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Synthesis of 1-Azacoumarins Linked Benzimidazoles via Traceless Tandem Transformation

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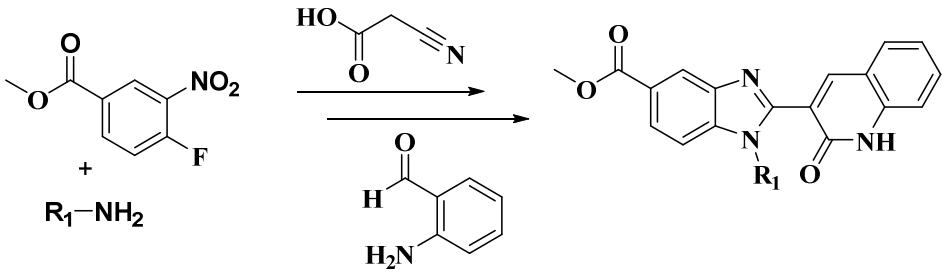
Abstract

A fast and efficient synthesis was explored to access the benzimidazole constituted azacoumarins. 4-Fluoro3-nitrobenzoic acid was used as a structural building block to generate these structural frameworks. By taking the benzimidazole constituted cyanoaceticacid treated with 2-amino banzaldehydes the described decorated structural scaffolds was obtained in the presence of organic base such as triethylamine leaving the product in traceless tandem manner. The final compounds have been obtained high yield and purity making this procedure facile, practical, and rapid to execute.

Keywords: Benzimidazole, azacoumarins, triethylamine, Traceless synthesis

Graphical Abstract



1. Introduction

Benzimidazole fused or benzimidazoles constituted molecules major source for new leads to explore, and many successful drugs were originally synthesized to mimic the action of benzimidazole molecules found in nature [1-2]. The numerous benzimidazole embracing heterocyclic derivatives structural scaffolds containing compounds are highly diverse and often provide highly specific biological activities [3]. To this end essentially all benzimidazole structural frameworks have some

receptor binding capacity [4]. The benzimidazoles in combination with various quinazolines [5], chromen [6], and thiochromen [7] structures have attracted considerable attention. These heterocyclic ring-systems due to their presence in many naturally and synthetically derived molecules, which posses a wide range of biological properties and frequently, hold promising pharmaceutical potential [8]. 4-Amino-3-benzimidazol-2-ylhydroquinolin-2-ones are a class of potent RTK inhibitors involved in important signal transduction pathways within the cell with attractive physicochemical and pharmacokinetic properties and significant efficacy in murine and human xenograft tumor models [9]. Compounds possessing coumarin, imidazole, benzothienopyrimidine or thiophene, benzopyran moieties represented basic structures screened for inhibitory activity against EGF, PDGF receptor tyrosine kinases and their inhibitory effects on tyrosine kinase pp6O$^{c\text{-}src}$ and p56^{1ck} were evaluated [10]. Molecular scaffolds based on 3-benzimidazol-2-ylhydroquinolin-2-one analogues as inhibitors of VEGF, PDGF, and fibroblast growth factor (FGF) receptor tyrosine kinases [11]. These compounds were also found to possess attractive pharmacokinetic characteristics and efficacy in several human tumor xenograft models [12]. The biological activities having the structural template coumarin derivatives shown as anticoagulant and antithrombotic activity of certain natural and synthetic coumarin derivatives are known [13]. Certain coumarin derivatives are also reported as triplet sensitizers, anti-HIV agents; Lipid lowering agents antioxidents, inhibitors of lipid peroxidation and vasorelaxant agents, anti-inflammatory agents and free radical Scavengers[14]. Certain coumarin-3-carboxamides have been reported as inhibitors of protease, including A-chymotrypsin and human leukocyte elastase [15-16].

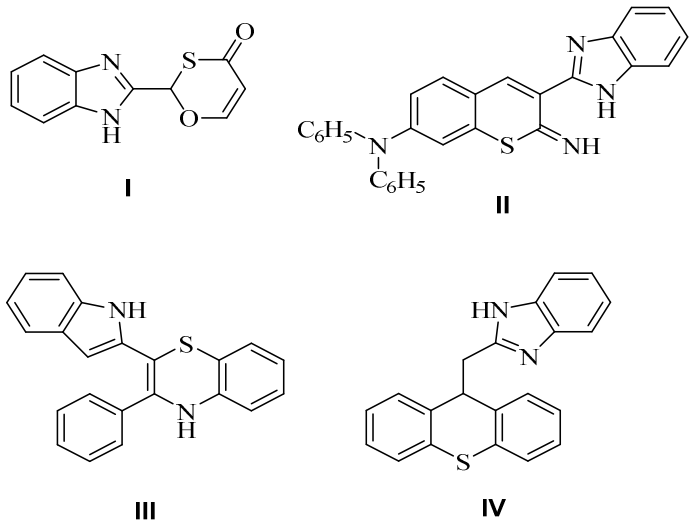


Figure 1. Biologically active benzimidazole derivatives.

The current acceleration of expensive and time-consuming process drug discovery is a result of the combinatorial chemistry to generate large libraries of high structural diversity molecules, which are subsequently used in the high-throughput screening (HTS) process [17]. The synergetic synthetic chemistry has emerged as one of the most promising approaches to chemical library synthesis for the purpose of drug discovery [18].

With the aim of develop more efficient synthetic methodologies and in continuation of our interest in developing combinatorial approaches to the synthesis of highly functionalized rapid access synthesis of azacoumarin linked benzimidazoles via traceless tandem transformation. Herein we describe a practical and rapid microwave-assisted method for the synthesis of highly functionalized benzimidazoles have been synthesized.

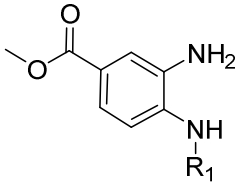
2. EXPERIMENTAL SECTION

General Remarks

Melting points were determined in open capillaries in electrical apparatus and are uncorrected. IR spectra were recorded on a Buck Scientific IR M500 instrument. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker instrument at 300 MHz and 75 MHz, respectively. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Data are given in the following order: δ value, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), number of protons, coupling constants J is given in Hertz. The mass spectra (HRMS) were taken respectively on a MS/MS ZABSpec TOF Micromass (EBE TOF geometry).

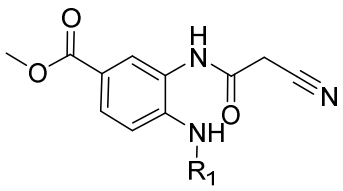
General Procedures

General procedure for the preparation of the methyl 3-amino-4-(substitutedamino)benzoate (3)



By taking the appropriate amount of the methyl 3-nitro-4-(substitutedamino)benzoate (**2**) compound and then the reaction mixture treated with the reducing agent Zinc (7 equiv.) and ammonium formate (15 equiv.) to reduce the nitrofunctional group. The reaction mixture was stirred in a flask for about 15 min of reaction time at 80^{0} C of reaction temperature. The crude reaction mixture washed several times with the ether. Then it has been dried and formation was confirmed by the melting point and ^{1}H NMR spectroscopy.

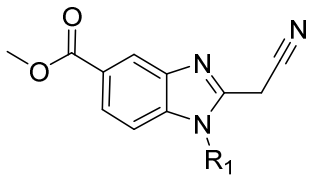
General procedure for the preparation of methyl 3-(2-cyanoacetamido)-4-(substitutedamino)benzoate (6)



By taking the appropriate amounts of diamine (**4**, 1.0 equiv.) and cyanoacetic acid (**5**, 1.0 equiv.) in dichloromethane, the coupling reagent DCC (1.5 equiv.) and DMAP (0.5 equiv.) was added at $0\text{-}5^{0}$ C

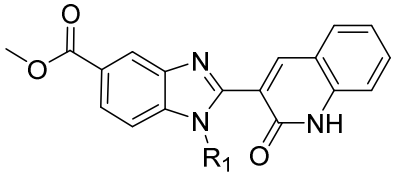
and allowed the reaction mixture to stir at room temperature for about 15 min and further at 120^0 C for 7-8 hrs. Then the reaction mixture subjected to the rota evaporator and then crude reaction mixture washed several times with the chilled ether. Then the reaction product has been confirmed by the ^{1}H NMR spectroscopy.

General procedure for the preparation of methyl 2-(cyanomethyl)-1-substituted-1*H*-benzo[*d*]imidazole-5-carboxylate (7)



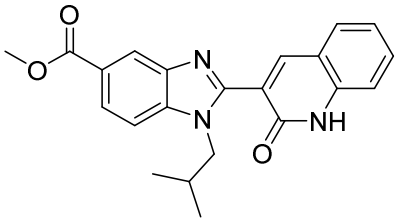
Added the solution of *p*-toluenesulphonic acid (2.5 equiv.) in EDC (30 mL) to the compound **6** (1.0 equiv.), subjected to stirring for 7 h at 80^0 C. Then the reaction mixture has been washed several times with the chilled ether and dried for the further scaffold preparation.

General procedure for the preparation of methyl 1-substituted-2-(2-oxo-1,2-dihydroquinolin-3-yl)-1*H*-benzo[d]imidazole-5-carboxylate (9)



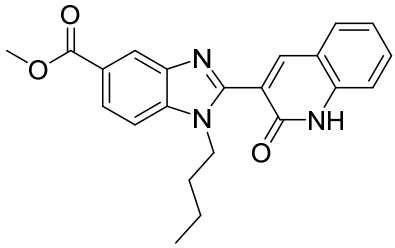
To a methanolic (20 mL) solution of **7a** (1.0 mmol) and *o*-amino benzaldehyde (**8**, 1.2 mmol) in a 100 mL round-bottom flask was added triethylamine (1.01 g, 10 mmol). The reaction mixture was heated at 65 °C for 4 h. After cooling the reaction mixture to room temperature, HCl solution (10 mL, 1 N) was added and the reaction mixture was continuously stirred for 2 h at the same temperature until the reaction was completed (monitored by TLC). The organic solvent was removed by reduced pressure distillation and the residue obtained was washed with saturated sodium bicarbonate solution and extracted with dichloromethane (2 × 30 mL). The combined organic phase was dried over anhydrous magnesium sulfate and concentrated under vacuum to give the crude product. Further purification was achieved by column chromatography (EA:hexane = 1:2) to give **9a** (88% yield)

Methyl 1-isobutyl-2-(2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzo[d]imidazole-5-carboxylate **(9a)**



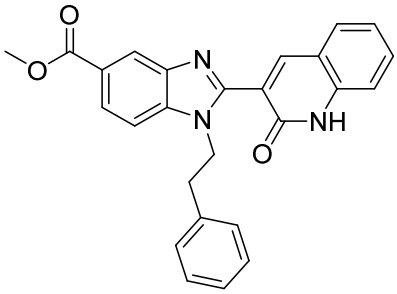
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, J = 0.7 Hz, 1H), 8.36 (s, 1H), 8.06 (dd, J = 8.6, 1.35 Hz, 1H), 7.70-7.63 (m, 1H), 7.47-7.35 (m, 1H), 4.09 (d, J = 7.7 Hz, 2H), 3.92 (s, 3H), 2.12 (p, J = 6.8 Hz, 1H), 0.78 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 158.8, 154.4, 147.4, 142.0, 133.4, 129.0, 125.1, 124.8, 122.3, 118.5, 116.9, 110.4, 52.7, 52.2, 33.8, 28.9, 24.9, 20.0. MS (ESI): *m/z* 377.0 $(M+H)^+$; HRMS (ESI): calcd for $C_{22}H_{20}N_2O_4$: *m/z* 376.4052; Found 377.0 $(M+1)^+$; IR(neat): 2958, 1718, 1608 cm^{-1}. Yield 75%.

Methyl 1-butyl-2-(2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzo[d]imidazole-5-carboxylate **(9b)**



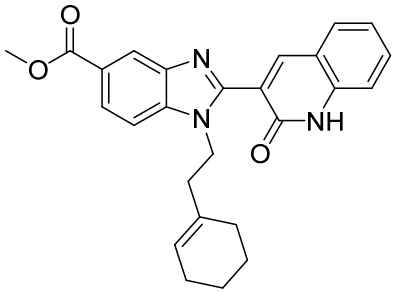
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J = 1.1 Hz, 1H), 8.33 (s, 1H), 8.06 (dd, J = 8.6, 1.56 Hz, 1H), 7.69-7.62 (m, 2H), 7.48-7.36 (m, 2H), 4.26 (d, J = 7.5 Hz, 2H), 3.93 (s, 3H), 1.81 (p, J = 7.6 Hz, 1H), 1.26 (hex, J = 7.7 Hz, 2H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 159.4, 157.4, 154.8, 150.2, 147.8, 142.9, 139.3, 136.2, 134.8, 133.8, 130.2, 129.4, 125.6, 125.2, 125.1, 123.4, 122.9, 119.5, 118.9, 117.2, 110.6, 52.6, 45.8, 34.3, 32.0, 25.3, 20.5, 13.9; MS (ESI): *m/z* 377.1 $(M+H)^+$; HRMS (ESI): calcd for $C_{22}H_{20}N_2O_4$: *m/z* 376.4052; Found 377.1 $(M+1)^+$; IR(neat): 2952, 1718, 1608 cm^{-1}. Yield 80%.

Methyl 2-(2-oxo-1,2-dihydroquinolin-3-yl)-1-phenethyl-1H-benzo[d]imidazole-5-carboxylate **(9c)**



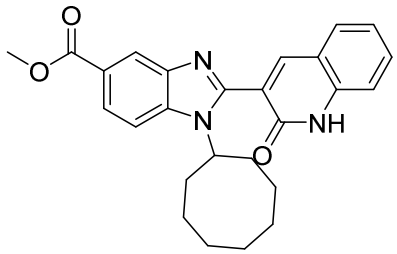
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J = 0.9 Hz, 1H), 8.11 (dd, J = 8.5 Hz, xH), 7.63-7.50 (m, 1H), 7.41-7.29 (m, 2H), 6.95 (t, J = 3.5 Hz, 1H), 4.26 (d, J = 7.5 Hz, 2H), 3.93 (s, 3H), 1.81 (p, J = 7.6 Hz, 1H), 1.26 (hex, J = 7.7 Hz, 2H), 0.87 (t, J = 7.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 166.9, 158.9, 154.1, 150.2, 148.5, 146.6, 142.5, 138.4, 137.8, 133.0, 128.9, 128.8, 128.5, 127.1, 124.9, 122.5, 118.5, 117.9, 116.6, 109.9, 52.2, 47.1, 35.3; MS (ESI): *m/z* 425.2 $(M+H)^+$; HRMS (ESI): calcd for $C_{26}H_{20}N_2O_4$: *m/z* 424.4480; Found 425.2 $(M+1)^+$; IR(neat): 2925, 1718, 1608 cm^{-1}. Yield 85%.

Methyl 1-(2-(cyclohex-1-en-1-yl)ethyl)-2-(2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzo[d]imidazole-5-carboxylate **(9d)**



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 1.0 Hz, 1H), 8.32 (s, 1H), 8.1 (dd, J = 1.4, 8.5 Hz, 2H), 7.67-7.59 (m, 1H), 7.48-7.34 (m, 2H), 5.17 (s, 1H), 4.35 (t, J = 7.2 Hz, 2H), 3.95 (s, 3H), 2.39 (t, J = 7.2 Hz, 2H), 1.92-1.87 (m, 2H), 1.80-1.78 (m, 4H), 1.43-1.33 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 158.9, 154.4, 149.8, 147.4, 142.4, 133.4, 133.3, 128.9, 125.2, 124.8, 124.7, 124.5, 122.4, 119.1, 118.5, 116.8, 110.2, 52.1, 49.1, 44.4, 37.6, 33.8, 32.5, 28.2, 25.5, 25.0, 24.8, 22.5, 21.8; MS (ESI): *m/z* 429.1 $(M+H)^+$; HRMS (ESI): calcd for $C_{26}H_{24}N_2O_4$: *m/z* 428.4798; Found 429.1 $(M+1)^+$; IR(neat): 2925, 1718, 1608 cm^{-1}; yield 80%.

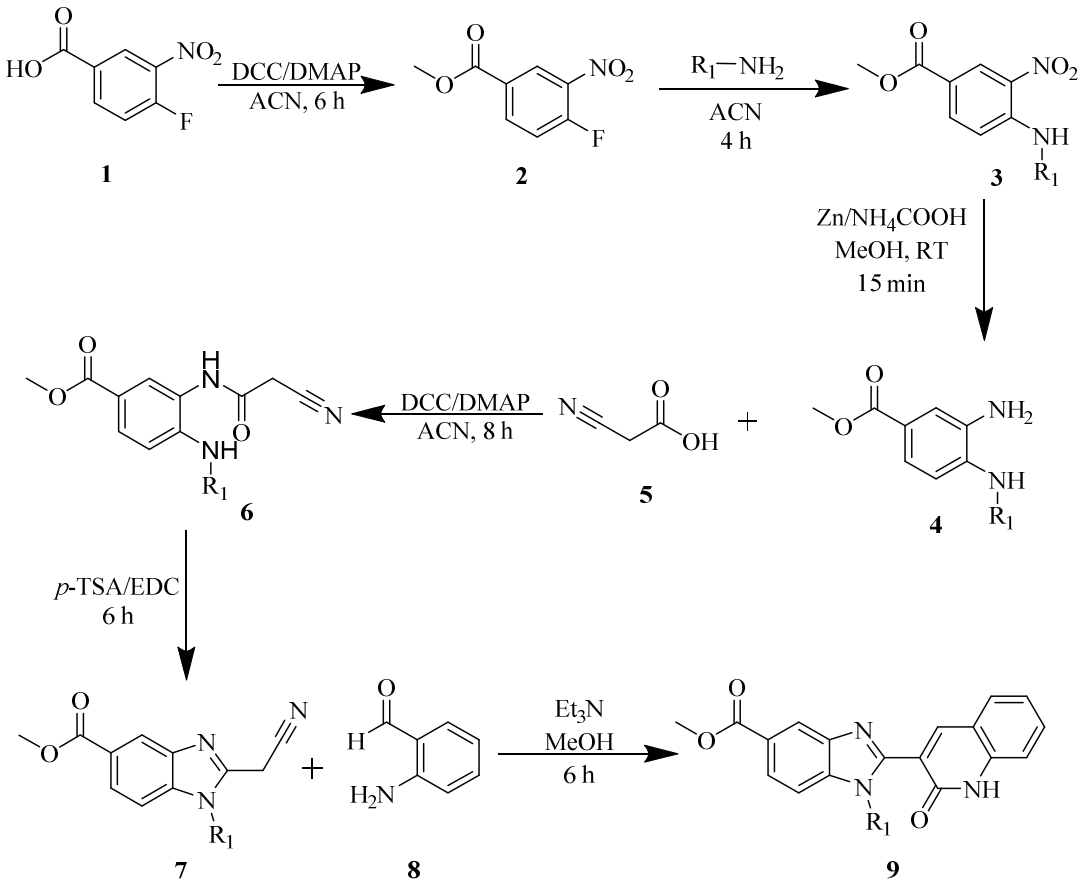
Methyl 1-cyclooctyl-2-(2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzo[d]imidazole-5-carboxylate **(9e)**



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.28 (s, 1H), 8.02 (dd, J = 1.4, 8.6 Hz, xH), 7.66-7.55 (m, 1H), 7.47-7.31 (m, 2H), 4.47-4.46 (m, 1H), 3.95 (s, 3H), 2.45-2.34 (m, 4H), 2.18-2.04 (m, 4H), 1.93-1.79 (m, 4H), 1.70-1.52 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 159.4, 157.4, 154.8, 150.2, 147.8, 142.9, 139.3, 136.2, 134.8, 133.8, 130.2, 129.4, 125.6, 125.2, 125.1, 123.4, 122.9, 119.5, 118.9, 117.2, 110.6, 52.6, 45.8, 34.3, 32.0, 24.1, 20.5, 13.5; MS (ESI): *m/z* 452.2 $(M+Na)^+$; HRMS (ESI): calcd for $C_{26}H_{26}N_2O_4$: *m/z* 430.4956; Found 452.2 $(M+Na)^+$; IR(neat): 2923, 1716, 1608 cm^{-1}. Yield: 81%.

3. Results and Discussion

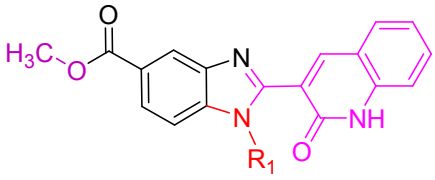
By taking the sample of the diethyl amine and the 2.0 equivalent of 4-fluoro-3-nitro-benzoicacid **1** and the corresponding amount of coupling reagent DCC and the catalytic amount of DMAP has been taken in the acetonitrile as solvent (Scheme 1). The reaction mixture has been allowed to stir at room temperature for about 10 hrs at 80^{o}C of temperature.

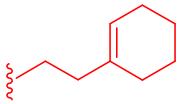
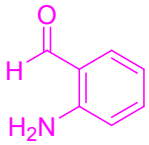
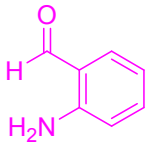
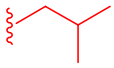
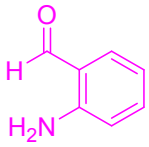
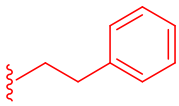
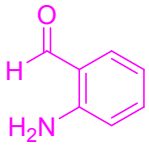
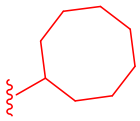
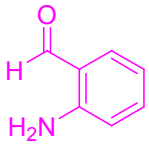


Scheme 1. Synthetic scheme for the preparation of the targeted library **9**.

The reaction crude has been filtered through the filter paper in order to remove the undissolved DCU in the reaction mixture. After that the reaction mixture has been subjected to the rotavapor and the solvent residues are removed. The obtained crude product has been washed several times with the diethyl ether until the product has been precipitated. The precipitated product has been dissolved into the acetonitrile solvent and the various range of amine has been added to form the nucleophilic substituted products. This reaction has been done at the room temperature conditions for about one hour. Then the reaction crude residue has been subjected to the rotavapour and the obtained crude washed several times with the ethyl ether until the formation of product in the form of precipitation. Further, the obtained product has been taken to reduce the nitro functional group in the presence of zinc and ammonium formate as the reducing reagent using methanol as a solvent. After the reaction completion the crude has been filtered and the solvent was evacuated. The ammonium formate was removed by dissolving the crude in the dichloromethane and precipitation. All these subsequent reaction intermediate are taken and submitted to the mass. The mass been matched to the expected value on accurate actual value. After the confirmation of formation of **4**, it was coupled with the cyanoacetic acid. This reaction has been done in the presence of:

Table 1. Library of synthetic analogues **9**.



Entry	R_1	R_2	Mass	Yields[b](%)
9a			429	85%
9b			377	80%
9c			376	85%
9d			425	80%
9e			417	81%

DCC as the coupling reagent and catalytic amount of DMAP as the reaction catalyst in acetonitrile in room temperature for about 10 hrs of reaction of time. The reaction mixture was subjected to the rotavapor to evacuate the acetonitrile solvent. There by the reaction crude has been washed several times with diethyl ether. The obtained substrate has been taken for to generate the benzimidazole attached methyl cyanide substance. This reaction has been done in the presence of *p*-toluenesulphonic acid in EDC solvent under reflux conditions for about 10 hrs of reaction time. After the completion of the reaction the reaction crude has been washed with the diethyl ether for several times. The obtained crude product has taken and added the appropriate amounts of 2-aminobenzaldehyde and the triethylamine in methanol for about of 10 hrs of reaction time under reflux condition. Monitored the reaction with the help of TLC and usual workup of the reaction afforded the desired azacoumarin linked benzimidazole in excellent yields. Several synthetic analogues with excellent yields were synthesized using the same methodology (Table 1).

4. Conclusion

In summary, we have described highly automated multistep procedure for the synthesis of azacoumarin linked benzimidazoles via traceless tandem transformation strategy with a generic protocol of coupling and purification. Final compounds were obtained in efficient yields with excellent purity and may further evaluated for their biological activity.

Acknowledgement

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