 135.5, 151.1, 152.5. *Anal.* calcd. for $C_{14}H_{12}ClNO_2$: C, 64.25; H, 4.62; N, 5.35%. Found: C, 64.21; H, 4.59; N, 5.38%.

2-(6-Methoxy-2*H*-benzo[*e*][1,3]oxazin-3(4*H*)-yl)phenol (3e). This compound was obtained as brown crystals (Ethanol), yield 93%, mp 94-96 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 3.76 (s, 3H), 4.34 (s, 2H), 4.99 (s, 2H), 6.50-7.17 (m, 7H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 51.3, 55.6, 80.8, 111.1, 114.1, 114.6, 117.7, 120.3, 121.1, 124.2, 127.1, 135.8, 147.7, 151.1, 153.8. *Anal.* calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44%. Found: C, 70.05; H, 5.90; N, 5.48%.

2-(6-*tert*-Pentyl-2*H*–benzo[*e*][1,3]oxazin-3(4*H*)-yl)phenol (3f). This compound was obtained as brown crystals (Ethanol), yield 82%, mp 68-70 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 0.70 (t, J = 7.5 Hz, 3H), 1.24 (s, 6H), 1.59 (q, J = 7.5 Hz, 2H), 4.38 (s, 2H), 5.02 (s, 2H), 6.78 (td, J = 7.5, 1.5 Hz, 1H), 6.85 (d, J = 8.7 Hz, 1H), 6.93-7.19 (m, 5H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 9.2, 28.5, 36.9, 37.3, 51.5, 81.0, 114.6, 116.4, 119.7, 120.3, 124.1, 124.3, 125.7, 127.2, 136.0, 142.3, 151.3, 151.4. *Anal.* calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71%. Found: C, 76.77; H, 7.83; N, 4.74%.

2-(6-(2-Phenylpropan-2yl)-2*H*–benzo[*e*][1,3]oxazin-3(4*H*)-yl)phenol (3g). This compound was obtained as brown crystals (Ethanol), yield 77 %, mp 112-114 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.69 (s, 6H), 4.31 (s, 2H), 5.02 (s, 2H), 6.74-7.35 (m, 12H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 30.8, 42.4, 51.5, 81.0, 114.6, 116.5, 119.7, 120.3, 124.2, 124.8, 125.6, 126.6, 127.2, 127.9, 128.2, 135.9, 143.5, 150.6, 151.3, 151.6. *Anal.* calcd. for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.05%. Found: C, 79.94; H, 6.67; N, 4.07%.

2-(6-Bromo-2*H*-benzo[*e*][1,3]oxazin-3(4*H*)-yl)phenol (3h). This compound was obtained as a brown crystals (Ethanol), yield 82%, mp 67-69 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 4.47 (s, 2H), 5.18 (s, 2H), 6.88-7.43 (m, 5H), 7.75 (dd, J = 9, 2.1 Hz, 1H), 7.82 (d, J = 2.1 Hz, 1H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 50.8, 81.1, 114.9, 118.8, 120.5, 122.5, 124.1, 127.4, 129.4, 131.0, 135.6, 139.7, 151.1, 153.0. *Anal.* calcd. for $C_{14}H_{12}BrNO_2$: C, 54.92; H, 3.95; N, 4.58%. Found: C, 54.94; H, 3.97; N, 4.61%.

2-(6-Ethyl-2*H*-benzo[*e*][1,3]oxazin-3(4*H*)-yl)phenol (3i). This compound was obtained as brown crystals (Ethanol), yield 85%, mp 65-67 °C; ^{1}H nmr (300 MHz, $CDCl_3$): δ 1.36 (t, J = 7.5 Hz, 3H), 2.74 (q, J = 7.5 Hz, 2H), 4.48 (s, 2H), 5.15 (s, 2H), 6.91 (td, J = 7.5, 1.5 Hz, 1H), 6.96-7.41 (m, 6H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 15.7, 28.1, 51.4, 81.0, 114.6, 116.8, 120.3, 120.4, 124.3, 125.9, 127.2, 127.5, 135.9, 137.0, 151.3, 151.8. *Anal.* calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49%. Found: C, 75.31; H, 6.75; N, 5.51%.

The *in vitro* activities of the compounds were tested in Muller hintan agar for bacteria by the two fold serial dilution method. The test compounds were dissolved in dimethyl sulfoxide to obtain 5 mg mL^{-1} stock solutions. Seeded broth (broth containing microbial spores) was prepared in Nutrient broth from 24 old bacterial cultures on Nutrient agar at 37 °C. The final inoculum's size was 10^5 (colony forming units) cfu mL^{-1} for antibacterial assay. Testing was performed at pH 7.4. The minimum inhibitory concentrations were recorded by visual observations after 24 h (for bacteria). Penicillin G and Streptomycin were used as a standards.

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