Palladium-Catalyzed Heteroannulation Leading to Heterocyclic Structures with Two Heteroatoms: A Highly Regio- and Stereoselective Synthesis of (*Z*)-4-Alkyl-2-alkyl(aryl)idene-3,4-dihydro-2*H*-1,4-benzoxazines and (*Z*)-3-Alkyl(aryl)idene-4-tosyl-3,4-dihydro-2*H*-1,4-benzoxazines†

Nitya G. Kundu,* Gopeswar Chaudhuri, and Anup Upadhyay‡

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta - 700 032, India

ocngk@mahendra.iacs.res.in

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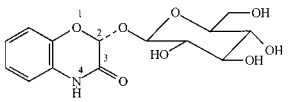
A highly convenient method has been developed for the synthesis of (Z)-4-alkyl-2-alkyl(aryl)idene-3,4-dihydro-2*H*-1,4-benzoxazines **9** and (Z)-3-alkyl(aryl)idene-4-tosyl-3,4-dihydro-2*H*-1,4-benzoxazines **34**−**38** through palladium−copper-catalyzed reactions. Aryl halides **7** reacted with 2-[*N*-alkyl(benzyl)-*N*-prop-2′-ynyl]aminophenyl tosylate **6** in the presence of $(PPh_3)_2PdCl_2$ (3 mol %), CuI(5 mol %) in triethylamine at room temperature to yield 2-[*N*-alkyl(benzyl)-*N*-(3-aryl-prop-2′-ynyl)]-aminophenyl tosylates **8** in extremely good yields (72−96%). The latter could then be cyclized with KOH in ethanol−water to *Z*-**9** in a highly regio- and stereoselective manner. Similarly, palladium−copper-catalyzed reaction of 2-(prop-2′-ynyloxy)aniline (**21**) with aryl iodides **7** led to **22**−**26** which after tosylation and cyclization with cuprous iodide in CH_3CN in the presence of K_2CO_3 and Bu_4-NBr led to the (*Z*)-3-alkyl(aryl)idene-4-tosyl 3,4-dihydro-2*H*-1,4-benzoxazines **34**−**38** in good overall yields. The *Z*-stereochemistry of the products was established from ^{1}H NMR spectra, $^3J_{CH}$ values (between vinylic proton and methylenic carbon of the heterocyclic ring), NOE experiments, and X-ray analysis. The method was also found to be suitable for the synthesis of bis(benzoxazinylated) derivatives **17**, **39**, and 2-alkyl-3,4-dihydro-2*H*-1,4-benzoxazines **18**. Our method for the synthesis of 3,4-dihydro-2*H*-1,4-benzoxazines is highly efficacious, using easily available starting materials under very mild conditions. Also the synthesis of some novel 5-substituted uracil derivatives **40** and **41** containing the benzoxazinyl moiety and of potential biological interest is being reported.

The 2*H*-1,4-benzoxazine[1] structure has been the integral part of many naturally occurring substances. For example, blepharin, [(2*R*)-2-*β*-D-glucopyranosyloxy-2*H*-1,4-benzoxazine-3(4*H*)-one] (**I**), and other glycosides of the 2-hydroxy-2*H*-1,4-benzoxazine-3(4*H*)-one skeleton have been found to occur in gramineous plants such as maize, wheat, rye, rice, etc., and have been suggested to act as plant resistance factors against microbial diseases and insects.[2]



(I)

Similarly, actinomycin-D, an anticancer drug isolated from streptomyces, has the benzoxazine structural moiety as part of the chromophoric unit of the drug molecule.[3] The 1,4-benzoxazine structure has also been found in the antibiotic C-1027,[4] a novel antitumor chromoprotein, isolated from the broth filtrate of *Streptomyces globisporus* C-1027[5] which shows extreme cytotoxic potency against KB carcinoma cells in vitro[6] and antitumor activity toward tumor-bearing mice in vivo.[7] Various benzoxazine derivatives have shown to have interesting pharmacological properties. Thus, nazasetran hydrochloride (Y-25130), *N*-(1-azabicyclo[2.2.2]oct-3-yl)-6-chloro-3,4-dihydro-4-methyl-3-oxo-2*H*-1,4-benzoxazine-8-carboxamide hydrochloride, a highly potent 5-HT_3 receptor antagonist, has been reported as an antiemetic agent for severe nausea and vomiting induced by chemotherapy

† Dedicated to Professor Dr. (Mrs.) Asima Chatterjee, Department of Chemistry, Calcutta University, Calcutta, on the occasion of her 83rd birthday in the beginning year of the new millennium.

‡ In part only.

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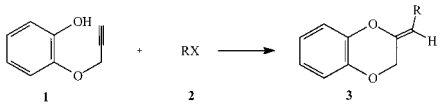
in cancer patients.[8] Several 3,4-dihydro-2*H*-1,4-benzoxazine derivatives have been reported to be potassium channel openers(PCOs)in vascular smooth muscle.[9] Benzoxazino-rifamycin KRM-1648 has been shown to have in vitro and in vivo activities against *Mycobacterium tuberculosis*.[10] Recently, a number of methotrexate derivatives incorporating the benzoxazine moiety have been synthesized. Some of these compounds have proved to be potent and safe candidate antirheumatic agents.[11] Moreover, benzoxazine derivatives have been used as intermediates for the synthesis of other heterocyclic structures of biological importance.[12,13] Photochemical transformation of 1,4-benzoxazines to other heterocyclic structures have also been reported.[14]

Due to the importance of 2*H*-1,4-benzoxazine structure, several syntheses of this compound and its derivatives have been reported by various investigators over the last few decades.[1,15−17] However, most of the methods reported were targeted toward the synthesis of some specific benzoxazine derivative and lacked generality and hence were of limited synthetic utility. Moreover, recent developments in the field of metal-catalyzed reactions have almost been completely ignored to develop general methods for the synthesis of benzoxazine compounds.

Over the last few decades, palladium-catalyzed arylation of olefins (Heck reaction)[18] and cross-coupling reactions[19] have been of greatest significance in the formation of carbon−carbon bonds. The application of different strategies utilizing palladium-catalyzed reactions have led to the synthesis of various carbocyclic[20] and heterocyclic structures.[21] Our own efforts in the field of palladium-catalyzed heteroannulation reactions have been the use of terminal alkynes with aromatic iodo compounds[22] having a nucleophilic group in the *ortho*-position to the iodo-substituent, and these have led to the synthesis of various benzo-fused heterocyclic systems with one heteroatom, e.g., benzofurans,[23] phthalides,[24] quinolines and quinolones,[25] isoindolinones,[26] and flavanones,[27] which are the integral part of many naturally occurring and biologically active compounds.

Scheme 1



Very recently, in a different strategy we have used monoprop-2-ynylated catechol **1** as the source of both terminal alkyne moiety and the nucleophilic center and have utilized its reaction with aromatic iodo compounds **2** under palladium−copper catalysis to develop a general and a highly regio- and stereoselective synthesis of (*Z*)-2,3-dihydro-2-alkylidene-1,4-benzodioxins **3** (Scheme 1).[28]

In continuation of those studies, we felt that it will be interesting to develop general methods for the synthesis of other benzo-fused heterocycles containing two heteroatoms in the same ring following the above strategy. Herein, we report our results on the synthesis of (*Z*)-2-alkylidene-3,4-dihydro-2*H*-1,4-benzoxazines[29] and (*Z*)-3-alkylidene-3,4-dihydro-2*H*-1,4-benzoxazines.

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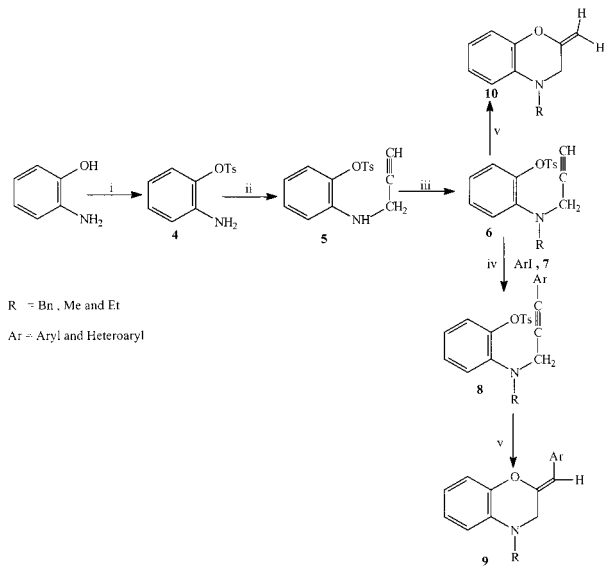
Scheme 2[a]



[a] Reaction conditions: (i) TsCl (1 equiv, 0.01 mmol), Et_3N (0.01 mmol), CH_2Cl_2 (20 mL). (ii) Propargyl bromide (1.2 equiv, 22.8 mmol), K_2CO_3 (19.0 mmol), DMF (35 mL), 80 °C, 48 h. (iii) Benzyl bromide (1.5 equiv, 9.94 mmol), K_2CO_3 (6.63mmol), DMF (20 mL), 80 °C, 48 h. (iv) $(PPh_3)_2PdCl_2$ (3.0 mol %), CuI (5.0 mol %), Et_3N (12 mL), stirring at room temperature, 16 h. (v) KOH (19 equiv), $EtOH/H_2O$, 80 °C, 8−10 h.

Results and Discussion

2-[*N*-Alkyl (or benzyl)-*N*-prop-2′-ynyl)aminophenyl tosylate **6** was treated with aryl iodides **7** in the presence of bis(triphenylphosphine)palladium(II) chloride (3 mol %) and cuprous iodide (5 mol %) in triethylamine at room temperature for 16 h where the disubstituted alkynes **8** were produced. These did not undergo cyclization under the palladium−copper catalysis condition (in contrast to the case of benzodioxans). However, they could be cyclized by refluxing with KOH in ethanol/H_2O for 8−10 h to the (*Z*)-2-alkylidene-4-alkyl(benzyl)-3,4-dihydro-2*H*-1,4-benzoxazines **9** in excellent yields (Scheme 2, Table 1).

2-[*N*-Alkyl (or, benzyl)-*N*-prop-2′-ynyl)aminophenyl tosylate **6** was used as the substrate for the palladium-catalyzed reaction with aryl iodides **7**. Compound **6** was synthesized starting from *ortho*-aminophenol which was O-tosylated with *p*-toluenesulfonyl chloride in the presence of triethylamine in dichloromethane to yield **4**.[30] Tosylation in the presence of pyridine leads to N-tosylation. Compound **4** was then propargylated with propargyl bromide in the presence of K_2CO_3 in DMF to yield compound **5**. 2-(*N*-Prop-2′-ynyl)aminophenyl tosylate **5** was then benzylated or alkylated to compound **6**.

The palladium-catalyzed reaction of **6** with aryl iodides **7** was carried out with bis(triphenylphosphine)palladium-(II) chloride as the catalyst of choice and cuprous iodide as the cocatalyst. The presence of the *O*-tosyl group was found to be essential since any prior removal of it through alkaline hydrolysis led to spontaneous cyclization to 3,4-dihydro-2*H*-2-methylene-1,4-benzoxazine (**10**) (Scheme 2). The palladium-catalyzed reactions of **6** with aryl iodides **7** could be carried out under very mild conditions. The reactions were usually carried out at room temperature in an inert atmosphere (N_2 or argon) for 16 h. Heating at 60 °C reduced the time of reaction but lowered the yields considerably. We have also explored the role of various solvents (e.g. CH_3CN, DMF, Et_3N) in the palladium-catalyzed reactions and found triethylamine to be the most effective solvent which could act also as a base. The use of DMF with triethylamine led to the formation of much-colored materials which lowered the yields of the disubstituted alkynes **8**. A variety of aryl iodides were utilized for the arylation of the terminal alkyne **6** most effecively (yields 72−96%). It was observed that both aromatic and heteroaromatic iodides were equally effective. However, electron-donating substituent (e.g., OMe) reduced the yield to some extent (72−80%).

The disubstituted alkynes **8** did not cyclize to the benzoxazines **9** under the palladium−copper-catalyzed condition of their formation as was observed in the case of the synthesis of benzodioxans.[28] The compounds **8** neither could be cyclized with CuI in triethylamine.[31] However, **8** could be smoothly cyclized with KOH in ethanol−water by refluxing for 8−10 h under argon atmosphere. The yields of the benzoxazines were usually high (70−93%) except in case of the *o*-nitro compound (entry 10) where the yield of the cyclized product was found to be extremely poor (35%) due to the formation of much-colored materials. The presence of a benzyl or an alkyl group on the N-atom in **8** was found to be essential for the successful cyclization of **8** to the benzoxazines **9**. Thus, it was observed that 2-(*N*-prop-2′-ynyl)aminophenyl tosylate **5** could be C-arylated to **11** with aryl iodides under palladium−copper catalysis (Scheme 3).

However, compounds **11** did not cyclize to the benzoxazines when refluxed with KOH in EtOH. Similarly, 2-(*N*-prop-2′-ynyl)amino phenol **12**, obtained from **5** by alkaline hydrolysis, underwent the usual arylation with aryl iodides **7** under palladium−copper catalysis (albeit at a higher temperature, e.g., 100 °C for 16 h). However, no cyclic products (benzoxazines) were obtained under this condition. This is in contrast to the case of benzo-1,4-dioxans where palladium−copper-catalyzed arylation and cyclization to benzo-1,4-dioxans took place in one step.[28] Cyclization of compounds **13** could neither be effected with NaOEt in EtOH at 80 °C for 16−24 h nor with CuI (10−40 mol %) in Et_3N[31] at 80 °C for 16−48 h. Finally, the disubstituted alkynes **13** could be cyclized with $Pd(OAc)_2$ (5 mol %), LiCl (0.5 equiv), and K_2CO_3 (2.5 equiv) in DMF at 100 °C for 16 h[32] to the benzoxazines **14** only in poor yields (10−20%). However, we have already observed that the N-benzylated or N-alkylated disubstituted alkynes **8** underwent smooth cyclization to **9** with KOH in $EtOH/H_2O$.

Nature of the Products, Structure, and Stereochemistry. 4-Alkyl(benzyl)-2-alkyl(aryl)idene-3,4-dihydro-2*H*-1,4-benzoxazines **9** were found to be highly unstable in halogenated solvents such as $CHCl_3$, CH_2Cl_2, and $CDCl_3$. Therefore, workup, purification, and crystallization were done either with diethyl ether−petroleum ether (bp 60−80 °C) or with diethyl ether−ethyl acetate. Column chromatography was done on neutral alumina instead of silica gel. The structure of the benzoxazines were established from analytical and spectroscopic (IR, ^1H NMR, ^{13}C NMR, and mass spectral) data. In IR spectra, the absorption peaks at 1680−1660 and 1600 cm^{-1} indicated the presence of conjugated

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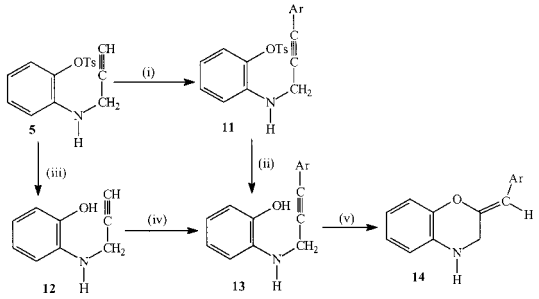
Table 1. Reaction of 2-[*N*-Benzyl(or alkyl)-*N*-prop-2′-ynyl]amino Phenyl Tosylate 6 with Aryl Iodides 7 in Presence of Palladium Catalyst, Copper(I) Iodide, and Et_3N and Subsequent Treatment with KOH in EtOH/H_2O (Scheme 2)

entry	prop-2-ynylated aminophenyl tosylates, **6**, R	aryl iodides **7**, Ar	disubstituted alkynes **8**, Ar (%)[a]	2-alkylidene-benzoxazines **9**, (%)[b], [%][c]
1	Bn, **6a**	C_6H_5, **7a**	C_6H_5, **8a** (92)	**9a** (93) [85]
2	Bn, **6a**	3-ClC_6H_4, **7b**	3-ClC_6H_4, **8b** (96)	**9b** (70) [69]
3	Bn, **6a**	2-$MeOC_6H_4$, **7c**	2-$MeOC_6H_4$, **8c** (72)	**9c** (82) [59]
4	Bn, **6a**	4-MeC_6H_4, **7d**	4-MeC_6H_4, **8d** (89)	**9d** (93) [83]
5	Bn, **6a**	1-naphthyl, **7e**	1-naphthyl, **8e** (95)	**9e** (87) [83]
6	Bn, **6a**	2-thienyl, **7f**	2-thienyl, **8f** (94)	**9f** (84) [79]
7	Bn, **6a**	2,4-dimethoxy-5-pyrimidinyl, **7g**	2,4-dimethoxy-5-pyrimidinyl, **8g** (80)	**9g** (76) [61]
8	Me, **6b**	C_6H_5, **7a**	C_6H_5, **8h** (84)	**9h** (70) [59]
9	Me, **6b**	3-ClC_6H_4, **7b**	3-ClC_6H_4, **8i** (95)	**9i** (75) [71]
10	Me, **6b**	2-$O_2NC_6H_4$, **7h**	2-$O_2NC_6H_4$, **8j** (92)	**9j** (35) [32]
11	Et, **6c**	3-ClC_6H_4, **7b**	3-ClC_6H_4, **8k** (90)	**9k** (93) [84]

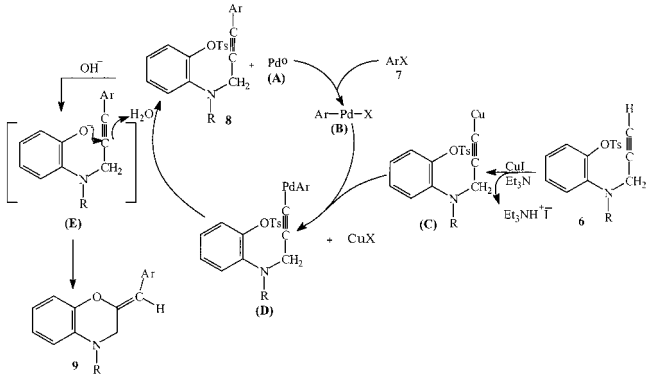
[a] The yields refer to chromatographically isolated pure materials and based on compound **7**. [b] Yields of pure benzoxazines **9** are based on **8**. [c] Overall yields of benzoxazines are based on **7**.

Scheme 3[a]



[a] Reaction conditions: (i) ArI (0.83 equiv), $(PPh_3)_2PdCl_2$ (0.02 mmol), CuI (0.04 mmol), Et_3N (9 mL). (ii) KOH in EtOH/H_2O, 80 °C, 8−10 h; (iii) same as (ii). (iv) same as (i) (v) $Pd(OAc)_2$(5 mol %, 0.12 mmol), LiCl (1.21 mmol), K_2CO_3 (6.02 mmol), DMF, 100 °C, 16 h.

Scheme 4



double bonds. In the ^1H NMR spectra, the exocyclic vinylic hydrogen could be easily seen at δ 5.29−6.03 and the methylenic group (−N−CH_2−) of the heterocyclic ring was noted at δ 3.65−3.84 as singlets, confirming the benzoxazine structures. This was further confirmed by the ^{13}C NMR data at δ_c 48.7−52.5 ppm for the N−CH_2 of the heterocyclic ring and δ_c 99.7−104.7 ppm for the methine carbon (C═CH) of the exocyclic bond of compounds **9**.

The heteroannulation process was found to be completely regio- and stereoselective. No seven-membered ring compounds or compounds of *E*-stereochemistry were isolated. The *Z*-stereochemistry of the compounds **9** follows from the chemical shift position of the vinylic hydrogen at δ_H 5.29−6.03. If the compounds had the *E*-stereochemistry, it was expected that due to the deshielding effect of the proximal ring oxygen atom, the δ_H values of the vinylic hydrogen will be much higher than 6 ppm.[33] The *Z*-stereochemistry was also assigned from the consideration of the $^3J_{CH}$ values for the interaction between the vinylic proton and the methylenic carbon (N−CH_2) of the heterocyclic ring. It has been reported in the literature[34] that the $^3J_{CH}$ values more than 7 Hz or less than 5 Hz could be attributed to *E* -or *Z*-isomers, respectively. We have observed the $^3J_{CH}$ values for compounds **9** in the range of 3.65−4.3 Hz confirming the *Z*-stereochemistry. Further validation of the *Z*-stereochemistry was obtained from NOE experiments. When methylenic protons of the heterocyclic ring of compounds **9** were irradiated, a strong enhancement of the vinylic proton signal of the exocyclic double bond was noticed and vice versa, supporting the *Z*-stereochemistry. Finally, an X-ray diffraction study on compound **9c** was carried out which supported its structure and the *Z*-stereochemistry.[35]

Mechanism. The mechanism of the reaction can be shown as envisaged in Scheme 4.

The Pd^0(A) generated[22c] from $(Ph_3P)_2PdCl_2$ will undergo oxidative addition with ArX (**7**) to produce ArPdX (**B**). The ArPdX on transmetalation with the Cu-acetylide (**C**) derived from **6** will lead to **D** which on reductive elimination of palladium will generate the disubstituted alkynes **8**. On alkaline hydrolysis of **8**, the phenoxide ion (**E**) generated undergoes an exo-dig attack on the triple bond forming the (*Z*)-**9** in a highly stereoselective manner.

Scope of the Reaction

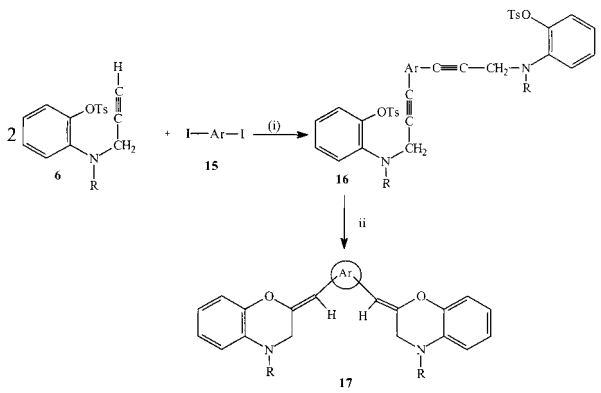
Synthesis of Bis(benzoxazinyl) Derivatives. We have extended the scope of the reaction by synthesizing bis(benzoxazinyl) derivatives. Thus, the treatment of **6** with di-iodo compounds **15** under palladium−copper

(33) In case of (*E*)- and (*Z*)-isomers, different chemical shift values of vinylic proton of exocyclic double bond due to deshielding effect of oxygen of some heterocyclic rings have been invoked to account for the results: (a) Jager, V.; Gunther, H. J. *Tetrahedron Lett.* **1977**, 2543. (b) Yamamoto, M. *J. Chem. Soc., Chem. Commun.* **1978**, 649. (c) Arcadi, A.; Burini, A.; Cacchi, S.; Delmastro, M.; Marinelli, F.; Pictroni, B. R. *J. Org. Chem.* **1992**, *57*, 976.

(34) (a) Moreau, P.; Neirabeyeh, M. Al.; Guillaumet, G.; Coudert, G. *Tetrahedron Lett.* **1991**, *32*, 5525. (b) Cabiddu, S.; Floris, C.; Melis, S.; Sotgiu, F.; Cerioni, G. *J. Heterocycl. Chem.* **1986**, *23*, 1815. (c) U. Vogelli, W. Von Phillipsborn, *Org. Magn. Reson.* **1975**, *7*, 617. See also refs 28 and 31a.

(35) Maiti, S.; Mukherjee, M.; Chaudhuri, G.; Helliwell, M.; Kundu, N. G. *Acta Crystallogr.* **1999**, *C55*, 1154.

Scheme 5[a]



[a] Reaction conditions: (i) $(PPh_3)_2PdCl_2$ (6 mol%, with respect to **15**), CuI (10 mol % with respect to **15**) Et_3N, rt, 16 h. (ii) KOH (25 equiv) EtOH/H_2O, 80 °C, 8−10 h.

catalysis resulted in the substituted dialkynyl compounds **16** which on cyclization with KOH in EtOH/H_2O resulted in the bis(benzoxazinyl) derivatives **17** in good yields (Scheme 5 and Table 2).

It was noticed that the palladium-catalyzed reactions of the di-iodo compounds proceeded in modest yields only due to considerable polymerization of the alkyne **6** taking place under the reaction conditions. However, the cyclization proceeded in better yields (58−84%). The bis(benzoxazinyl) derivatives were characterized by their analytical and spectral data. Particularly, the mass spectra of the compounds **17**, which showed the M^+ ions, confirmed the bis(benzoxazinyl) structures (see Experimental Section).

Synthesis of 2-Alkyl-3,4-dihydro-2*H*-1,4-benzoxazines. We have also extended the scope of this reaction by synthesizing the 2-alkyl-3,4-dihydro-2*H*-1,4-benzoxazines **18** by the hydrogenation of the corresponding (*Z*)-4-alkyl-2-alkylidene-3,4-dihydro-2*H*-1,4-benzoxazines **9** as shown in Scheme 6 and Table 3. The hydrogenation was carried out with Pd/C as catalyst in excellent yields.

It was observed that the benzyl group on the N-atom was removed during the hydrogenation procedure. The hydrogenation products contain the skeleton of many naturally occurring benzoxazine-containing structures.

Synthesis of (*Z*)-3-Alkylidene-4-tosyl-3,4-dihydro-2*H*-1,4-benzoxazines. We have synthesized the regioisomers of compounds **9**, e.g., (*Z*)-3-alkylidene-4-tosyl-3,4-dihydro-2*H*-1,4-benzoxazines **34**−**38** through palladium−copper-catalyzed reactions as shown in Scheme 7 and Table 4.

o-Nitrophenol **19** on treatment with propargyl bromide in the presence of K_2CO_3 in acetone yielded 2-(prop-2′-ynyloxy)nitrobenzene **20** which was reduced with iron powder in acetic acid to 2-(prop-2′-ynyloxy)aniline **21**. Compound **21** underwent C-arylation with aryl iodides under palladium−copper catalysis in triethylamine to the disubstituted alkynes **22**−**26**. Interestingly, in contrast to the case of the *O*-tosylates **6**, the *N*-tosylate of **21** did not undergo the arylation reaction. Again, the free amines **22**−**26** could not be cyclized to the corresponding benzoxazines under various conditions, e.g., i. $Pd(OAc)_2$, LiCl, K_2CO_3 in DMF, 100 °C, 16 h;[32] ii. $PdCl_2$ in CH_3CN, reflux, 24 h; iii. CuI, Et_3N in CH_3CN, 80 °C, 24 h; iv. CuI, Bu_4NBr, K_2CO_3 in CH_3CN at 80 °C, 24 h. Hence **22**−**27** were converted to the corresponding tosylates with tosyl chloride in the presence of pyridine in dichloromethane. The tosylates could then be very simply cyclized with CuI in the presence of K_2CO_3 and tetrabutylammonium bromide in acetonitrile by heating at 80 °C, to the corresponding 3-alkylidene-4-tosyl-3,4-dihydro-2*H*-1,4-benzoxazines **34**−**38** in excellent yields (Table 4).[36] Acetonitrile was found to be the best solvent for cyclization. Attempted cyclization in Et_3N, THF, or DMF yielded poorer results. Also, cyclization with CuI and Et_3N in THF,[31] CuI/K_2CO_3 in CH_3CN, NaH in THF, and NaOEt in EtOH failed. When $Pd(OAc)_2$ (20 mol %) was used in place of CuI, with K_2CO_3 (2.5 equiv) and *n*-Bu_4NBr (1 equiv) in acetonitrile at 80 °C, cyclization did occur, but the yields were comparatively lower (about 50%).

3-Alkylidene-4-tosyl-3,4-dihydro-2*H*-1,4-benzoxazines **34**−**38**, in contrast to the regioisomers, e.g., 2-alkylidene-4-benzyl(alkyl)-3,4-dihydro-2*H*-1,4-benzoxazines **9**, were found to be stable in chloroform and on the silica gel column. The structures of the compounds were established through usual analytical and spectroscopic (^1H NMR, ^{13}C NMR, IR) methods.The compounds **34**−**38** were assigned the *Z*-stereochemistry on the basis of their $^3J_{CH}$ values.[34] For example compound **34** had the $^3J_{CH}$ value equal to 4.73 Hz. We have also synthesized a bis-benzo-oxazinyl derivative **39** of 3-alkylidene-4-tosyl-3,4-dihydro-2*H*-1,4-benzoxazine starting from compound **21** by using 1,2-diiodobenzene **15a** as the aryl iodide (see Table 4 and Scheme 7) and following the procedures as described.

Synthesis of Some Potentially Biologically Active Compounds. Through our synthetic protocol, we have been able to synthesize some pyrimidine ring substituted benzoxazine derivatives, e.g., (*Z*)-4-benzyl-2-[(2,4-dimethoxypyrimidin-5-yl)methylidene]-3,4-dihydro-2*H*-1,4-benzoxazine, **9g**, and (*Z*)-3-[(2,4-dimethoxypyrimidin-5-yl)methylidene)-4-tosyl-3,4-dihydro-2*H*-1,4-benzoxazine, **37**. Compound **37** could be demethylated with chlorotrimethylsilane and sodium iodide in acetonitrile[37] to a novel 5-substituted uracil derivative **40** (Scheme 8).

Similar attempted demethylation of **9g**, however, led to the breakdown of the compound. Hence, **9g** was hydrogenated to the corresponding saturated derivative **18g** which was then demethylated to the uracil derivative **41** (Scheme 8). The importance of uracil derivatives as anticancer and antiviral agents is well established.[38] We believe **40** and **41** could have interesting biological activities.[39]

Conclusion

Thus, we have described for the first time a highly successful general method for the synthesis of 2-alkyl-

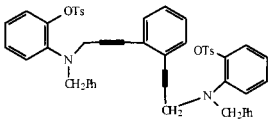
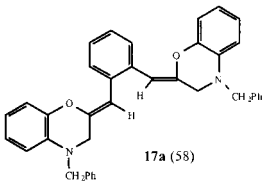
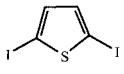
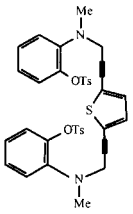
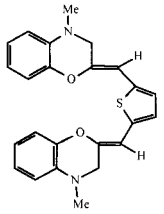
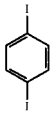
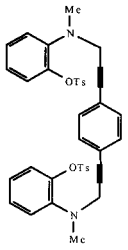
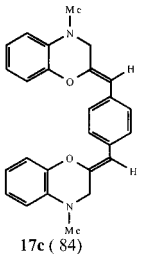
(36) For other methods of hydroamination of alkynes, see: (a) through imidozirconium complexes: Baranger, A. M.; Walsh, P. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1993**, *115*, 2753 and references therein; (b) through imidotitanium complexs: McGrane, P. L.; Jensen, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1992**, *114*, 5459. McGrane, P. L.; Livinghouse, T. *J. Org. Chem.* **1992**, *57*, 1323. McGrane, P. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1993**, *115*, 11485.

(37) Morita, T.; Okamoto, Y.; Sakurai, H. *J. Chem. Soc., Chem. Commun.*, **1978**, 874.

(38) (a) Heidelberger, C. *Pyrimidine and Pyrimidine Antimetabolites in Cancer Medicine*; Holland, J. F., Frei, E., Eds.; Lea and Febiger: Philadelphia, PA, 1984; pp 801−824. (b) De Clercq, E. *J. Med. Chem.* **1995**, *38*, 2491. (c) Kundu, N. G.; Das, B.; Spears, C. P.; Majumdar, A.; Kang, S. I. *J. Med. Chem.* **1990**, *33*, 1975. (d) Kundu, N. G.; Mahanty, J. S.; Chowdhury, C.; Dasgupta, S. K.; Das, B.; Spears, C. P.; Balzarini, J.; De Clercq, E. *Eur. J. Med. Chem.* **1999**, *34*, 389 and refeences cited therein.

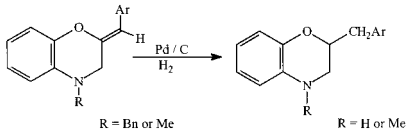
(39) The biological (anticancer and antiviral) studies on these compounds are in progress.

Table 2. Synthesis of Bis(benzoxazinyl) Derivatives (Scheme 5)

Entry	2-(Prop-2'-ynyl) aminophenyl tosylates **6**, R	Aryl iodides **15**	Disubstituted diynes, **16** yields(%) [a]	Bis(benzoxazinyl) derivatives, **17** yields (%) [b]
1	Bn , **6a**	 **15a**	 **16a** (55)	 **17a** (58)
2	Me , **6b**	 **15b**	 **16b** (32)	 **17b** (76)
3	Me , **6b**	 **15c**	 **16c** (38)	 **17c** (84)

[a] Yields are of chromatographically pure material and based on compound **15**. [b] Yields of chromatographically pure materials are based on **16**.

Scheme 6



9 (a , b, d, e, g, h) **18** (a, b, d, e, g, h)

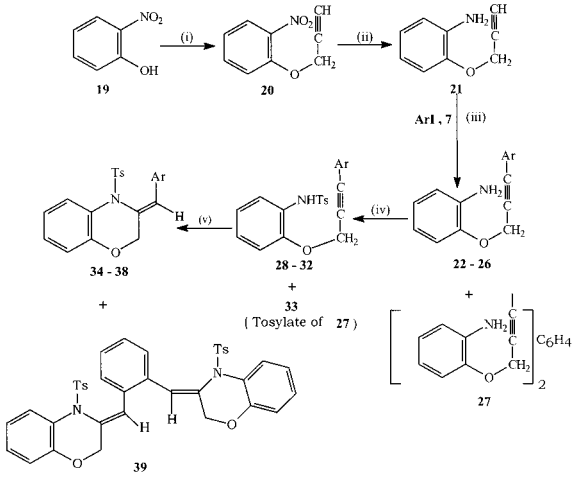
Table 3. Hydrogenation of (*Z*)-*N*-Aryl(alkyl)-2-alkylidene-3,4-dihydro-2*H*-1,4-benzoxazines (Scheme 6)[a]

entry	starting materials **9**	products **18** (Ar, R)	yields (%)
1	**9a**	**18a** (C_6H_5, H)	81
2	**9b**	**18b** (3-ClC_6H_4, H)	86
3	**9d**	**18d** (4-MeC_6H_4, H)	81
4	**9e**	**18e** (1-naphthyl, H)	83
5	**9g**	**18g** (2,4-dimethoxy-5-pyrimidinyl, H)	85
6	**9h**	**18h** (C_6H_5, Me)	82

[a] Hydrogenation was carried out by treatment of compound **9** (0.20 mmol) in dry ethyl acetate (9 mL) with hydrogen at room temperature under atmospheric pressure with Pd−C (10%) as catalyst. Yields refer to chromatographically isolated pure products.

idene- and 3-alkylidene-3,4-dihydro-2*H*-benzo-1,4-oxazines through palladium−copper-catalyzed reactions. The method is characterized by the use of readily available inexpensive starting materials, nonhazardous reagents, mild reaction conditions, and relatively good to excellent yields of products. The method is also highly regio- and stereoselective in nature. Thus the process is

Scheme 7[a]



[a] Reaction conditions: (i) propargyl bromide (1.2 equiv, 43.08 mmol), K_2CO_3 (35.9 mmol), in acetone (40 mL), reflux, 16 h. (ii) Fe in AcOH. (iii) ArI (0.83 equiv, 2.03 mmol), $(PPh_3)_2PdCl_2$ (0.06 mmol), CuI (0.1 mmol), Et_3N (12 mL). (iv) Tosyl chloride (1 equiv, 1.3 mmol), Py (1.3 mmol), CH_2Cl_2 (9 mL), rt, 2 h. (v) CuI (20 mol %), K_2CO_3 (2.5 equiv), Bu_4NBr (1 equiv), CH_3CN (11 mL), 12 h, 80 °C.

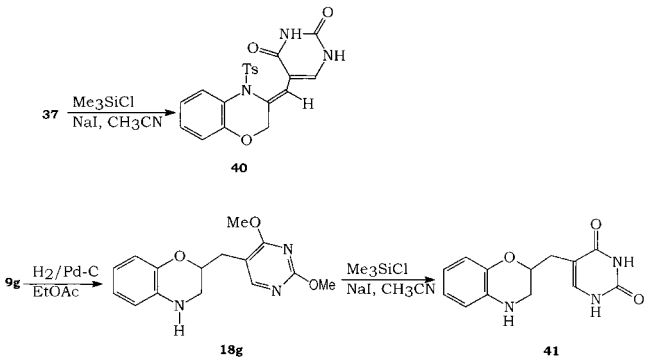
amenable for the synthesis of a large number of 2- and 3-substituted benzoxazines, bis-benzoxazines, and various potentially biologically active compounds containing the benzoxazine structure.

Table 4. Synthesis of (*Z*)-3-Alkyl(aryl)idene-4-tosyl-3,4-dihydro-2*H*-1,4-benzoxazines (34−38) and a Bis-benzoxazinyl Derivative (39) from 2-(Prop-2′-ynyloxy)aniline 21 (Scheme 7)

entry	aryl iodides (ArI) **7**, Ar	disubstituted alkynes **22**−**27** (%)[a]	tosylates **28-33** (%)[b]	3-alkyl(aryl)idene benzoxazines **34-38** and bis-benzoxazinyl derivative **39** (%)[c]
1	C_6H_5, **7a**	**22** (78)	**28** (72)	**34** (88)
2	3-ClC_6H_4, **7b**	**23** (77)	**29** (82)	**35** (86)
3	4-MeC_6H_4, **7d**	**24** (70)	**30** (80)	**36** (82)
4	2,4-dimethoxy-5-pyrimidinyl, **7g**	**25** (78)	**31** (73)	**37** (71)
5	4-$MeOC_6H_4$, **7i**	**26** (65)	**32** (68)	**38** (69)
6	2-IC_6H_4, **15a**	**27** (56)	**33** (61)	**39** (38)

[a] The yields refer to chromatographically isolated pure materials and based on compound **7**. [b] Yields of tosylates are based on corresponding disubstituted alkynes. [c] Yields of benzoxazines and bis-benzoxazine are based on corresponding tosylates.

Scheme 8



Experimental Section

Melting points are uncorrected. Reactions were performed in an argon or nitrogen atmosphere. Bis(triphenylphosphine)-palladium(II) chloride was obtained from Aldrich Chemical Co, Milwaukee, WI. Petroleum ether used was the fraction boiling between 60 and 80 °C, and distilled ether refers to diethyl ether. Column chromatography was done on neutral alumina and silica gel. TLC was performed on 60F-254 precoated sheets. Aryl iodides (**7b**, **7c**, etc.) were prepared according to the procedure given for the synthesis of iodobenzene.[40] 2-Iodothiophene,[41] 2,5-diiodothiophene,[41] and 5-iodo-2,4-dimethoxypyrimidine[42] were synthesized according to known procedures.

^{1}H NMR in $CDCl_3$ solutions were recorded at 300 MHz and that of CCl_4 solutions at 60 MHz. ^{13}C NMR spectra were recorded at 75 MHz. $^3J_{CH}$ values were obtained, performing ^{13}C NMR experiments under proton-coupled mode.

2-(*N*-Prop-2′-ynylamino)phenyl *p*-Toluenesulfonate (5). A mixture of 2-aminophenyl *p*-toluenesulfonate[30] **4** (5 g, 19.0 mmol) and anhydrous potassium carbonate (2.62 g, 19.0 mmol) in dry DMF (30 mL) was stirred at room temperature for about 16 h under nitrogen atmosphere. Propargyl bromide (2.71 g, 22.8 mmol) in dry DMF (5 mL) was then added slowly during 15 min. The mixture was heated at 80 °C for 48 h with constant stirring under nitrogen atmosphere. DMF was removed from the reaction mixture under reduced pressure, and the residue was extracted with chloroform (3 × 40 mL) and distilled water (50 mL). The chloroform extract was washed with water (2 × 50 mL) and dried over anhydrous sodium sulfate. After removal of solvent, the residue was purified by column chromatography over silica gel using 1:1 chloroform−light petroleum ether as eluent to yield 2-(*N*-prop-2′-ynylamino)phenyl *p*-toluenesulfonate **5** as a colorless solid (3.3 g, 58%). The product was finally crystallized from petroleum ether, mp 105−107 °C; IR 3402, 3286 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18 (t, 1H), 2.45 (s, 3H), 3.80 (d, J = 3.0 Hz, 2H), 4.28 (s, 1H, br), 6.61−6.66 (m, 1H), 6.72 (d, J = 9.0 Hz, 1H), 6.89 (d, J = 9.0 Hz, 1H), 7.13 (m, 1H), 7.31 (m, 2H), 7.76 (m, 2H). Anal. Calcd for $C_{16}H_{15}NSO_3$: C, 63.76; H, 5.01; N, 4.64. Found: C, 63.67; H, 4.91; N, 4.72.

2-(*N*-Benzyl-*N*-prop-2′-ynylamino)phenyl *p*-Toluenesulfonate (6a). A mixture of 2-(*N*-prop-2′-ynylamino)phenyl *p*-toluenesulfonate **5** (2 g, 6.63 mmol) and anhydrous K_2CO_3 (920 mg, 6.63 mmol) in dry DMF (15 mL) was stirred for 16 h at room temperature under nitrogen atmosphere. Benzyl bromide (1.7 g, 9.94 mmol) in DMF (5 mL) was then added slowly during 10 min. The whole mixture was heated at 80 °C for 48h with constant stirring under nitrogen atmosphere. The residue obtained after removal of DMF under reduced pressure was extracted with chloroform (3 × 30 mL) and water (50 mL). The combined chloroform layer was washed with water (2 × 50 mL) and dried over anhydrous sodium sulfate. After removal of solvent, the residue was purified by column chromatography over silica gel using chloroform as eluent. 2-(*N*-Benzyl-*N*-prop-2′-ynylamino)phenyl *p*-toluenesulfonate **6a** was obtained as a colorless oil (1.6 g, 62%). IR (liquid film) 3290, 1600 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 2.16 (t, 1H), 2.36 (s, 3H), 3.60 (d, J = 3.0 Hz, 2H), 4.30 (s, 2H), 6.51−7.24 (m, 11H), 7.66−7.81 (m, 2H). Anal. Calcd for $C_{23}H_{21}NSO_3$: C, 70.56; H, 5.40; N, 3.57. Found: C, 70.43; H, 5.16; N, 3.36.

For the preparation of *N*-methyl and *N*-ethyl derivatives, **6b** and **6c**, respectively, the same procedure was used with methyl iodide or ethyl iodide instead of benzyl bromide.

2-(*N*-Methyl-*N*-prop-2′-ynylamino)phenyl *p*-toluenesulfonate (6b): yield 83%; mp 55−56 °C; IR 3280, 1598 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 2.00 (t, 1H), 2.30 (s, 3H), 2.36 (s, 3H), 3.54 (d, J = 3.0 Hz, 2H), 6.66−7.24 (m, 6H), 7.51−7.66 (m, 2H). Anal. Calcd for $C_{17}H_{17}NSO_3$: C, 64.73; H, 5.43; N, 4.44. Found: C, 64.47; H, 5.30; N, 4.18.

2-(*N*-Ethyl-*N*-prop-2′-ynylamino)phenyl *p*-toluenesulfonate (6c): yield 71%; mp 65 °C; IR 3285, 1600 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 1.0 (t, 3H), 2.03 (t, 1H), 2.39 (s, 3H), 3.03 (q, 2H), 3.6 (d, J = 2.0 Hz, 2H), 6.9−7.26 (m, 6H), 7.56−7.66 (m, 2H). Anal. Calcd for $C_{18}H_{19}NSO_3$: C, 65.62; H, 5.81; N, 4.25. Found: C, 65.35; H, 5.77; N, 4.20.

Typical Procedure for the Synthesis of 2-[*N*-Benzyl-*N*-(3′-phenylprop-2′-ynyl)amino]phenyl *p*-Toluenesulfonate 8a. A mixture of iodobenzene **7a** (360 mg, 1.76 mmol), $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), and CuI (17 mg, 0.09 mmol) was stirred in triethylamine (9 mL) for 20 min under N_2 atmosphere. The acetylenic compound **6a** (830 mg, 2.11 mmol) in Et_3N (3 mL) was added very slowly, and the whole reaction mixture was stirred at room temperature for about 16 h. After removal of solvent under reduced pressure, the reaction mixture was poured in water (100 mL) and extracted with chloroform (3 × 50 mL). The combined chloroform layer was washed with water and dried over anhydrous Na_2SO_4. After the removal of solvent, the residue was chromatographed over silica gel, eluent being chloroform/petroleum ether (75/25, V/V), affording compound **8a** (760 mg, 92%) as a colorless oil; IR (liquid film) 2210, 1597 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.69 (s, 2H), 4.26 (s, 2H), 7.01−7.02 (m, 1H), 7.19−7.39 (m, 15H), 7.75 (d, J = 8.1 Hz, 2H). Anal. Calcd for $C_{29}H_{25}NSO_3$: C, 74.49; H, 5.38; N, 2.99. Found: C, 74.14; H, 5.42; N, 2.72.

Similar reaction conditions were used for compounds **8b**−**k**.

2-[*N*-Benzyl-*N*-{3′-(3-chlorophenyl)prop-2′-ynyl}amino]-

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(41) Barker, J. M.; Huddleston, P. R.; Wood, M. L. *Synth. Commun.* **1975**, *5*, 59.
(42) Das, B.; Kundu, N. G. *Synth. Commun.* **1988**, 855.

phenyl *p*-toluenesulfonate (8b): IR (liquid film) 2220, 1596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3H), 3.64 (s, 2H), 4.15 (s, 2H), 6.89−6.93 (m, 1H), 7.06−7.30 (m, 14H), 7.65 (d, J = 9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 40.0, 55.6, 83.4, 85.1, 121.6, 122.2, 122.5, 123.7, 126.4, 126.5, 127.3, 127.4, 127.4, 128.2, 128.4, 128.5, 128.7, 130.4, 132.3, 133.0, 136.0, 142.2, 142.9, 144.0; ^{13}C NMR (75 MHz, $CDCl_3$, DEPT 135) δ 21.8, 41.2 (inverted), 55.8 (inverted), 122.9, 123.4, 123.7, 127.6, 127.7, 128.5, 128.6, 129.4, 129.6, 129.7, 130.0, 131.6. Anal. Calcd for $C_{29}H_{24}NSO_3Cl$: C, 69.38; H, 4.81; N, 2.79. Found: C, 69.03; H, 4.42; N, 2.30.

2-[*N*-Benzyl-*N*-{3′-(4-methylphenyl)prop-2′-ynyl}amino]-phenyl *p*-toluenesulfonate (8d): mp 118−119 °C; IR 2230, 1598 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.37 (s, 3H), 3.68 (s, 2H), 4.26 (s, 2H), 6.98−7.39 (m, 15H), 7.73−7.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 22.0, 41.5, 56.0, 84.4, 86.4, 120.4, 123.2, 123.7, 123.8, 127.8, 127.9, 128.7, 128.9, 129.5, 129.8, 129.8, 131.9, 133.8, 137.6, 138.7, 143.6, 144.5, 145.4; ^{13}C NMR (75 MHz, $CDCl_3$, DEPT 135) δ 21.6, 21.8, 41.2 (inverted), 55.7 (inverted), 122.9, 123.4, 123.5, 127.5, 127.6, 128.4, 128.6, 129.2, 129.5, 129.5, 131.6. Anal. Calcd for $C_{30}H_{27}NSO_3$: C, 74.81; H, 5.65; N, 2.90. Found: C, 74.86; H, 5.74; N, 2.85.

2-[*N*-Benzyl-*N*-{3′-(2-thienyl)prop-2′-ynyl}]aminophenyl *p*-toluenesulfonate (8f): IR (liquid film) 2240, 1598 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.72 (s, 2H), 4.24 (s, 2H), 6.94−6.95 (m, 2H), 7.12−7.38 (m, 12H), 7.74 (d, J = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 41.2, 55.6, 88.8, 122.7, 122.9, 123.2, 123.5, 126.7, 126.9, 127.4, 127.5, 128.3, 128.4, 129.2, 129.4, 131.7, 133.3, 137.0, 143.1, 143.9, 145.0; ^{13}C NMR (75 MHz, $CDCl_3$, DEPT 135) δ 21.8, 41.4 (inverted), 55.8 (inverted), 122.9, 123.4, 123.7, 126.9, 127.1, 127.6, 127.7, 128.5, 128.6, 129.5, 129.6, 131.9. Anal. Calcd for $C_{27}H_{23}NS_2O_3$: C, 68.32; H, 5.09; N, 2.95. Found: C, 68.08; H, 4.93; N, 2.83.

Typical Procedure for the Synthesis of (Z)-4-Benzyl-2-benzylidene-3,4-dihydro-2*H*-1,4-benzoxazine 9a. The disubstituted alkyne **8a** (670 mg, 1.42 mmol) was refluxed with KOH/H_2O (1.5 g, 26.8 mmol/3 mL) in ethanol (20 mL) for 8 h under Ar atmosphere. It was then cooled to room temperature and neutralized with glacial acetic acid, and after the removal of solvent the residue was worked up with diethyl ether (100 mL) and water (2 × 50 mL). The ether layer was dried over anhydrous Na_2SO_4. After the removal of solvent, the residue was chromatographed over neutral alumina eluting with petroleum ether/diethyl ether (80/20, V/V), affording compound **9a** (415 mg, 93%) as a colorless solid. The product was finally crystallized from petroleum ether/diethyl ether, mp 57−59 °C; IR 1680, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.71 (s, 2H), 4.41 (s, 2H), 5.39 (s, 1H), 6.84−6.96 (m, 3H), 7.16−7.42 (m, 9H), 7.73−7.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.7 ($^3J_{CH}$ = 4.3 Hz), 54.7, 104.7, 114.0, 116.2, 119.6, 122.6, 126.2, 127.7, 128.3, 128.5, 128.7, 135.1, 136.1, 137.2, 143.6, 145.6; ^{13}C NMR (75 MHz, $CDCl_3$, DEPT 135) δ 49.9 (inverted), 54.9 (inverted), 104.9, 114.2, 116.4, 119.8, 122.8, 126.4, 127.6, 127.9, 128.5, 128.7, 128.9. Anal. Calcd for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.18; H, 6.24; N, 4.34.

Similar reaction conditions were used for the synthesis of compounds **9b**−**k**.

(Z)-4-Benzyl-2-[(4-methylphenyl)methylidene]-3,4-dihydro-2*H*-1,4-benzoxazine (9d): mp 114−116 °C; IR 1680, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H), 3.65 (s, 2H), 4.37 (s, 2H), 5.32 (s, 1H), 6.78−6.92 (m, 3H), 7.09−7.15 (m, 3H), 7.24−7.36 (m, 5H), 7.57 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 49.7 ($^3J_{CH}$ = 3.65 Hz), 54.8, 104.7, 114.0, 116.1, 119.6, 122.5, 127.4, 127.7, 128.4, 128.7, 129.0, 132.3, 135.8, 136.1, 137.3, 143.7, 144.8; ^{13}C NMR (75 MHz, $CDCl_3$, DEPT 135) δ 21.4, 49.9 (inverted), 55.0 (inverted), 104.9, 114.2, 116.3, 119.8, 122.7, 127.6, 127.9, 128.6, 128.9, 129.2. Anal. Calcd for $C_{23}H_{21}NO$: C, 84.36; H, 6.46; N, 4.27. Found: C, 84.21; H, 6.68; N, 4.31.

(Z)-4-Benzyl-2-[(2-α-naphthyl)methylidene]-3,4-dihydro-2*H*-1,4-benzoxazine (9e): mp 117−119 °C; IR 1660, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.84 (s, 2H), 4.62 (s, 2H), 6.03 (s, 1H), 6.82−7.06 (m, 4H), 7.38−7.57 (m, 8H), 7.76−8.44 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.8; 54.8, 100.9, 114.0, 116.2, 119.6, 122.5, 123.9, 125.4, 125.5, 125.7, 126.8, 127.2, 127.5, 127.7, 128.6, 128.7, 130.8, 131.3, 133.6, 136.1, 137.2, 143.6, 146.2; ^{13}C NMR (75 MHz, $CDCl_3$, DEPT 135) δ 50.0 (inverted), 55.0 (inverted), 101.1, 114.2, 116.4, 119.8, 122.7, 124.2, 125.6, 125.7, 125.9, 127.0, 127.4, 127.7, 128.0, 128.8, 128.9. Anal. Calcd for $C_{26}H_{21}NO$: C, 85.91; H, 5.82; N, 3.85. Found: C, 85.82, H, 6.02; N, 3.74.

(Z)-4-Benzyl-2-[(2-thienyl)methylidene]-3,4-dihydro-2*H*-1,4-benzoxazine (9f): mp 99−101 °C; IR 1680, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 2H), 4.35 (s, 2H), 5.71 (s, 1H), 6.81−7.04 (m, 6H), 7.16−7.35 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.7 ($^3J_{CH}$ = 4.18 Hz), 54.7, 99.5, 113.9, 116.2, 119.6, 122.7, 124.8, 125.3, 126.3, 127.4, 127.7, 128.7, 135.8, 137.1, 137.4, 143.4, 143.5; ^{13}C NMR (75 MHz, $CDCl_3$, DEPT 135) δ 48.9 (inverted) 54.9 (inverted), 99.7, 114.2, 116.4, 119.8, 122.9, 125.0, 125.5, 126.5, 127.6, 127.9, 128.9. Anal. Calcd for $C_{20}H_{17}NSO$: C, 75.20; H, 5.36; N, 4.38. Found: C, 75.20; H, 5.47; N, 4.24.

(Z)-4-Benzyl-2-[(2,4-dimethoxypyrimidin-5-yl)methylidene]-3,4-dihydro-2*H*-1,4-benzoxazine (9g): mp 130−132 °C; IR 1680, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.71 (s, 2H), 4.39 (s, 2H), 4.40 (s, 3H), 4.42 (s, 3H), 5.46 (s, 1H), 6.78−6.91 (m, 3H), 7.05−7.08 (m, 1H), 7.26−7.37 (m, 5H), 9.06 (s, 1H). Anal. Calcd for $C_{22}H_{21}N_3O_3$: C, 70.38; H, 5.63; N, 11.19. Found: C, 70.01; H, 5.98; N, 11.01.

(Z)-4-Methyl-2-benzylidene-3,4-dihydro-2*H*-1,4-benzoxazine (9h): colorless oil; IR (liquid film) 1680, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.88 (s, 3H), 3.67 (s, 2H), 5.45 (s, 1H), 6.74−6.77 (m, 2H), 6.81−6.84 (m, 1H), 6.94−6.97 (m, 1H), 7.06−7.36 (m, 4H), 7.68 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.2, 52.5, 104.6, 112.9, 115.8, 119.5, 122.6, 126.1, 128.2, 128.5, 128.5, 129.9, 135.1, 136.9, 143.4, 145.8; ^{13}C NMR (75 MHz, $CDCl_3$, DEPT 135) δ 38.4, 52.7 (inverted), 104.8, 113.1, 116.0, 119.7, 122.8, 126.3, 128.4, 128.7, 130.2. Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.70; H, 6.45; N, 5.88.

(Z)-4-Ethyl-[(3-chlorophenyl)methylidene]-3,4-dihydro-2*H*-1,4-benzoxazine (9k): colorless oil; IR (liquid film) 1680, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (t, 3H), 3.30 (q, 2H), 3.66 (s, 2H), 5.34 (s, 1H), 6.74−6.91 (m, 3H), 7.04−7.23 (m, 3H), 7.49 (d, J = 7.8 Hz, 1H), 7.67 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.3, 44.4, 48.7, 103.1, 113.3, 116.1, 119.0, 122.8, 125.9, 126.4, 128.2, 129.4, 134.0, 135.3, 137.0, 143.3, 146.9; ^{13}C NMR (75 MHz, $CDCl_3$, DEPT 135) δ 10.6, 44.6 (inverted), 48.9 (inverted), 103.3, 113.5, 116.3, 119.2, 123.0, 126.2, 126.6, 128.4, 129.6. Anal. Calcd for $C_{17}H_{16}NOCl$: C, 71.44; H, 5.64; N, 4.90. Found: C, 71.26; H, 5.58; N, 4.87.

Synthesis of 4-Methyl-2-methylene-3,4-dihydro-2*H*-1,4-benzoxazine (10). The monosubstituted alkyne **6b** (300 mg, 0.95 mmol) was refluxed with KOH/H_2O (18.05 mmol/1.5 mL) in ethanol (10 mL) for 8 h under Ar atmosphere. It was cooled to room temperature and neutralized with glacial acetic acid, and after the removal of solvent the residue was worked up with diethyl ether (50 mL) and water (2 × 20 mL). The ether layer was dried over anhydrous Na_2SO_4. After the removal of solvent, the residue was chromatographed over neutral alumina eluting with petroleum ether/diethyl ether (90/10, V/V), affording compound **10** (140 mg, 91%) as a colorless oil; IR (liquid film) 1680, 1600 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.8 (s, 3H), 3.70 (s, 2H), 4.10 (s, 1H), 4.8 (s, 1H), 6.9−7.2 (m,4H). Anal. Calcd for $C_{10}H_{11}NO$: C, 74.5; H, 6.87; N, 8.69. Found: C, 74.25; H, 6.62; N, 8.57.

Synthesis of (*Z*)-2-Benzylidene-3,4-dihydro-2*H*-1,4-benzoxazine (14). A mixture of iodobenzene **7a** (150 mg, 0.73 mmol), $(PPh_3)_2PdCl_2$ (15 mg, 0.02 mmol), and CuI (7 mg, 0.04 mmol) in triethylamine (9 mL) was stirred under argon atmosphere for 15 min. Then compound **5** (264 mg, 0.87 mmol) in Et_3N (3 mL) was added very slowly. The resulting solution was stirred at room temperature for about 16 h under N_2 atmosphere. After usual workup with chloroform−water and purification by chromatography on silica gel with chloroform−petroleum ether (75/25, V/V) as eluent, the disubstituted alkyne **11** was obtained as an oil, which was hydrolyzed with aqueous ethanolic solution of KOH at 80 °C for about 8−10 h to yield **13**. Compound **13** (540 mg, 2.41 mmol) was stirred

with the mixture of $Pd(OAc)_2$ (5 mol %, 0.12 mmol), LiCl (1.21 mmol), and K_2CO_3 (6.02 mmol) at 100 °C in DMF for 16 h under argon atmosphere. After usual workup with ether−water, and purification by chromatography on neutral alumina, ether−petroleum ether (20/80, V/V) as eluent, product **14** was obtained in 15% yield. The product **14** could also be obtained by hydrolyzing **5** to compound **12**, which was then subsequently arylated and then cyclized with $Pd(OAc)_2$, LiCl, and K_2CO_3 in DMF at 100 °C for 16 h; mp 116−118 °C; IR 3390, 1680, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.96 (s, 2H), 5.53 (s, 1H), 6.75−6.93 (m, 3H), 7.12−7.45 (m, 5H), 7.73−7.80 (m, 2H). Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.86; N, 6.27. Found: C, 80.65; H, 5.80; N, 6.18.

Synthesis of Substituted Dialkynes 16a, 16b, 16c. The substituted dialkynes (**16a**−**c**) were synthesized following the same procedure as for the disubstituted alkynes (**8a**−**k**) using di-iodo aryl compounds (**15**) instead of the aryl iodides (**7**).

(16a): mp 118−120 °C; IR 2225, 1600 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.35 (s, 6H), 3.61 (s, 4H), 4.18 (s, 4H), 6.78−7.45 (m, 18H), 7.46−7.78 (m, 12H). Anal. Calcd for $C_{52}H_{44}N_2S_2O_6$: C, 72.87; H, 5.17; N, 3.26. Found: C, 72.66; H, 4.99; N, 2.98.

(16b): mp 97−98 °C; IR 2230, 1598 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.36 (s, 6H), 2.48 (s, 6H), 3.75 (s, 4H), 6.75−7.24 (m, 14H), 7.48−7.66 (m, 4H). Anal. Calcd for $C_{38}H_{34}N_2S_3O_6$: C, 64.20; H, 4.28; N, 3.94. Found: C, 64.06; H, 4.61; N, 3.80.

(16c): mp 109−110 °C; IR 2225, 1600 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.30 (s, 6H), 2.39 (s, 6H), 3.72 (s, 4H), 6.84−7.36 (m, 12H), 7.48−7.69 (m, 8H). Anal. Calcd for $C_{40}H_{36}N_2S_2O_6$: C, 68.15; H, 5.14; N, 3.97. Found: C, 67.92; H, 4.95; N, 3.80.

Synthesis of Bis(benzoxazinyl) Derivatives 17a−c. Bis(benzoxazinyl) derivatives (**17a**−**c**) were synthesized following similar reaction conditions as described for the synthesis of compound **9** from **8**. The only difference was that, in case of compounds **17a**−**c**, workup was done with ethyl acetate−water instead of diethyl ether−water in order to overcome solubility problem, and also the products were purified by chromatography over neutral alumina, eluent being petroleum ether−ethyl acetate (80/20, V/V). Crystallization was done with petroleum ether−ethyl acetate.

1,2-Bis[(*Z*)-4′-benzyl-2′-methylidene-3′,4′-dihydro-2′*H*-1′,4′-benzoxazinyl]benzene (17a): mp 132−134 °C; IR 1680, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.65 (s, 4H), 4.37 (s, 4H), 5.47 (s, 2H), 6.78−6.88 (m, 6H), 6.99−7.02 (m, 2H), 7.22−7.36 (m, 12H), 7.90 (dd, J_1 = 5.70 Hz, J_2 = 3.3 Hz, 2H), MS *m/e* (rel inten) 548 (M^+, 15). Anal. Calcd for $C_{38}H_{32}N_2O_2$: C, 83.18; H, 5.87; N, 5.10. Found: C, 83.15; H, 5.86; N, 5.02.

2,5-Bis[(*Z*)-4′-methyl-2′-methylidene-3′,4′-dihydro-2′*H*-1′,4′-benzoxazinyl]thiophene (17b): mp 151−152 °C; IR 1674, 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.87 (s, 6H), 3.69 (s, 4H), 5.78 (s, 2H), 6.75−6.78 (m, 2H), 6.85−6.88 (m, 2H), 6.95−6.97 (m, 4H), 7.18−7.21 (m, 2H); MS *m/e* (rel inten) 402 (M^+,100). Anal. Calcd for $C_{24}H_{22}N_2SO_2$: C, 71.61; H, 5.51; N, 6.96. Found: C, 71.72; H, 5.41; N, 6.86.

1,4-Bis[(*Z*)-4′-methyl-2′-methylidene-3′,4′-dihydro-2′*H*-1′,4′-benzoxazinyl]benzene (17c): mp 186−187 °C; IR 1672, 1605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.87 (s, 6H), 3.67 (s, 4H), 5.44 (s, 2H), 6.74−6.85 (m, 4H), 6.94−6.96 (m, 2H), 7.13 (dd, J_1 = 7.7 Hz, J_2 = 1.4 Hz, 2H), 7.66 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.7, 53.0, 105.1, 113.4, 116.3, 119.9, 123.0, 128.9, 133.5, 137.4, 143.9, 146.0; ^{13}C NMR (75 MHz, $CDCl_3$, DEPT 135) δ 38.4, 52.7 (inverted), 104.8, 113.1, 116.0, 119.6, 122.7, 128.6; MS *m/e* (rel inten) 396 (M^+, 50). Anal. Calcd for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.06. Found: C, 78.89; H, 5.94; N, 6.79.

Typical Procedure for the Synthesis of 2-Benzyl-3,4-dihydro-2*H*-1,4-benzoxazine (18a). Compound **9a** (100 mg,0.32 mmol) was hydrogenated in the presence of 10% Pd/C catalyst in dry ethyl acetate (9 mL) under atmospheric pressure. After 24 h, the catalyst was removed by filtration and washed with ethyl acetate (3 mL). The combined filtrate was evaporated to dryness to give a gummy material which was purified by column chromatography over neutral alumina with petroleumether/diethyl ether (80/20,V/V) as eluent. This afforded **18a** as a colorless oil (58 mg, 81%); IR (liquid film) 3388, 2918, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.84 (dd, J_1 = 15.0 Hz, J_2 = 6.0 Hz, 1H), 3.09−3.19 (m, 2H), 3.24 (dd, J_1 = 11.7 Hz, J_2 = 2.7 Hz, 1H), 4.34 (m, 2H), 6.59−6.66 (m, 2H), 6.75−6.85 (m, 2H), 7.20−7.33 (m, 5H). Anal. Calcd for $C_{15}H_{15}NO$: C, 79.96; H, 6.71; N, 6.21. Found: C, 79.81; H, 6.52; N, 6.09.

Similarly, compounds **18b**,**d**,**e**,**g**,**h** were synthesized through hydrogenation of the corresponding unsaturated analogues **9b**,**d**,**e**,**g**,**h**, respectively.

2-[(3-Chlorophenyl)methyl]-3,4-dihydro-2*H*-1,4-benzoxazine(18b): colorless oil; IR (liquid film) 3390, 2918, 1608 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.84 (dd, J_1 = 14.1 Hz, J_2 = 6.9 Hz, 1H), 3.03−3.13 (m, 2H), 3.30 (dd, J_1 = 11.4 Hz, J_2 = 2.7 Hz, 1H), 4.31 (m, 1H), 6.57−6.60 (m, 1H), 6.66−6.69 (m, 1H), 6.74−6.81 (m, 2H), 7.14−7.26 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.7; 44.3, 74.2, 115.3, 116.8, 118.9, 121.2, 126.7, 127.5, 129.4, 129.6, 133.0, 134.1, 139.3, 143.4. ^{13}C NMR (75 MHz, $CDCl_3$, DEPT 135) δ 38.9 (inverted), 44.5 (inverted), 74.4, 115.5, 117.0, 119.1, 121.4, 126.9, 127.8, 129.6, 129.8. Anal. Calcd for $C_{15}H_{14}NOCl$: C, 69.36; H, 5.43; N, 5.39. Found: C, 69.17; H, 5.31; N, 5.26.

2-[(4-Methylphenyl)methyl]-3,4-dihydro-2*H*-1,4-benzoxazine (18d): colorless oil; IR (liquid film) 3388, 2918, 1608 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.26 (s, 3H), 2.74 (dd, J_1 = 12.0 Hz, J_2 = 6.0 Hz, 1H), 2.99−3.07 (m, 2H), 3.22 (dd, J_1 = 12.0 Hz, J_2 = 3.0 Hz, 1H), 4.19−4.26 (m, 1H), 6.50−6.75 (m, 4H), 7.06−7.09 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 39.3, 44.8, 75.2, 115.7, 117.3, 119.3, 121.5, 129.6, 129.7, 133.7, 134.6, 136.5, 144.1; ^{13}C NMR (75 MHz, $CDCl_3$, DEPT 135) δ 20.0, 37.8 (inverted), 43.4 (inverted), 73.8, 114.3, 115.8, 117.9, 120.1, 128.1, 128.3. Anal. Calcd for $C_{16}H_{17}NO$: C, 80.33; H, 7.11; N, 5.85. Found: C, 80.08; H, 7.01; N, 6.69.

2-(Prop-2′-ynyloxy)nitrobenzene (20). A mixture of 2-nitrophenol (5.0 g, 35.9 mmol) and anhydrous K_2CO_3 (7.45 g, 35.9 mmol) in dry acetone (30 mL) was stirred for 2 h at room temperature. Propargyl bromide (5.12 g, 43.08 mmol) in dry acetone (10 mL) was then added during 20 min. The whole mixture was then heated under reflux for 16 h with constant stirring under nitrogen atmosphere. Acetone was removed from the mixture, and the residue was poured in distilled water (100 mL) and extracted with chloroform (3 × 50 mL). The combined organic layer was washed with water (100 mL) and dried over anhydrous Na_2SO_4. After removal of solvent, the residue was purified through column chromatography over silica gel using chloroform−petroleum ether (1:1) as eluent. Finally the product was crystallized from petroleum ether−chloroform. A colorless white crystalline solid (4.8 g, 76%); mp 77−78 °C; IR 3300,1600 cm^{-1}; ^1H NMR (60 Mz, CCl_4) δ 2.49 (t, 1H), 4.46 (d, J = 2 Hz, 2H), 6.85−7.82 (m, 4H). Anal. Calcd for $C_9H_7NO_3$: C, 61.01; H, 3.98; N, 7.90. Found: C, 61.17; H, 3.83; N, 7.74.

2-(Prop-2′-ynyloxy)aniline (21). It was prepared by the reduction of compound **20** with Fe/AcOH following the usual procedure.[43]

Compound **21** was obtained as colorless oil; IR (liquid film) 3466, 3375, 1604 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.4 (t, 1H), 3.5 (s, 2H), 4.56 (d, J = 2.0 Hz, 2H), 6.4−6.9 (m, 4H). Anal. Calcd for C_9H_9NO: C, 73.41; H, 6.16; N, 9.55. Found: C, 73.29; H, 6.05; N, 9.40.

Typical Procedure for the Synthesis of Compound 22. A mixture of iodobenzene (415 mg, 2.03 mmol), $(PPh_3)_2PdCl_2$ (42 mg, 0.06 mmol), and CuI (20 mg, 0.10 mmol) in triethylamine (9 mL) was stirred under N_2 atmosphere for 20 min. Then 2-(prop-2′-ynyloxy)aniline (**21**) (360 mg, 2.44 mmol) in triethylamine (3 mL) was added very slowly. The resulting reaction mixture was stirred at room temperature for 16 h under N_2 atmosphere. After the removal of triethylamine, the reaction mixture was poured in water (50 mL) and extracted with chloroform (3 × 40 mL). The combined chloroform layer was washed with water and dried over anhydrous Na_2SO_4. After the removal of solvent, the residue was chromatographed over silica gel using chloroform/petroleum ether (75/25,V/V)

(43) Vogel, A. I. *A Text Book of Practical Organic Chemistry*, 4th ed.; ELBS, Longman Group Limited: London, 1978; p 658.

as eluent, affording compound **22** (355 mg, 78%) as a colorless oil; IR (liquid film) 3464, 3375, 2233, 1600 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 3.66 (s, 2H), 4.92 (s, 2H), 6.39−7.0 (m, 4H), 7.09−7.46 (m, 5H). Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.86; N, 6.27. Found: C, 80.55; H, 5.78; N, 6.18.

Compounds **23**−**27** were synthesized by following the above procedure.

23: colorless oil; IR (liquid film) 3465, 3375, 2242, 1614 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 3.62 (s, 2H), 4.82 (s, 2H), 6.4−6.92 (m, 4H), 7.20−7.50 (m, 4H). Anal. Calcd for $C_{15}H_{12}NOCl$: C, 69.90; H, 4.68; N, 5.43. Found: C, 69.83; H, 4.53; N, 5.31.

27: colorless sticky oil; IR (liquid film) 3466, 3375, 2241, 1605 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 3.76 (s, 4H, broad), 4.86 (s, 4H), 6.43−6.92 (m, 8H), 7.0−7.43 (m, 4H). Anal. Calcd for $C_{24}H_{20}N_2O_2$: C, 78.23; H, 5.47; N, 7.60. Found: C, 78.14; H, 5.40; N, 7.56.

General Procedure for the Synthesis of 28−33. Compound **22** (290 mg, 1.3 mmol) was dissolved in dry dichloromethane (9 mL). Then under ice-cold conditions, pyridine (103 mg, 1.3 mmol) and tosyl chloride (248 mg, 1.3 mmol) were added to it. The reaction mixture was then stirred for about 2 h at room temperature under nitrogen atmosphere. After the removal of solvent, the residue was poured in 50 mL of water and extracted with chloroform (3 × 40 mL). The combined chloroform layer was washed with water and dried over anhydrous Na_2SO_4. After the removal of solvent the residue was purified by column chromatography over silica gel using chloroform/petroleum ether (75/25,V/V) as eluent. The product was finally crystallized from petroleum ether−chloroform. A white crystalline solid **28** was obtained (350 mg, 72%); mp 111 °C; IR 3259, 1599 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.16 (s, 3H), 4.7 (s, 2H), 6.75−7.72 (m, 14H). Anal. Calcd for $C_{22}H_{19}NSO_3$: C, 70.00; H, 5.07; N, 3.71. Found: C, 69.84; H, 4.99; N, 3.58.

29: mp 109 °C; IR 3267, 1597 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.23 (s, 3H), 4.70 (s, 2H), 6.80−7.82 (m, 13H). Anal. Calcd for $C_{22}H_{18}NSO_3Cl$: C, 64.14; H, 4.40; N, 3.40. Found: C, 64.31; H, 4.47; N, 3.82.

33: mp 64 °C; IR 3261, 1598 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 2.23 (s, 6H), 4.60 (s, 4H), 6.70−7.33 (m, 14H), 7.36−7.75 (m, 8H). Anal. Calcd for $C_{38}H_{32}N_2S_2O_6$: C, 67.43; H, 4.76; N, 4.14. Found: C, 67.30; H, 4.71; N, 4.12.

Typical Procedure for the Synthesis of (*Z*)-3-Benzylidene-4-tosyl-3,4-dihydro-2*H*-1,4-benzoxazine 34. A mixture of **28** (250 mg, 0.66 mmol), CuI (25 mg, 0.13 mmol), K_2CO_3 (229 mg, 1.65 mmol), and Bu_4NBr (213 mg, 0.66 mmol) in dry acetonitrile (11 mL) was stirred for about 15 min under argon atmosphere. It was then refluxed for about 12 h under argon atmosphere. After removal of acetonitrile under reduced pressure, the reaction mixture was poured in 50 mL of water and extracted with chloroform (3 × 40 mL). The combined chloroform layer was washed with water and dried over anhydrous Na_2SO_4. After removal of solvent, the residue was chromatographed over silica gel eluting with chloroform/petroleum ether (75/25,V/V), affording compound **34** (220 mg, 88%) as a colorless solid. It was finally crystallized from petroleum ether−chloroform; mp 176 °C; IR 1678, 1599 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H), 4.01 (d, J = 11.4 Hz, 1H), 4.37 (d, J = 11.4 Hz, 1H), 6.58 (s, 1H), 6.78 (d, J = 8.1 Hz,1H), 6.97−7.14 (m, 4H), 7.26−7.42 (m, 5H), 7.73 (d, J = 7.2 Hz, 2H), 7.92 (dd, J_1 = 8.1 Hz, J_2 = 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 68.1, ($^3J_{CH}$ = 4.73 Hz), 117.7, 121.4, 125.2, 126.2, 127.6, 127.8, 128.4, 128.8, 129.3, 130.1, 130.3, 131.7, 134.3, 135.2, 145.0, 148.3; ^{13}C NMR (75 MHz, $CDCl_3$, DEPT 135) δ 21.7, 67.8 (inverted), 117.4; 121.1, 126.0, 127.3, 128.1, 128.5, 129.0, 129.8, 130.0, 131.5. Anal. Calcd for $C_{22}H_{19}NSO_3$: C, 70.00; H, 5.07; N, 3.71. Found: C, 69.86; H, 5.13; N, 3.49.

Similar Reaction Conditions were Employed for the Synthesis of 35−39

35: mp 160 °C; IR 1670, 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H), 4.07 (d, J = 10.5 Hz, 1H), 4.39 (d, J = 10.6 Hz, 1H), 6.51 (s, 1H), 6.80 (dd, J_1 = 10.8 Hz, J_2 = 1.0 Hz, 1H), 6.98−7.30 (m, 6H), 7.40−7.66 (m, 4H), 7.87 (dd, J_1 = 8.1 Hz, J_2 = 1.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0 67.9, 117.7, 121.5, 124.9, 126.2, 127.7, 128.2, 128.4, 129.1, 129.4, 130.0, 130.0, 130.1, 130.2, 134.5, 134.9, 136.1, 145.2, 148.2; ^{13}C NMR (75 MHz, $CDCl_3$, DEPT 135) δ 21.7, 67.6 (inverted), 117.5, 121.2, 125.9, 127.5, 127.9, 128.1, 128.8, 129.7, 129.8, 129.9. Anal. Calcd for $C_{22}H_{18}NSO_3Cl$: C, 64.14; H, 4.40; N, 3.40. Found: C, 64.26; H, 4.39; N, 3.64.

36: mp 136−137 °C; IR 1668, 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 6H), 3.96 (d, J = 11.5 Hz, 1H), 4.35 (d, J = 11.5 Hz, 1H), 6.56 (s, 1H), 6.77 (dd, J_1 = 8.1 Hz, J_2 = 1.4 Hz, 1H), 6.97−7.24 (m, 6H), 7.41 (d, J = 8.2 Hz, 2H), 7.66 (d, J = 8.1 Hz, 2H), 7.93 (dd, J_1 = 8.1 Hz, J_2 = 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4, 20.5, 66.6, 116.2, 119.8, 123.8, 124.7, 125.3, 126.1, 126.9, 128.0, 128.6, 128.8, 130.0, 130.3, 133.8, 137.9, 143.5, 146.7; ^{13}C NMR (75 MHz, $CDCl_3$, DEPT 135) δ 21.6, 21.7, 67.8 (inverted), 117.4, 121.0, 125.9, 127.3, 128.1, 129.2, 129.8, 130.0, 131.5. Anal. Calcd for $C_{23}H_{21}NSO_3$: C, 70.56; H, 5.40; N, 3.57. Found: C, 70.53; H, 5.32; N, 3.48.

39: mp 169 °C; IR 1668, 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 6H), 4.21 (s, broad, 4H), 6.64 (s, 2H), 6.81 (dd, J_1 = 8.4 Hz, J_2 = 1.4 Hz, 2H), 6.92−6.97 (m, 2H), 7.05−7.14 (m, 6H), 7.22−7.25 (m, 2H), 7.31−7.35 (m, 4H), 7.4 (s, 2H), 7.61 (d, J = 7.4 Hz, 2H). Anal. Calcd. for $C_{38}H_{32}N_2S_2O_6$: C, 67.43; H, 4.76; N, 4.14. Found: C, 67.83; H, 4.49; N, 4.14.

Synthesis of (*Z*)-4-Tosyl-2-[(5-uracilyl)methylidene]-3,4-dihydro-2*H*-1,4-benzoxazine (40). To a magnetically stirred solution of compound **37** (150 mg, 0.34 mmol) in dry acetonitrile (9 mL) under argon atmosphere were added anhydrous sodium iodide (154 mg, 1.02 mmol) and trimethylchlorosilane (0.13 mL, 1.02 mmol). The resulting mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was washed with a few drops of sodium metabisulfite solution and then water, filtered and dried to yield compound **40** as light yellow solid (105 mg; 75%); crystallized from H_2O−MeOH (1:9); mp >200 °C; IR 3384, 3008, 2852, 1732, 1703, 1678, 1660, 1597 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.36 (s, 3H), 3.84 (d, J = 11.8 Hz, 1H), 4.66 (d, J = 11.9 Hz, 1H), 6.70 (s, 1H) 6.79−6.82 (m, 1H), 7.02−7.19 (m,2H), 7.33−7.44 (m, 4H), 7.65−7.68 (m,1H), 8.13 (d, J = 4.4 Hz, 1H), 11.15 (s, broad, 1H), 11.34 (s, 1H). Anal. Calcd for $C_{20}H_{17}N_3SO_5$: C, 58.38; H, 4.16; N, 10.21. Found: C, 58.24; H, 4.20; N, 10.23.

Similar reaction condition was used for the synthesis of compound **41** from **18g**.

Compound **41**: (70.00%); crystallized from H_2O−MeOH (9:1), mp > 200 °C; IR 3300, 3037, 2868, 1708, 1686, 1662, 1606 cm^{-1}; ^1H NMR (300 MHz, DMSO d_6) δ 2.50 (m, 2H), 2.92 (dd, J_1 = 11.8 Hz, J_2 = 7.5 Hz, 1H), 3.19−3.26 (m, 2H), 4.11 (m, 1H), 6.43−6.48 (m, 1H), 6.54−6.68 (m, 3H), 7.30 (d, J = 5.28 Hz, 1H), 10.74 (d, J = 4.35 Hz, 1H), 11.09 (s, 1H). For correct analysis the analytical sample need to be dried at 80 °C/0.5 mm of Hg for 6 h. Anal. Calcd for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.20. Found: C, 60.11; H, 5.17; N, 16.21.

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Supporting Information Available: Spectroscopic and analytical data for compounds **8c**, **8e**, **8g**−**k**, **9b**, **9c**, **9i**, **9j**, **18e**, **18g**, **18h**, **24**−**26**, **30**−**32**, **37**, and **38** (22 compounds). This material is available free of charge via the Internet at http://pubs.acs.org.

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