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An efficient, ionic liquid mediated one-pot, three component sequential synthesis of 3-benzothiazolyl-2-styrylquinazolin-4(3*H*)-ones

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ABSTRACT

An efficient and diversity oriented one-pot three component sequential synthetic method has been presented for the synthesis of 3-benzothiazolyl-2-styrylquinazolin-4(3*H*)-ones. The synthetic method involves the reaction of 3,1-benzoxazinone with 2-aminobenzothiazole and subsequently with aromatic aldehyde using SO_3H-functionalized ionic liquids (SFILs) as solvent/ catalyst.

Recently, combretastatin A-4 (CA-4) and its analogs have shown unique potentialities for treatment of cancer and for cancer chemoprevention.[1] The styryltriazole and resveratrol derivatives have been evaluated as potential radio ligands for Aβ plaque imaging. The hybrid pharmacophores of stilbene-chalcones have also been reported as antimalarial scaffolds that trigger cell death through stage specific apoptosis.[2,3] Quinazolin-4(3*H*)-one (compounds **1**, **2**) is considered to be a privileged structure and has been extensively utilized as a drug like scaffold in medicinal chemistry.[4] Among the various classes of stilbene-based compounds, 2-styrylquinazolin-4(3*H*)-ones derivatives form an interesting class of pharmacologically active compounds.[5] The 2-styrylsubstituted derivatives of quinazolin-4(3*H*)-one **3** are associated with inhibitory effects on tubulin polymerization and the growth of L1210 murine leukemia cells, while *N*-3-aryl-substituted analogs (piriqualone, **4**) have been shown to exhibit potent anticonvulsant activity.[6] The stilbene based quinazolin-4-one derivatives CP-465,022 **5** have also been reported as potent noncompetitive alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonists (Fig. 1).[7] As a privileged structural fragment, benzothiazoles are also the important key building blocks in drug discovery.[8]

Among various studies on the structure–activity relationship of stilbene, most of them concern with the modification in aromatic rings and in linker alkene. The literature demonstrates that the structural modification of one ring of stilbene with quinazolin-4(3*H*)-one skeleton improves biological activity.[5] Furthermore, N3-substitution of the quinazolin-4(3*H*)-one ring with aromatic/ heteroaromatic rings considerably enhances their biologically activity.[6] There are only a few reports on the synthesis of 2-styrylquinazolin-4(3*H*)-ones and generally involves multistep procedures.[9] The reported synthetic protocols suffer from disadvantages such as relying on multi-step reactions, having low yields,

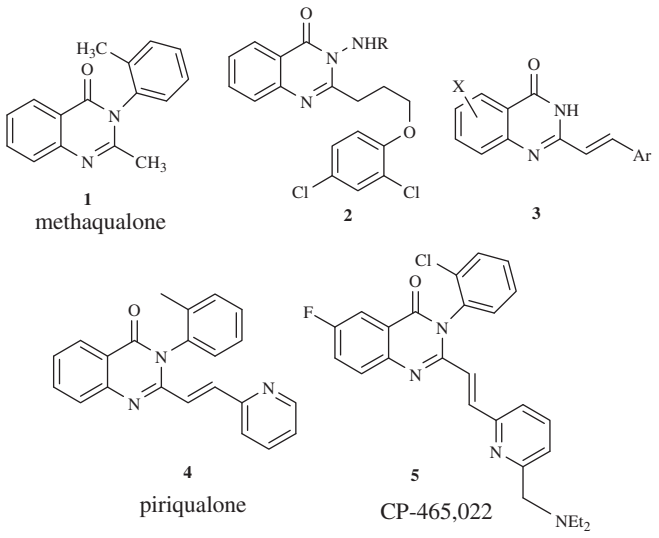

Figure 1. Biologically active quinazolinones and 2-styrylquinazolinones.

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harsh reaction conditions, prolonged reaction times, and using acid catalysts. Therefore, the development of new, efficient, and environmentally benign routes for the synthesis of 2-styrylquinazolinones incorporating medicinally privileged heterosystems by employing non-toxic reagents and solvents is highly desirable from the point of view of green chemistry and would be of great relevance to both synthetic and medicinal chemists.

Recently, the quinazolin-4(3*H*)-ones have been synthesized by green protocols involving the reaction of 3,1-benzoxazin-4-one with substituted anilines/ammonium acetate (as source of ammonia) and substituted aldehydes.[10] But in view of synthetic potentialities of multicomponent reactions to incorporate structural diversity and in continuation of our research program on the synthesis of therapeutically interesting heterocycles,[11–17] we have synthesized structurally diverse 3-benzothiazolyl-2-styrylquinazolin-4(3*H*)-ones **5** involving one-pot sequential reaction of 2-methyl-3,1-benzoxazin-4-one **1** with 2-aminobenzothiazoles **2** and subsequently with substituted aromatic aldehyes **4** using SO_3H-functionalized ionic liquids (SFILs) as solvent/catalyst. Higher yields, simplicity of the method, ease of the product isolation, mild reaction conditions, and use of ionic liquid as the reaction medium/catalyst make this method more attractive. To the best of our knowledge the synthesis of 3-benzothiazolyl-2-styrylquinazolin-4(3*H*)-ones in SO_3H functionalized ionic liquid has not been documented in the literature.

We started our study with the optimization of the one pot sequential synthesis of 3-benzothiazolyl-2-styrylquinazolin-4(3*H*)-ones as model reaction (Scheme 1). Because of the advantages of the use of ionic liquid in terms of their unique solvating, catalytic, and recycling abilities, we also investigated the effects of ionic liquids on the reaction time and the product yield of the model reaction.

The reaction was performed in the different organic solvents (entries 1–4, Table 1) and ionic liquids (entries 5–9, Table 1) and the effects of the different solvents and ionic liquids were evaluated on the basis of reaction time and product yield for this model reaction and the results are summarized in Table 1.

The ionic liquids provided higher yields with shorter reaction times as compared with those obtained using organic solvents (Table 1, entries 5–9 vs entries 1–4). The IL $[MIM(CH_2)_4SO_3H][HSO_4]$ also proved to be slightly superior to their analogous as well as other ionic liquids for this reaction (Table 1, entry 6). It was also observed that the $[MIM(CH_2)_4SO_3H][HSO_4]$ ionic liquid system provided comparatively a better yield of the product in lesser time than other catalytic systems. Moreover, it was also observed that SO_3H-functionlized ionic liquids (IL-1 and IL-2) provided a better yield of the product as compared to that obtained when the reactions were carried out with halogen containing ionic liquids (entries 5 and 6). It was also observed that the 5 mol % ionic liquid is sufficient to provide excellent results and further increase in the amount up to 10 mol % did not improve the results to a greater extent.

Table 1
Optimization of the reaction conditions

Entry	Solvent	Time (h)	Yield (%)
1	DMF	24	35
2	Acetonitrile	25	33
3	Glacial acetic acid	19	68
4	Ethanol	24	43
5	$[MIM(CH_2)_4SO_3H][CH_3PhSO_3]$ IL-1	12	81
6	$[MIM(CH_2)_4SO_3H][HSO_4]$ IL-2	09	87
7	Zwitterion $[MIM(CH_2)_4SO_3^-]$ IL-2	09	79
8	$[bmim][PF_6]$	18	68
9	$[bmim][BF_4]$	17	61

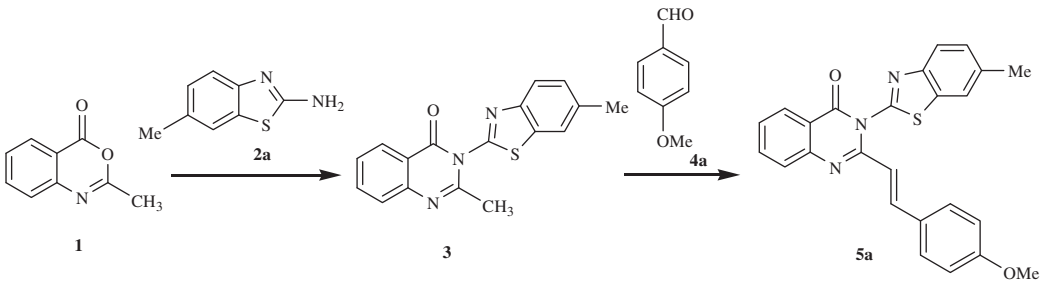
2-Methyl-3,1-benzoxazin-4-one **1** (1 mmol), 2-amino-5-methylbenzothiazole **2a** (1 mmol), *p*-anisaldehye **4a** (1 mmol), temperature 80 °C.

The proposed mechanism for the formation of 3-benzothiazolyl-2-styrylquinazolin-4(3*H*)-ones catalyzed by SO_3H functionalized ionic liquid is presented in Scheme 2. In this reaction the ionic liquid not only behaves as solvent but also facilitates the reaction as a catalyst.

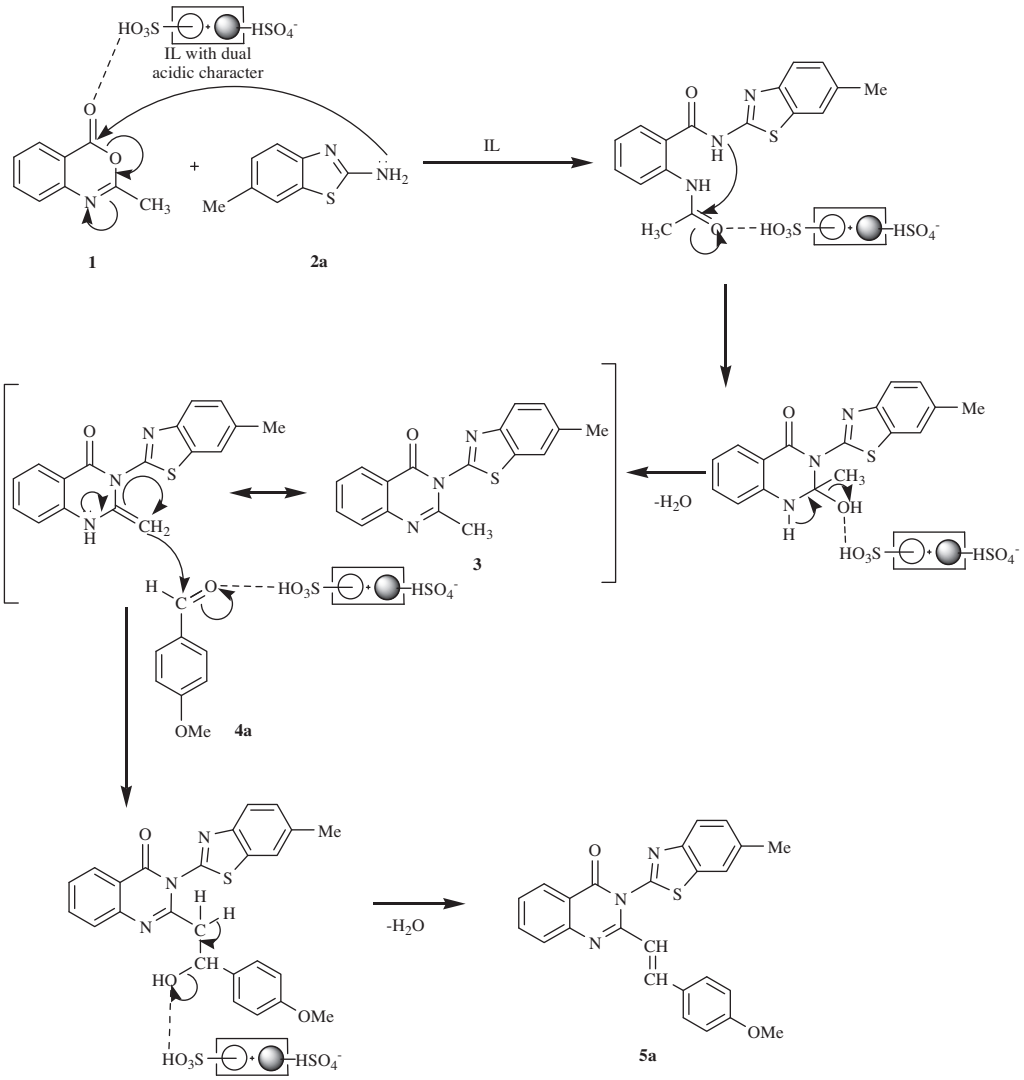
Under these optimal conditions, the sequential reaction of 2-methyl-3,1-benzoxazin-4-one **1** with substituted 2-aminobenzothiazoles **2**(**a–d**) and subsequently with aromatic aldehydes **4**(**a–b**) were carried out in the presence of SO_3H-functionalized ionic liquid (IL-1/IL-2) as catalyst/solvent in a single vessel to obtain 3-benzothiazolyl-2-styrylquinazolin-4(3*H*)-ones **5**(**a–h**) in excellent yields.[18] The results in terms of product yields and reaction time were compared and are summarized in Table 2. The overall yields obtained are excellent considering the number of steps involved in the sequential reaction. The SO_3H-functionlized ionic liquids were prepared by the method reported.[12]

It was observed that the ionic liquid, SFILs, could be easily quantitatively recovered after completion of the reaction and readily recycled and reused for at least five cycles without any appreciable loss of activity to provide structurally diverse 3-benzothiazolyl-2-styrylquinazolin-4(3*H*)-ones in excellent yields (Fig. 2).

In conclusion, we have developed an efficient and eco-compatible synthetic methodology for the synthesis of structurally diverse 3-benzothiazolyl-2-styrylquinazolin-4(3*H*)-ones in excellent yields using a halogen-free SO_3H functionalized ionic liquid as recyclable medium. The present method demonstrates the favorable reasons for using ionic liquid as a reaction medium ('greenness', solvent recoverability, non-inflammability, etc.) in parallel to the synthesis of target compounds in conventional organic reaction media such as DMF, CH_3CN, glacial acetic acid, and ethanol. This method is bestowed with its unique merits, such as mild reaction conditions, operational simplicity, and use of ionic liquid as a solvent.



Scheme 1. Model reaction.



Scheme 2. Proposed mechanism for the synthesis of 3-benzothiazolyl-2-styrylquinazolin-4(3*H*)-ones catalyzed by SO_3H functionalized ionic liquid.

Table 2
Comparison of ionic liquids (IL-1 & IL-2)

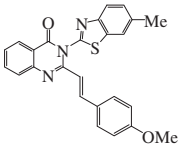
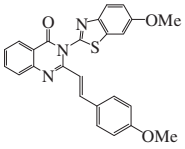
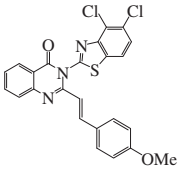
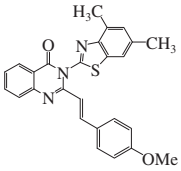
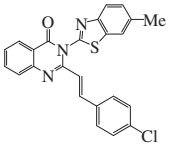
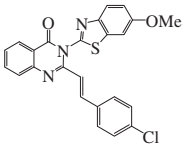
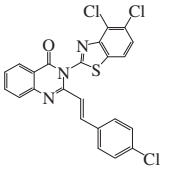
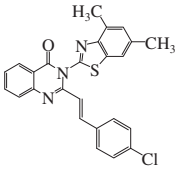
Entry	3-Benzothiazolyl-2-styryl-quinazolin-4(3*H*)-ones	IL-1		IL-2	
		Time (h)	Yield (%)	Time (h)	Yield (%)
5a		12.0	81	09.0	87
5b		12.30	80	10.15	90

Table 2 (*continued*)

Entry	3-Benzothiazolyl-2-styryl-quinazolin-4(3*H*)-ones	IL-1		IL-2	
		Time (h)	Yield (%)	Time (h)	Yield (%)
5c		12.5	81	11.5	85
5d		12.10	81	10.15	88
5e		11.0	79	09.5	87
5f		11.5	80	09.40	88
5g		13.25	75	12.1	86
5h		11.35	77	10.20	89

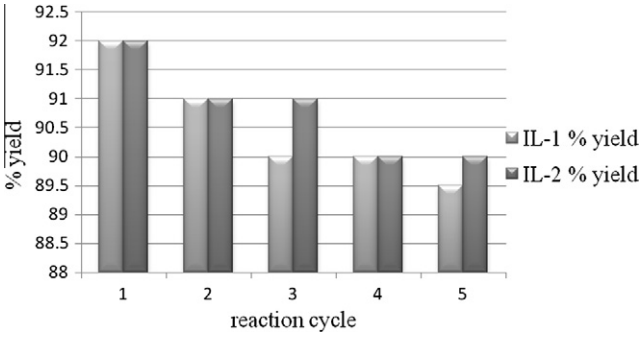


Figure 2. Reusability of IL-1 and IL-2.

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18. **Typical Experimental Procedure:** A dry 50 mL round bottom flask was charged with 2-methyl-3,1-benzoxazin-4-one **1** (1 mmol), 2-aminobenzothiazoles **2**(**a–d**) (1 mmol) and ionic liquid, SFILs (IL-1/IL-2) (0.05 g). The mixture was stirred at 80 °C for 4–7 h to complete the reaction (monitored by TLC). The aromatic aldehyde **4**(**a–b**) (1 mmol) was added to the above reaction mixture, and stirred at 80 °C for 9–13 h until the reaction was completed as monitored by TLC using *n*-hexane/EtOAc; 7:3 as eluent. The mixture was cooled and 10 mL water was added. The solid was filtered off and washed with water. The crude product was purified by recrystallization from ethanol to give **5**. The ionic liquid was reused after drying under vacuum at 90 °C.

Spectral data of synthesized of 3-benzothiazolyl-2-styrylquinazolin-4(3H)-ones. *3-(6′-Methylbenzothiazol-2-yl)-2-(4′-methoxystyryl)quinazolin-4(3H)-one* (***5a***). Mp 210–212 °C, IR (KBr): 1710, 1542, 1642, 1220–1162 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 2.14 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 6.90 (1H, d, olefinic CH), 7.02–8.77 (11H, m, ArH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 20.2, 55.6, 114.9, 117.2, 118.4, 120.5, 120.7, 121.1, 124.2, 126.2, 127.7, 128.0, 129.3, 130.4, 133.6, 134.5, 138.1, 139.3, 149.4, 150.2, 152.2, 161.6, 162.4, 163.1; Anal. Calcd. (%) for $C_{25}H_{19}N_3O_2S$: C (70.57%), H (4.50%), N (9.88%). Found: C (70.56%), H (4.50%), N (9.89%).

3-(6′-Methoxybenzothiazol-2-yl)-2-(4′-methoxystyryl)quinazolin-4(3H)-one (***5b***). Mp 238–240 °C; IR (KBr): 1740, 1532, 1640, 1250–1164 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 3.49 (3H, s, OCH_3), 3.58 (3H, s, OCH_3), 6.93 (1H, d, olefinic CH), 6.97–8.43 (11H, m, ArH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 55.6, 57.4, 108.2, 110.6, 114.9, 117.2, 118.4, 121.2, 123.4, 126.2, 127.7, 128.0, 129.3, 130.4, 133.6, 138.1, 145.2, 149.4, 152.2, 159.2, 161.6, 162.4, 163.1; Anal. Calcd. (%) for $C_{25}H_{19}N_3O_3S$: C (68.01%), H (4.39%), N (9.52%). Found: C (68.01%), H (4.35%), N (9.51%).

3-(4′,5′-Dichlorobenzothiazol-2-yl)-2-(4′-methoxystyryl)quinazolin-4(3H)-one (***5c***). Mp 215–217 °C, IR (KBr): 1692, 1555, 1610, 1280–1154, 1085 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 3.69 (3H, s, OCH_3), 6.80 (1H, d, olefinic CH), 7.01–8.71 (10H, m, ArH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 55.6, 114.9, 117.2, 118.4, 121.1, 122.1, 122.9, 126.2, 127.7, 128.0, 129.3, 130.4, 130.9, 133.6, 138.1, 145.2, 150.2, 152.2, 161.6, 162.4, 163.1. Anal. Calcd. (%) for $C_{24}H_{15}Cl_2N_3O_2S$: C (60.01%), H (3.15%), N (8.75%). Found: C (60.03%), H (3.17%), N (8.73%).

3-(4′,6′-Dimethylbenzothiazol-2-yl)-2-(4′-methoxystyryl)quinazolin-4(3H)-one (***5d***). Mp 183–185 °C, IR (KBr): 1700, 1592, 1668, 1260–1145 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 2.25 (3H, s, CH_3), 2.29 (3H, s, CH_3), 3.78 (3H, s, OCH_3), 6.71 (1H, d, olefinic CH), 6.78–7.96 (10H, m, ArH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 16.2, 20.8, 55.5, 114.1, 118.9, 120.1, 121.5, 122.7, 125.3, 126.1, 127.7, 128.2, 129.3, 130.4, 131.4, 134.0, 138.5, 145.3, 150.2, 152.4, 160.4, 162.3, 163.1. Anal. Calcd. (%) for $C_{26}H_{21}N_3O_2S$: C (71.05%), H (4.82%), N (9.56%). Found: C (71.09%), H (4.80%), N (9.55%).

3-(6′-Methylbenzothiazol-2-yl)-2-(4′-chlorostyryl)quinazolin-4(3H)-one (***5e***). Mp 218–220 °C; IR (KBr): 1693, 1535, 1615, 1035 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 2.36 (3H, s, CH_3), 6.99 (1H, d, olefinic CH), 7.12–8.75 (11H, m, ArH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 20.8, 117.4, 121.1, 121.7, 122.4, 126.3, 126.2, 126.9, 127.1, 128.5, 129.2, 130.7, 133.3, 134.1, 134.6, 135.2, 137.2, 149.4, 150.8, 151.4, 162.2, 163.1. Anal. Calcd. (%) for $C_{24}H_{16}ClN_3OS$: C (67.05%), H (3.75%), N (9.77%). Found: C (67.08%), H (3.78%), N (9.79%).

3-(6′-Methoxybenzothiazol-2-yl)-2-(4′-chlorostyryl)quinazolin-4(3H)-one (***5f***). Mp 203–206 °C, IR (KBr): 1737 1520, 1635, 1290–1145, 1070 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 3.68 (3H, s, OCH_3), 6.73 (1H, d, olefinic CH), 6.86–7.54 (12H, m, ArH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 55.7, 104.8, 114.2, 118.5, 121.4, 122.9, 126.7, 126.9, 127.6, 128.1, 129.7, 131.9, 133.4, 134.8, 135.7, 137.8, 145.2, 149.1, 151.2, 155.4, 162.6, 163.1; Anal. Calcd. (%) for $C_{24}H_{16}ClN_3O_2S$: C (64.64%), H (3.62%), N (9.42%). Found: C (64.65%), H (3.62%), N (9.41%).

3-(4′,5′-Dichlorobenzothiazol-2-yl)-2-(4′-chlorostyryl)quinazolin-4(3H)-one (***5g***). Mp 185–187 °C, IR (KBr): 1739, 1534, 1612, 1090 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 6.81 (1H, d, olefinic CH), 6.88–7.61 (10H, m, ArH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 120.9, 121.7, 122.3, 126.7, 126.8, 127.0, 127.6, 127.4, 128.2, 129.8, 130.2, 131.1, 133.4, 134.2, 135.9, 137.5, 148.8, 150.1, 151.9, 162.8, 163.1. Anal. Calcd. (%) for $C_{23}H_{12}Cl_3N_3OS$: C (56.98%), H (2.49%), N (8.67%). Found: C (56.95%), H (2.45%), N (8.67%).

3-(4′,6′-Dimethylbenzothiazol-2-yl)-2-(4′-chlorostyryl)quinazolin-4(3H)-one (***5h***). Mp 227–232 °C, IR (KBr): 1700, 1530, 1650, 1020 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 2.24 (3H, s, CH_3), 2.56 (3H, s, CH_3), 6.83 (1H, d, olefinic CH), 7.02–8.65 (10H, m, ArH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 18.4, 21.2, 39.4, 118.2, 120.7, 122.1, 124.2, 126.1, 126.9, 127.2, 127.9, 128.5, 129.5, 131.2, 133.4, 134.0, 134.7, 135.9, 137.8, 144.5, 149.1, 150.7, 162.9, 163.1. Anal. Calcd. (%) for $C_{25}H_{18}ClN_3OS$: C (67.64%), H (4.09%), N (9.47%). Found: C (67.68%), H (4.06%), N (9.42%).