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## Diversity oriented green synthesis of novel benzoxazole clubbed chromene arylsulfonamide derivatives using reusable catalyst

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### Abstract

A group of novel heterocyclic arylsulfonamide derivatives were synthesized by three steps process using the organic and inorganic catalyst in less solvent at ambient temperature. One out of the three-steps process, one-pot multiple component reaction using the reusable organic catalyst. These compounds reactions proceed through Knoevenagel condensation accompanied by Michael addition to obtaining suspicious products. The synthesized compound's structure was characterized by spectral data (UV-vis, FTIR and <sup>1</sup>H-NMR). Subsequently, the obtained novel final products are "benzoxazole clubbed chromene aryl sulfonamide derivatives". The green synthesis process was used to obtain optimum yield products to fulfil the required conditions such as nontoxic, inexpensive, minimum solvent and reusable catalyst.

**Keywords:** Heterocyclic arylsulfonamide, green synthesis, reusable catalyst

### Introduction

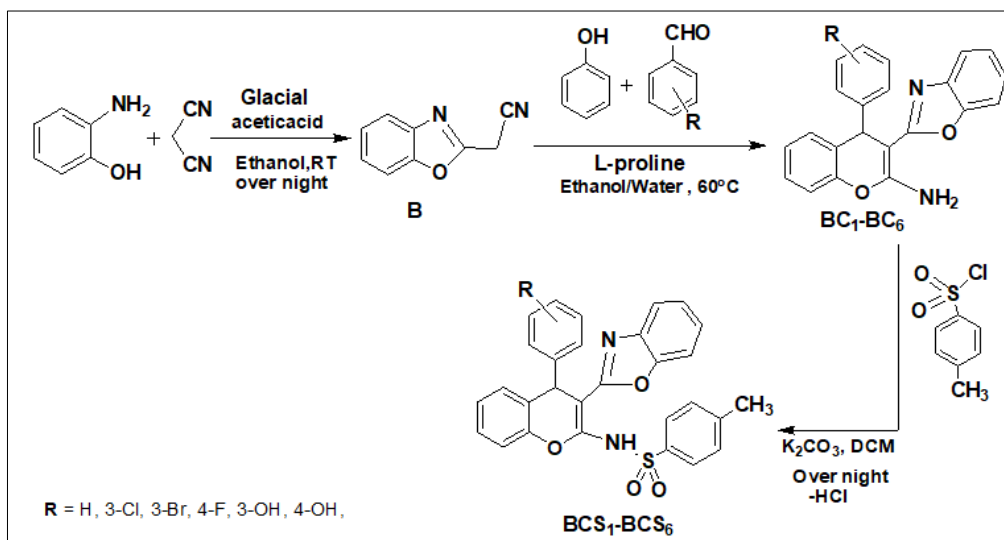
In pharmaceutical chemistry heterocycles are significant molecules. Heterocyclic moiety scaffolds, design and development of protocols for the synthesis of medically promising organic compounds [1-5]. Partially necessity of enviro-economic development which is use of green synthesis multi-component reaction (MCRs) to enhanced the awareness and interest of both industry and academic. The literature in order to carry out current research follows green pathways.

The benzoxazoles structural moiety possessing a wide spectrum of medicinal an activity were reported in literature such as antibacterial, antimicrobial [6-7], analgesic [8], antiviral, anticancer [9], anti-inflammatory [10] and anti-helminthic [11] as well as effectively acts against diabetes [12], hypoglycemia [13], local anesthesia. Benzoxazoles and its derivatives elicit pharmacological activates for the treatment of various diseases such as Parkinson's [14], endometriosis, Pneumocystis pneumonia [15], toxoplasmosis [16], psoriatic arthritis [17], anxiety disorders [18] etc. An impressive weapon store of synthetic pathway has been developed for the significantly increases biological activities. The chromenes structural moiety available in many natural compounds (alkaloids, flavonoids and anthocyanins) with wide spectrum of biological application [19-23]. Chromenes ingredient compounds widely used in the field of medicinal, cosmetic, pigments and biodegradable agrochemical [24-26]. Natural and promising synthetic compounds literature survey reveals biologically active broad spectrums such as antiviral [27-29], anticoagulation, anticancer [30], antivasular [31], antihypertensive [32] and antibacterial [33-35]. Moreover, derivatives of chromene also have been reported applications for the treatment of various diseases such as Alzheimer's, schizophrenia, hypertension, myoclonus and insomnia [36-40] etc. Heterocyclic arylsulfonamide scaffolds have promising biological properties [41]. The majority of pharmacologically active compounds mentioned in the literature contain a heterocyclic ring as an integral part of their structure. Heterocyclic rings, such as chromene thiophene, indole, pyrrole, tetrazole, triazole, pyrrolidine, imidazole, quinoline, isoquinoline, benzoxazole, benzothiazole, benzimidazole arylsulfonamide scaffolds are present in most pharmaceutically active compounds [42]. p-Toluene sulfonamide is one of the aryl sulfonamide which containing heterocyclic rings are extensively used in medicinal chemistry [43].

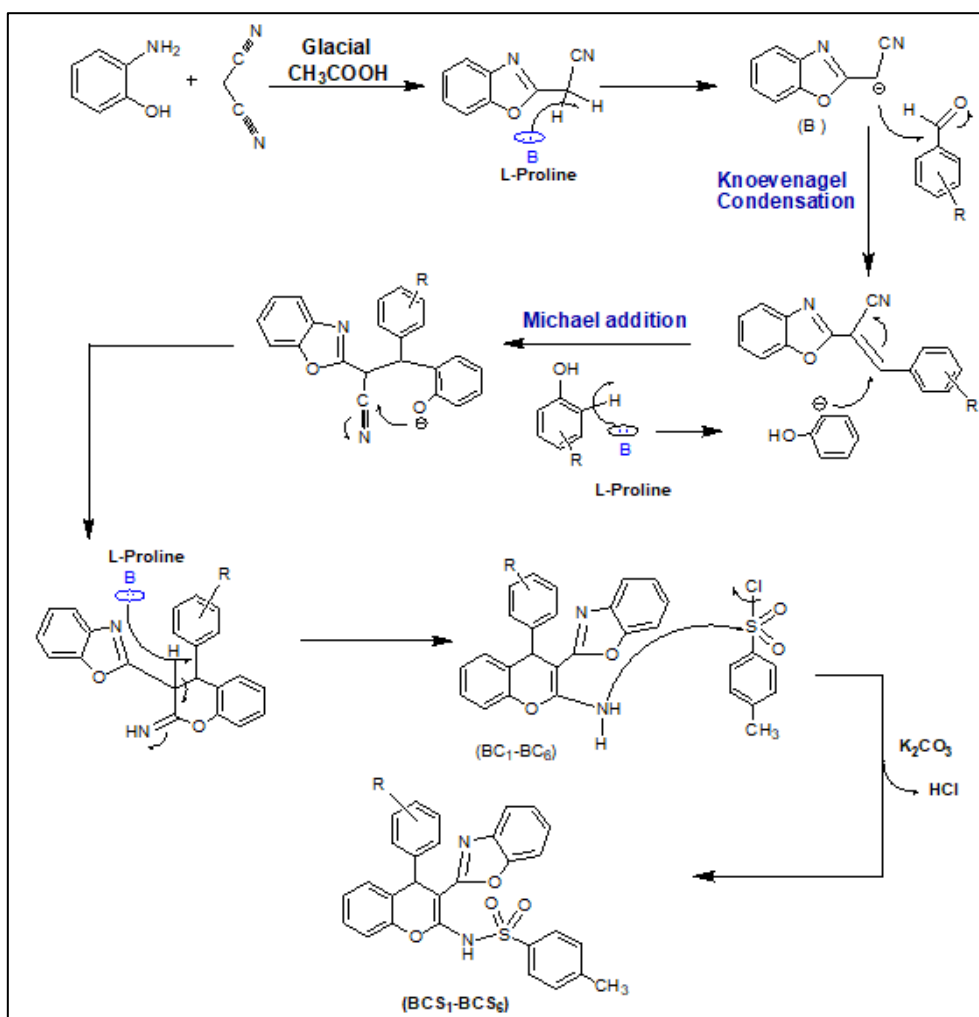
## Results and Discussion

The synthesis of compounds B, BC (1-6), BCS (1-6) has been outlined in (Schemes 1). The structure of BCS and its derivatives were confirmed via UV-vis, FTIR, and <sup>1</sup>H-NMR. The formation of suspicious products of BCS derivatives (Figure 1) was obtained in three steps. Initially, synthesis of 2-(benzoxazol-2-yl) acetonitrile (B) was prepared by an equimolar mixture reactant (2-amino phenol and malonanitrile). Different derivatives of 3-(benzoxazole-2-yl)-

4-phenyl-4H-chromene-2-amine (BC<sub>1</sub>-BC<sub>6</sub>) were prepared by an equimolar mixture of substituted benzaldehyde, phenol and (B) in one pot MCRs using reusable L-proline catalyst. The plausible mechanism of BCS (Schemes 2) proceeds through Knoevenagel condensation accompanied by Michael addition. The obtained (BC<sub>1</sub>-BC<sub>6</sub>) were further reacted with p-toluene sulfonylchloride to form different derivatives of N-(3-(benzoxazol-2-yl)-4-phenyl-4H-chromen-2-yl)-4-methylbenzenesulfonamide (BCS<sub>1</sub>-BCS<sub>6</sub>).



**Scheme 1:** Synthesis of substituted benzoxazole clubbed chromene containing aryl sulfonamide derivatives.



**Scheme 2:** Plausible mechanism for synthesized BCS compounds

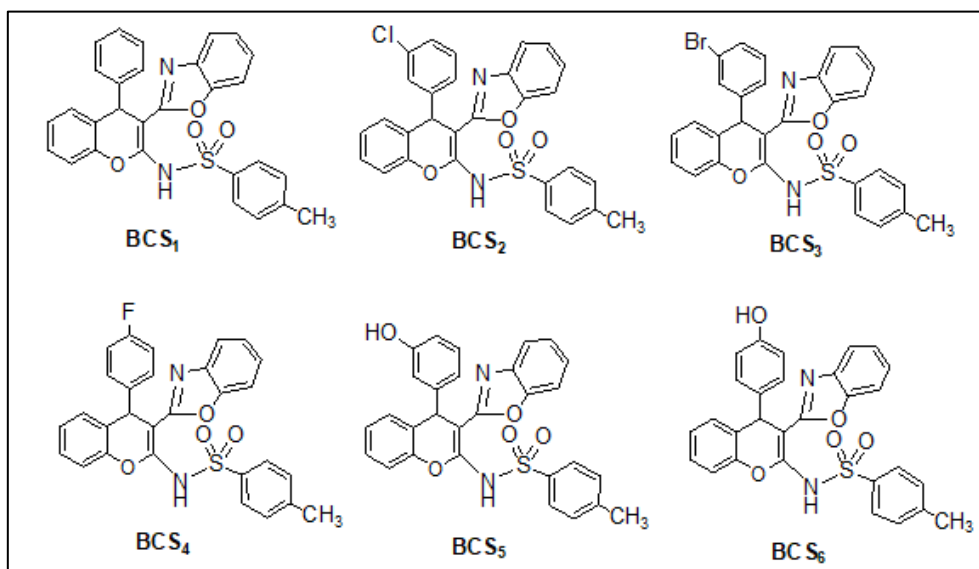


Fig 1: Library of synthesized benzoxazole clubbed chromene aryl sulfonamide derivatives

### Experimental section

#### Synthesis of 2-(benzoxazol-2-yl) acetonitrile (B)

A mixture of 2-amino phenol (1mmol), malanonitrile (1mmol) and catalyst glacial acetic acid (1mol %) was dissolved in the minimum amount of ethanol. The reaction mixture was magnetically stirred at ambient temperature until no precipitation was formed. The mixture was kept overnight. Next day shining brown crystal were obtained. The crystals were filtered and recrystallized from methanol.

#### General procedure for the synthesis of 3-(benzoxazole-2-yl)-4-phenyl-4H-chromene-2-amine (BC<sub>1</sub>-BC<sub>6</sub>)

In MCR, Phenol (1mmol), benzaldehyde (1mmol) and 2-(benzoxazol-2-yl) acetonitrile (1mmol) were taken in a round

bottom flask containing solvent (5mL water and 5mL ethanol) and L-Proline (1mol %) as catalyst was added to it. The reaction mixture was magnetically stirred at 60°C. Progress of reaction was monitored on TLC plates using solvent hexane: ethyl acetate (80:20). After completion of reaction, ethanol was distilled off. Resultant reaction mixture was extracted with ethyl acetate and washed with distilled water 3-4 times and air dried. The solid product obtained was recrystallized from methanol. One pot MCRs using reusable organic catalyst (L-proline). After completing of MCRs reaction, extracted aqueous containing catalyst was separated and washed with 10ml of dichloromethane (DCM) thrice and was used for three times (Figure.2).

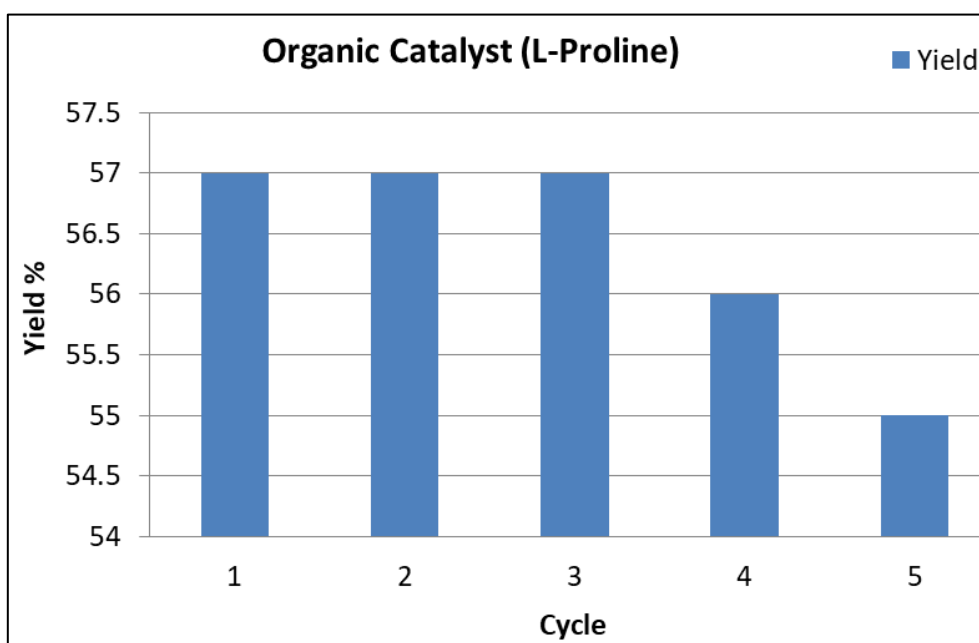


Fig 2: Reusability of organic catalyst (L-Proline) in the MCRs.

#### General procedure for the synthesis of N-(3-(benzoxazole-2-yl)-4-phenyl-4H-chromene-2-yl)-4-methylbenzenesulfonamide (BCS<sub>1</sub>-BCS<sub>6</sub>)

To the solution of 3-(benzoxazole-2-yl)-4-phenyl-4H-chromene-2-amine (1mmol) in dichloromethane (10mL) was

added potassium carbonate K<sub>2</sub>CO<sub>3</sub> (1mmol) as a catalyst. The reaction mixture was cooled to 0°C. p-Toluenesulfonyl chloride (1mmol) was dissolved in dichloromethane (10mL) and added drop-wise to the reaction mixture. The reaction mixture was stirred on magnetic stirrer. The progress of the

reaction was monitored by TLC in solvent system hexane: ethyl acetate (80:20). The mixture was stirred further at room temperature for overnight and extracted with saturated solution of NaHCO<sub>3</sub> and water (15mL). The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated. The colourless crystals were recrystallized from methanol.

**N-(3-(benzo[d]oxazole-2-yl)-4-phenyl-4H-chromen-2-yl)-4-methylbenzenesulfonamide (BCS<sub>1</sub>).** Yield: 57%; Brown; m.p. 67-98°C; UV-vis: 253.50nm, 423.60nm; FTIR (KBr, cm<sup>-1</sup>): 3312.23 (NH), 1419.09, 1162.35 (S=O), 2831.71 (C-H)<sub>Aliph</sub>, 2943.99 (C-H)<sub>Ar</sub>, 1598.88 (C=C)<sub>Ar</sub>, 1020.21 (C-O-C); <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>) δ(ppm): 2.35 (s, 3H), 3.78 (s,1H), 8.87 (s, NH-SO<sub>2</sub>), 6.61-6.96 (m, 4H, C-H<sub>Ar</sub>), 7.34 (d, 2H), 7.81 (d, 2H), 7.26-7.32 (m, 4H, C-H<sub>Ar</sub>), 7.04-7.16 (m, 4H, C-H<sub>Ar</sub>).

**N-(3-(benzo[d]oxazole-2-yl)-4-(3-chlorophenyl)-4H-chromen-2-yl)-4-methylbenzenesulfonamide (BCS<sub>2</sub>).**

Yield: 39%; Pale brown; m.p. 72-104°C; UVvis: 252.25nm, 339.00nm; FTIR (KBr, cm<sup>-1</sup>): 3313.47 (NH), 1448.63, 1112.70 (S=O), 2831.48 (C-H)<sub>Aliph</sub>, 2943.33 (C-H)<sub>Ar</sub>, 1448.63 (C=C)<sub>Ar</sub>, 1020.98 (C-O-C), 655.63(C-Cl); <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>) δ(ppm): 2.40 (s, 3H), 7.74 (d, 2H), 7.53 (d, 2H), 7.85 (s, NH-SO<sub>2</sub>), 6.59-6.96 (m, 4H, C-H<sub>Ar</sub>), 7.74 (d, 2H), 7.53 (d, 2H), 7.00-7.12 (m, 4H, C-H<sub>Ar</sub>) 7.22 (s, 1H), 6.92 (d, 1H), 7.19 (d,1H), 7.32 (dd,1H).

**N-(3-(benzo[d]oxazole-2-yl)-4-(3-bromophenyl)-4H-chromen-2-yl)-4-methylbenzenesulfonamide (BCS<sub>3</sub>).**

Yield: 41%; Brown; m.p. 69-102°C; UVvis: 257.15nm, 408.37; FTIR (KBr, cm<sup>-1</sup>): 3322.08 (NH), 1379.40, 1175.74 (S=O), 2831.53 (C-H)<sub>Aliph</sub>, 2943.74 (C-H)<sub>Ar</sub>, 1595.76 (C=C)<sub>Ar</sub>, 1020.97 (C-O-C), 654.60 (C-Br); <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)

δ(ppm): 2.49 (s, 3H), 3.73 (s,1H), 8.06 (s, NH-SO<sub>2</sub>), 6.70-6.98 (m, 4H, C-H<sub>Ar</sub>), 7.41 (d, 2H), 7.92(d, 2H), 7.26-7.35(m, 4H, C-H<sub>Ar</sub>), 7.35 (s, 1H), 7.79 (d, 1H), 7.49 (d, 1H), 7.70 (dd, 1H).

**N-(3-(benzo[d]oxazole-2-yl)-4-(4-fluorophenyl)-4H-chromen-2-yl)-4-methylbenzenesulfonamide (BCS<sub>4</sub>).**

Yield: 44%; Brown; m.p. 71-115°C; UVvis: 253.45nm, 415.98; FT IR (KBr, cm<sup>-1</sup>): 3314.88, (NH), 1378.36, 1162.79 (S=O), 2831.76 (C-H)<sub>Aliph</sub>, 2943.55 (C-H)<sub>Ar</sub>, 1600.19 (C=C)<sub>Ar</sub>, 1019.93 (C-O-C), 1093.44 (C-F); <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>) δ(ppm): 2.35 (s, 3H), 3.73 (s,1H), 7.18 (s, NH-SO<sub>2</sub>), 6.52-6.99 (m, 4H, C-H<sub>Ar</sub>), 7.58 (d, 2H), 7.73 (d, 2H), 7.25-7.35(m, 4H, C-H<sub>Ar</sub>), 6.72 (d, 2H), 7.34 (d, 2H).

**N-(3-(benzo[d]oxazole-2-yl)-4-(3-hydroxyphenyl)-4H-chromen-2-yl)-4-methylbenzenesulfonamide (BCS<sub>5</sub>).**

Yield: 53%; Dark Brown; m.p. 74-113°C; UVvis: 253.45nm, 428.39nm; FTIR (KBr, cm<sup>-1</sup>): 3324.44, (NH), 1374.99, 1177.49 (S=O), 2831.94 (C-H)<sub>Aliph</sub>, 2944.01 (C-H)<sub>Ar</sub>, 1596.81(C=C)<sub>Ar</sub>, 1020.99 (C-O-C); <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>) δ(ppm): 2.45 (s, 3H), 3.96 (s,1H), 9.85 (s, 1H, NH-SO<sub>2</sub>), 6.59-6.89 (m, 4H, C-H<sub>Ar</sub>), 7.32 (d, 2H), 7.75 (d, 2H), 7.62-7.99 (m, 4H, C-H<sub>Ar</sub>), 3.74 (s,1H, OH), 6.89 (s, 1H), 6.74 (d, 1H), 7.71 (d, 1H), 7.27 (dd, 1H).

**N-(3-(benzo[d]oxazole-2-yl)-4-(4-hydroxyphenyl)-4H-chromen-2-yl)-4-methylbenzenesulfonamide (BCS<sub>6</sub>).**

Yield: 54%; Dark brown; m.p. 73-108°C; UVvis: 254.70nm, 435.95nm; FTIR (KBr, cm<sup>-1</sup>): 3372.13 (NH), 1371.76, 1171.82 (S=O), 2839.51 (C-H)<sub>Aliph</sub>, 2950.68 (C-H)<sub>Ar</sub>, 1596.03 (C=C)<sub>Ar</sub>, 1090.24 (C-O-C); <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>) δ(ppm): 2.46 (s, 3H), 3.92 (s, 1H), 9.97 (s, NH-SO<sub>2</sub>), 6.60-6.98 (m, 4H, C-H<sub>Ar</sub>), 7.70 (d, 2H), 7.84 (d, 2H), 7.49-7.68 (m, 4H, C-H<sub>Ar</sub>), 3.74 (s, 1H, OH), 7.17 (d, 2H), 7.33 (d, 2H).

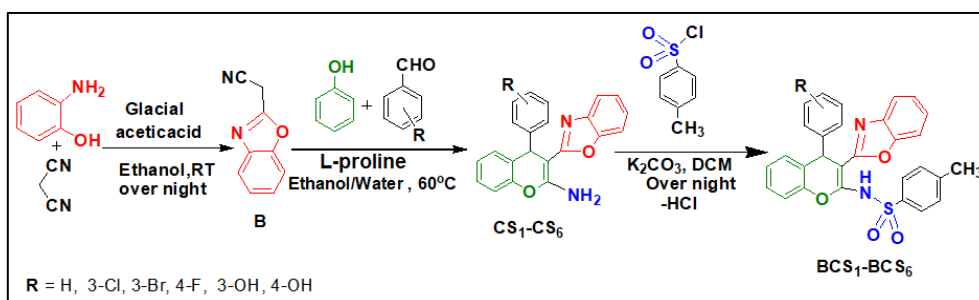


Fig 3: Graphical Abstract

## Conclusions

In the present work, we have reported a mild and efficient green protocol for the synthesis of benzoxazole-chromene containing aryl sulfonamide hybrid scaffolds. Such suspicious scaffolds obtained from Knoevenagel condensation accompanied by Michael addition via three steps process. The out of three, one step process is MCRs and reusable organic catalyst. However, the research characterization data matches with the theoretical data, and this clearly shows that the formation of synthesized novel scaffolds. On the basis of above findings, by adding myriads groups on the reactant itself, improvements are made to optimize the lead structure. This heterocyclic hybrid scaffolds was design and construction comprising can be used in different pharmaceutical applications.

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