

Microwave-assisted Sonogashira coupling of novel 2-[6-(arylethynyl)pyridin-3-yl]-1H-benzimidazole derivatives

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Abstract

A rapid and efficient method for the synthesis of novel 2-[6-(arylethynyl)pyridin-3-yl]-1H-benzimidazole derivatives under microwave-assisted Sonogashira coupling conditions has been developed. The method avoids the use of protecting groups for benzimidazole NH during Sonogashira coupling. The microwave-assisted method reported herein offers advantageous shorter reaction times, higher yields and is applicable to a large set of substrates.

Keywords: Benzimidazole, Sonogashira coupling, microwave-assisted synthesis

Introduction

Various benzimidazole derivatives are well known to possess pharmacological activities such as human and veterinary anti-helmentic,¹ anti-ulcer,²⁻⁴ cardiogenic,⁵ antihypertensive,⁶ etc. The literature precedence revealed that the substitutions at the 1, 2 and 5 positions of the benzimidazole moiety are crucial for exhibiting wide range of pharmacological activities. Specifically, 2-substituted analogs of benzimidazole are known to be potent biologically active compounds.⁷⁻⁹ Introduction of acetylene groups (integral part of several pharmacophores) in the 2-substituted benzimidazole have shown interesting biological activities e. g. alkynylbenzimidazoles as modulators of metabotropic glutamate receptors.¹⁰ Tazarotene¹¹ (tazorac[®] and zorac[®]) with a phenylacetylene substructure exhibits antiacne and antipsoriatic activities. Efavirenz¹² (stocrin[®]) possessing an acetylene substructure exhibits anti HIV activity.

The Sonogashira reaction, a Pd-catalyzed cross-coupling between aryl halides and terminal alkynes, is a powerful tool for the synthesis of various aryl alkynes, although the use of copper

salts, toxic phosphine ligands, amines and homogenous Pd catalysts are generally difficult to recover and reuse.

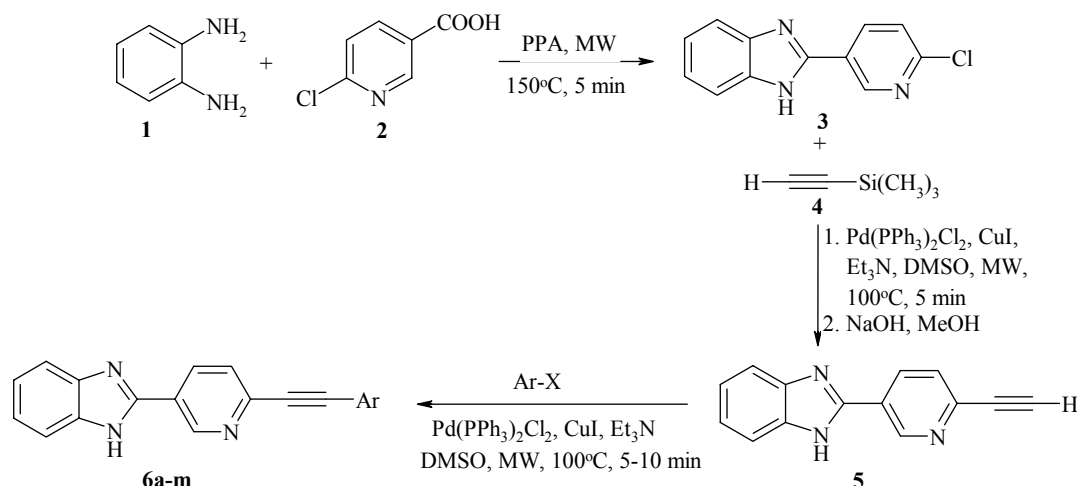
Microwave (MW) irradiation is widely used to promote chemical reactions and a number of reviews have advocated the use of MW technology in organic synthesis.¹³⁻¹⁴ Microwave activation as a non-conventional energy source is becoming a very popular and useful technique in organic chemistry. The combination of solvent-free reaction conditions and microwave irradiation leads to significantly reduced reaction times, enhanced conversions and sometimes higher selectivity with several advantages for the eco-friendly approach, termed green chemistry.¹⁵

Recently a fast and solvent less microwave-assisted heterogeneous and homogeneous Sonogashira coupling has been reported on aryl halides and acetylene moieties¹⁶⁻¹⁸ but not reported on benzimidazole compounds. Conventional synthesis of aryl benzimidazoles were reported¹⁹⁻²⁰ and Sonogashira coupling²¹ were done by standard procedure. Previously, the microwave-assisted syntheses of benzimidazoles were reported on aryl acid with *o*-phenylenediamine.²²

Herein, we report synthesis of novel 2-[6-(arylethynyl)pyridin-3-yl]-1*H*-benzimidazoles under an environment-friendly microwave irradiation method. The advantage of the microwave irradiation method is to avoid the homocoupling of terminal acetylene.²³ Ideally, the approach should allow access to the free -NH benzimidazole utilizing readily available components and catalysts directly without the need for subsequent deprotection.

Result and Discussion

All the reactions were carried out under both microwave irradiation and conventional methods. The title compounds **6a-m** were synthesized as shown in Scheme 1. The condensation of *o*-phenylenediamine (OPDA) **1** with 6-chloronicotinic acid **2** is carried out in polyphosphoric acid (PPA) irradiated in microwave oven at 100W for 5 minutes at 150 °C to obtain the 2-(6-chloropyridin-3-yl)-1*H*-benzimidazole **3** with 90 % yield, which was used as a precursor for the synthesis of 2-[6-(arylethynyl)pyridin-3-yl]-1*H*-benzimidazoles **6a-m**.



Scheme 1

In continuation of our research work, Sonogashira coupling of **3** (without protection of benzimidazole NH) with trimethylsilylacetylene **4** in presence of bis(triphenylphosphine)palladium(II)dichloride, CuI, triethylamine and dimethyl sulfoxide under microwave irradiation method followed by deprotection of 2-{6-[2-(trimethylsilyl)ethynyl]pyridine-3-yl}-1*H*-benzimidazole with methanolic sodium hydroxide solution, yielded 2-[6-(ethynyl)pyridin-3-yl]-1*H*-benzimidazole **5** in 87 % yield. The structure of compound **5** was confirmed by IR, ^1H NMR, ^{13}C NMR, Mass and elemental analysis.

The Sonogashira coupling of compound **5** having terminal acetylene and free -NH benzimidazole with electron-withdrawing groups such as CN, ester and electron-donating groups such as OMe, Me, OH substituted aryl halides in presence of CuI, triethylamine, bis (triphenylphosphine)palladium(II)dichloride as catalyst and dimethyl sulfoxide under microwave irradiation method at 100 °C and 80 W for 5-10 min in sealed vessel followed by simple work-up yielded compounds **6a-m**. The structures of compounds **6a-m** were characterized by IR, ^1H NMR, ^{13}C NMR, mass and elemental analysis; e.g. the IR spectrum of **6a** showed acetylenic band at 2203 cm^{-1} , the ^1H NMR spectrum showed a singlet at δ 9.24 for pyridine proton and broad singlet at δ 13.14 of benzimidazole -NH proton; the ^{13}C NMR spectrum showed of acetylenic carbons at δ 89.02 and 90.26. The mass spectrum of **6a** showed characteristics peak for $[\text{M}+1]$ at 296.6 m/z and at 220.66 m/z due to loss of phenyl ring and elemental analysis, which supports the proposed structure **6a**. It is noteworthy to mention here that, the side-product from homocoupling reaction of two terminal acetylenes in the Sonogashira reaction can be reduced due to the less reaction time in microwave irradiation method.

Comparison of time and yields of compounds **3**, **5** and **6a-m** by microwave and conventional methods are given in Table 1. The aryl halides with electron-donating substituents (entry- **6f**, **6h**, **6j** and **6l**) have slightly higher yield than aryl halides with electron-withdrawing substituents (entry-**6b**, **6c**, **6d**, **6e** and **6i**) under microwave irradiation method at 100 °C and 80 W for 5-10 min in sealed vessel as compare with the conventional heating. Only compound **6m** obtain the 60

% yield due to the less reactivity of bromo substituents in 4,4-dimethyl-6-bromothiochromane. Formations of desired compounds were accelerated by microwave irradiation being obtained in 5-10 minutes with higher yields as compared with the conventional method.

Table 1. Synthesis of compounds **3**, **5**, and **6a-6m** by microwave and conventional method

Compd.	Aryl halides	Microwave irradiation		Conventional heating	
		Time (min)	Yield (%) w/w	Time (min)	Yield (%) w/w
3	-	05	90	240	70
5	-	05	87	190	53
6a	Iodobenzene	05	90	180	70
6b	Methyl 6-chloronicotinate	05	85	120	68
6c	Ethyl 6-chloronicotinate	10	90	180	70
6d	2-Chloro-5-cyanopyridine	05	93	150	75
6e	Methyl 4-iodobenzoate	05	89	180	70
6f	4-Iodotoluene	10	94	180	72
6g	1-Iodonaphthalene	05	90	120	78
6h	4-Iodophenol	05	89	180	75
6i	4-Iodobenzonitrile	10	90	190	72
6j	2-Iodoanisole	05	95	150	78
6k	2-Iodopyrazine	05	91	120	75
6l	2-Iodobenzylalcohol	05	92	180	80
6m	4,4-dimethyl-6-bromothiochromane	10	60	360	40

Conclusions

We report a simple, rapid, efficient, economic and environment-friendly method for the synthesis of novel 2-[6-(arylethynyl)pyridin-3-yl]-1*H*-benzimidazole derivatives using microwave-assisted Sonogashira coupling. The advantages of the microwave irradiation were avoidance of the self condensation of 2-[6-(ethynyl)pyridin-3-yl]-1*H*-benzimidazole, even without protection of the free benzimidazole NH and shorter reaction times together with excellent yields compared to conventional method. Furthermore, we found that the reaction is generally tolerant of both electron-withdrawing and electron-donating substituents.

Experimental Section

General Procedures. All the analysis was carried out in Glenmark research center, Navi Mumbai-400709, (M.S.) India. Melting points were recorded on a MRVIS series, Lab India Instrument and are uncorrected. The monitoring of reaction and checking of purity of the product were done using pre-coated silica gel plates and visualization using iodine /UV lamp. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer. The presence of characteristic band of triple bond (acetylene) at ca. 2150 cm^{-1} was also noteworthy in IR spectra of all compounds. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian Mercury VX SWBB 300 MHz spectrometer. Chemical shifts (δ) are reported in ppm from internal tetramethylsilane standard. The solvents for NMR spectra were CD_3OD and $\text{DMSO}-d_6$. Mass spectra were recorded from an HP 1100 LC/MSD mass spectral instrument (positive and negative APCI ion source, 50-200 V, nitrogen). Elemental analysis was carried out on a Perkin-Elmer Series-II CHNS/O Analyzer 2400. Analytical work was carried out at Glenmark Research Center, Plot No. A-607, T.T.C. Industrial Area, M.I.D.C, Mahape, Navi Mumbai-400709, (M.S.), India. All microwave reactions were carried out in Biotage (InitiatorTM Eight) microwave synthesizer. Aryl halides, *o*-phenylenediamine and 6-chloronicotinic acid were obtained from commercial supplier. Trimethylsilylacetylene and palladium catalyst were obtained from Aldrich.

Compound 3 via microwave irradiation. A mixture of *o*-phenylenediamine **1** (1.08 g, 10 mmol), 6-chloronicotinic acid **2** (1.57 g, 10 mmol) and polyphosphoric acid (5 g) were stirred and irradiated in microwave oven at 100 W for 5 min at $150\text{ }^\circ\text{C}$ in sealed vessel (as monitored by TLC). The reaction mixture was then cooled to room temperature and neutralized with ice-cold aqueous ammonia solution to obtain neutral pH. The product was extracted with ethyl acetate (25 mL x 2). The ethyl acetate layer was washed with water (25 mL x 2) and concentrated under reduced pressure to afford the crude compound. The crude compound was recrystallized from ethyl acetate to obtain pure compound **3**.

Compound 5 via microwave irradiation. A mixture of dimethylsulfoxide (1.97 mL), trimethylsilylacetylene (1.97 g, 20 mmol), triethylamine (3.03 g, 30 mmol), CuI (0.1 g), compound **3** (2.29 g, 10 mmol) and bis(triphenylphosphine)palladium(II)dichloride catalyst (0.11 g) were irradiated in microwave oven at 80 W for 5 min at $100\text{ }^\circ\text{C}$ in sealed vessel. The reaction mixture was then cooled to room temperature and slowly added methanolic sodium hydroxide solution 10% (10 mL) in reaction mass. The solvent was removed under reduced pressure and water (50 mL) was added to the residue. The residue was extracted with ethyl acetate (25 mL x 2), washed with water (25 mL x 2) and evaporated under reduced pressure to yield crude product. The crude compound was recrystallized from ethyl acetate to obtain pure compound **5**.

Compounds 6a-m via microwave irradiation. A mixture of compound **5** (2.19 g, 10 mmol), dimethyl sulfoxide (2.19 mL), triethylamine (3.03 g, 30 mmol), CuI (0.1 g), respective aryl halides (12 mmol) and bis(triphenylphosphine)palladium(II)dichloride catalyst (0.11 g) were

irradiated in microwave oven for at 80 W for 5-10 min at 100 °C in sealed vessel. The reaction mixture was then cooled to room temperature and water (50 mL) was added to the residue. The compound was extracted with ethyl acetate (25 mL x 2), ethyl acetate layer washed with water (25 mL x 2) and evaporated solvent under reduced pressure, yielded crude compounds. The crude compounds were recrystallized from ethyl acetate to obtain pure compound **6a-m**.

Compounds 6a-m by conventional heating. A mixture of compound **5** (2.19 g, 10 mmol), dimethyl sulfoxide (2.19 mL), triethylamine (3.03 g, 30 mmol), CuI (0.1 g), respective aryl halides (12 mmol) and bis(triphenylphosphine)palladium(II)dichloride catalyst (0.11 g) were stirred at 100 °C for 120-360 min. The reaction mixture was then cooled to room temperature and water (50 mL) was added to the residue. The compound was extracted with ethyl acetate (25 mL x 2), washed with water (25 mL x 2), and evaporated solvent under reduced pressure, yielded crude compounds. The crude compounds were recrystallized from ethyl acetate to obtain pure compound **6a-m**.

2-(6-Chloropyridin-3-yl)-1H-benzimidazole (3). Off white solid. Mp 265-267 °C. IR (KBr): 3183, 2962, 1601, 1561, 1421, 1257, 1125, 765 cm⁻¹. ¹H-NMR (DMSO-d₆): δ 7.21-7.24 (m, 2H, Ar-H), 7.62-7.72 (m, 3H, Ar-H), 8.51 (dd, *J* = 2.4 and 8.4 Hz, 1H, Ar-H), 9.14 (s, 1H, Ar-H), 13.16 (bs, 1H, -NH). ¹³C-NMR (DMSO-d₆): δ 121.42, 123.52, 128.71, 129.8, 138.35, 138.35, 146.54, 147.14, 150.28, 152.18, 152.18, 153.86. Anal. Calcd. for C₁₂H₈ClN₃: C, 62.76; H, 3.51; N, 18.30%; Found: C, 62.51; H, 3.24; N, 18.32%. MI-MS: 230.7 (M+1).

2-[6-(Ethynyl)pyridin-3-yl]-1H-benzimidazole (5). Off white solid. Mp 260-262 °C. IR (KBr): 3142, 2968, 2211 (acetylene), 1605, 1518, 1471, 1269, 737 cm⁻¹. ¹H-NMR (DMSO-d₆): δ 3.21 (s, 1H, acetylene proton), 7.29-7.31 (m, 2H, Ar-H), 7.60-7.63 (m, 3H, Ar-H), 8.4 (d, *J* = 9.0 Hz, 1H, Ar-H), 9.18 (s, 1H, Ar-H), 13.21 (bs, 1H, -NH). ¹³C-NMR (DMSO-d₆): δ 87.08, 88.0 (acetylenic carbon), 127.74, 131.02, 132.62, 132.62, 139.08, 139.08, 146.89, 147.15, 151.54, 152.87, 152.87, 153.13. Anal. Calcd. for C₁₄H₉N₃: C, 76.70; H, 4.14; N, 19.17%; Found: C, 76.62; H, 4.20; N, 19.10%. MI-MS: 220.7 (M+1).

2-[6-(Phenylethynyl)pyridin-3-yl]-1H-benzimidazole (6a). White powder. Mp 245-248 °C. IR (KBr): 3388, 3020, 2960, 2203 (acetylene), 1590, 1453, 1148, 750 cm⁻¹. ¹H-NMR (CD₃OD): δ 7.30 (m, 2H, Ar-H), 7.41-7.43 (m, 3H, Ar-H), 7.60-7.62 (m, 4H, Ar-H), 7.78 (d, *J* = 8.1 Hz, 1H, Ar-H), 8.46-8.50 (m, 1H, Ar-H), 9.24 (s, 1H, Ar-H), 13.14 (bs, 1H, -NH). ¹³C-NMR (CD₃OD): δ 89.02, 90.26 (acetylenic carbon), 121.3, 122.89, 125.39, 125.39, 127.43, 128.97, 128.97, 128.97, 129.71, 131.83, 131.83, 131.83, 134.06, 134.06, 142.73, 148.01, 148.01, 148.28, (aromatic carbons). Anal. Calcd. for C₂₀H₁₃N₃: C, 81.34; H, 4.44; N, 14.23%; Found: C, 81.32; H, 4.32; N, 14.31%. MI-MS: 220.66, 296.6 (M+1).

Methyl 5-[[5-(1H-benzimidazol-2-yl)pyridin-2-yl]ethynyl]pyridine-2-carboxylate (6b). Off white powder. Mp 243-245 °C. IR (KBr): 3410, 2976, 1716, 2210 (acetylene), 1596, 1529, 1465, 1247, 759 cm⁻¹. ¹H-NMR (DMSO-d₆): δ 3.90 (s, 3H, -OCH₃), 7.24 (m, 2H, Ar-H), 7.56 (m, 1H, Ar-H), 7.69 (m, 1H, Ar-H), 7.87-7.92 (m, 2H, Ar-H), 8.33 (d, *J* = 6.3 Hz, 1H, Ar-H), 8.57 (d, *J* = 7.8 Hz, 1H, Ar-H), 9.11 (s, 1H, Ar-H), 9.37 (s, 1H, Ar-H), 13.21 (bs, 1H, -NH). ¹³C-NMR (DMSO-d₆): δ 51.48 (OCH₃), 88.76, 90.18 (acetylenic carbon), 115.32, 115.32, 118.65, 123.15,

123.15, 125.2, 125.84, 127.64, 128.78, 128.78, 130.10, 131.22, 131.22, 138.31, 145.26, 149.57, 152.15 (aromatic carbons), 168.76 (carbonyl). Anal. Calcd. for $C_{21}H_{14}N_4O_2$: C, 71.18; H, 3.98; N, 15.81%; Found: C, 71.24; H, 4.10; N, 15.68%. MI-MS: 354.4 (M+1).

Ethyl 5-{{5-(1*H*-benzimidazol-2-yl)pyridin-2-yl}ethynyl}pyridine-2-carboxylate (6c). White powder. Mp 251-253 °C. IR (KBr): 3423, 2925, 2226 (acetylene) 1722, 1590, 1442, 1287, 1131, 739 cm^{-1} . ^1H -NMR (DMSO- d_6): δ 1.33 (t, J = 5.4 Hz, 3H, -CH₃), 4.36 (q, J = 5.4 Hz, 2H, -CH₂), 7.24 (m, 2H, Ar-H), 7.63 (m, 2H, Ar-H), 7.87-7.95 (m, 2H, Ar-H), 8.34 (d, J = 6.3 Hz, 1H, Ar-H), 8.55 (d, J = 7.8 Hz, 1H, Ar-H), 9.1 (s, 1H, Ar-H), 9.4 (s, 1H, Ar-H), 13.18 (bs, 1H, -NH). ^{13}C -NMR (DMSO- d_6): δ 14.5 (-CH₃), 52.08 (-CH₂), 89.06, 92.10 (acetylenic carbon), 116.29, 116.29, 119.15, 123.07, 123.07, 125.06, 126.72, 127.84, 129.08, 129.08, 130.54, 131.75, 131.75, 138.45, 145.38, 150.37, 152.65 (aromatic carbons), 168.76 (carbonyl). Anal. Calcd. for $C_{22}H_{16}N_4O_2$: C, 71.73; H, 4.38; N, 15.21%; Found: C, 71.82; H, 4.32; N, 15.46%. MI-MS: 354.7, 369.3 (M+1).

5-{{5-(1*H*-benzimidazol-2-yl)pyridin-2-yl}ethynyl}pyridine-2-carbonitrile (6d). White powder. Mp 260-263 °C. IR (KBr): 3167, 3092, 2228 (acetylene), 2914, 1595, 1475, 1434, 1284, 1146, 758 cm^{-1} . ^1H -NMR (DMSO- d_6): δ 7.25 (m, 2H, Ar-H), 7.63 (m, 2H, Ar-H), 7.95 (d, J = 9.4 Hz, 2H, Ar-H), 8.42 (d, J = 7.8 Hz, 1H, Ar-H), 8.57 (d, J = 9.6 Hz, 1H, Ar-H), 9.08 (s, 1H, Ar-H), 9.4 (s, 1H, Ar-H), 13.21 (bs, 1H, -NH). ^{13}C -NMR (DMSO- d_6): δ 86.28, 90.15 (acetylenic carbon), 110.73, 111.38, 117.64, 119.82, 122.31, 123.58, 125.54, 126.72, 128.1, 131.84, 132.58, 132.58, 133.138, 134.64, 142.1, 142.82, 149.86, 151.27 (aromatic carbons). Anal. Calcd. for $C_{20}H_{11}N_5$: C, 74.75; H, 3.45; N, 21.79%; Found: C, 74.61; H, 3.52; N, 21.68%. MI-MS: 234.46, 263.77, 279.97, 322.4 (M+1).

Methyl 4-{{5-(1*H*-benzimidazol-2-yl)pyridin-2-yl}ethynyl}benzoate (6e). Off white powder. Mp 277-278 °C. IR (KBr): 3314, 3061, 2845, 2212 (acetylene), 1698, 1602, 1437, 1281, 1115, 763 cm^{-1} . ^1H -NMR (DMSO- d_6): δ 3.89 (s, 3H -OCH₃), 7.26 (m, 2H, Ar-H), 7.65 (m, 2H, Ar-H), 7.78 (d, J = 7.5 Hz, 1H, Ar-H), 7.89 (d, J = 8.4 Hz, 2H, Ar-H), 8.02-8.04 (m, 2H, Ar-H), 8.55 (d, J = 8.1 Hz, 1H, Ar-H), 9.38 (s, 1H, Ar-H), 13.20 (bs, 1H, -NH). ^{13}C -NMR (DMSO- d_6): δ 52.62 (-OCH₃), 89.10, 91.51 (acetylenic carbon), 115.37, 115.37, 119.81, 123.2, 123.2, 125.76, 125.95, 127.80, 129.59, 129.59, 129.59, 130.10, 132.17, 132.17, 132.17, 134.13, 142.18, 148.09 (aromatic carbons), 165.52 (carbonyl). Anal. Calcd. for $C_{22}H_{15}N_3O_2$: C, 74.78; H, 4.28; N, 11.89%; Found: C, 74.85; H, 4.07; N, 11.76%. MI-MS: 354.4 (M+1).

2-{{6-[(4-Methylphenyl)ethynyl]pyridin-3-yl}-1*H*-benzimidazole (6f). White powder. Mp 255-257 °C. IR (KBr): 3417, 3103, 2919, 2219 (acetylene), 1599, 1512, 1429, 1287, 1126, 729 cm^{-1} . ^1H -NMR (DMSO- d_6): δ 2.36 (s, 3H, -CH₃), 7.24-7.28 (m, 4H, Ar-H), 7.52 (d, J = 8.4 Hz, 3H, Ar-H), 7.69 (d, J = 5.4 Hz, 1H, Ar-H), 7.79 (d, J = 8.1 Hz, 1H, Ar-H), 8.50 (d, J = 6.3 Hz, 1H, Ar-H), 9.34 (s, 1H, Ar-H), 13.16 (s, 1H, -NH). ^{13}C -NMR (CD₃OD): δ 21.38 (CH₃), 88.10, 90.59 (acetylenic carbon), 111.68, 118.25, 119.23, 122.19, 123.28, 125.21, 127.28, 129.59, 129.59, 131.74, 131.74, 134.01, 135.04, 139.66, 142.90, 143.78, 147.96, 148.29 (aromatic carbons). Anal. Calcd. for $C_{21}H_{15}N_3$: C, 81.53; H, 4.89; N, 13.58%; Found: C, 81.66; H, 5.68; N, 13.50%. MI-MS: 310.28 (M+1).

2-[6-(1-Naphthylethynyl)pyridin-3-yl]-1H-benzimidazole (6g). Off white powder. Mp 250-253 °C. IR (KBr): 3410 (-NH), 3057, 2950, 2210 (acetylene), 1622, 1586, 1489, 1430, 1317, 743 cm^{-1} . ^1H -NMR (DMSO- d_6): δ 7.25 (m, 2H, Ar-H), 7.57-7.73 (m, 5H, Ar-H), 7.91-8.06 (m, 4H, Ar-H), 8.39 (d, J = 8.4 Hz, 1H, Ar-H), 8.56 (d, J = 8.1 Hz, 1H, Ar-H), 9.41 (s, 1H, Ar-H), 13.21 (bs, 1H, -NH). ^{13}C -NMR (DMSO- d_6): δ 88.29, 94.06 (acetylenic carbon), 111.82, 118.83, 119.40, 122.37, 123.48, 125.52, 125.62, 125.89, 127.17, 127.75, 127.87, 128.85, 130.29, 131.51, 132.74, 133.01, 134.25, 135.23, 142.95, 143.99, 148.29, 148.47 (aromatic carbons). Anal. Calcd. for $\text{C}_{24}\text{H}_{15}\text{N}_3$: C, 83.46; H, 4.38; N, 12.17%; Found: C, 83.58; H, 4.30; N, 12.22%. MI-MS: 346.3 (M+1).

4-{{5-(1H-Benzimidazol-2-yl)pyridin-2-yl}ethynyl}phenol (6h). Off white powder. Mp 293-295 °C. IR (KBr): 3062, 2925, 2211 (acetylene), 1599, 1514, 1434, 1387, 1278, 1159, 731 cm^{-1} . ^1H -NMR (DMSO- d_6): δ 6.83 (d, J = 7.5 Hz, 2H, Ar-H), 7.25 (m, 2H, Ar-H), 7.45 (d, J = 7.2 Hz, 2H, Ar-H), 7.56-7.75 (m, 3H, Ar-H), 8.47 (d, J = 7.5 Hz, 1H, Ar-H), 9.32 (s, 1H, Ar-H), 10.09 (bs, 1H, -OH), 13.14 (bs, 1H, -NH). ^{13}C -NMR (DMSO- d_6): δ 87.57, 91.48 (acetylenic carbon), 111.36, 111.70, 116.06, 116.06, 116.06, 119.27, 122.23, 123.29, 124.86, 126.98, 133.70, 133.70, 134.01, 135.70, 143.36, 147.92, 148.40, 158.91 (aromatic carbons). Anal. Calcd. for $\text{C}_{20}\text{H}_{13}\text{N}_3\text{O}$: C, 77.16; H, 4.21; N, 13.50%; Found: C, 77.34; H, 4.08; N, 13.47%. MI-MS: 230.5, 312.3 (M+1).

4-{{5-(1H-benzimidazol-2-yl)pyridin-2-yl}ethynyl}benzonitrile (6i). Off white powder. Mp 288-290 °C. IR (KBr): 3414 (-NH), 3140, 2228 (acetylene), 1603, 1501, 1434, 1341, 1241, 743 cm^{-1} . ^1H -NMR (DMSO- d_6): δ 7.24 (m, 2H, Ar-H), 7.57 (d, J = 6.9 Hz, 1H, Ar-H), 7.70 (d, J = 7.5 Hz, 1H, Ar-H), 7.81-7.95 (m, 5H, Ar-H), 8.55 (d, J = 8.1 Hz, 1H, Ar-H), 9.38 (s, 1H, Ar-H), 13.14 (bs, 1H, -NH). ^{13}C -NMR (DMSO- d_6): δ 88.40, 92.33 (acetylenic carbon), 111.73, 111.85, 118.40, 119.30, 122.26, 123.40, 125.29, 126.07, 127.89, 132.55, 132.55, 132.74, 132.74, 134.10, 135.04, 141.92, 143.76, 148.10, 148.10 (aromatic carbons). Anal. Calcd. for $\text{C}_{21}\text{H}_{12}\text{N}_4$: C, 78.73; H, 3.78; N, 17.49%; Found: C, 78.65; H, 3.70; N, 17.54%. MI-MS: 319.3 (M+1).

2-{6-[(2-Methoxyphenyl)ethynyl]pyridin-3-yl}-1H-benzimidazole (6j). White powder. Mp 218-220 °C. IR (KBr): 3249 (-NH), 3190, 2886, 2209 (acetylene), 1601, 1493, 1431, 1319, 1280, 738 cm^{-1} . ^1H -NMR (DMSO- d_6): δ 3.88 (s, 3H, -OCH₃), 7.00 (m, 2H, Ar-H), 7.12 (d, J = 6.9 Hz, 2H, Ar-H), 7.23 (d, J = 8.1 Hz, 1H, Ar-H), 7.44 (m, 1H, Ar-H), 7.56 (d, J = 7.4 Hz, 1H, Ar-H), 7.68 (m, 1H, Ar-H), 7.76 (d, J = 8.4 Hz, 1H, Ar-H), 8.51 (d, J = 8.4 Hz, 1H, Ar-H), 9.34 (s, 1H, Ar-H), 13.16 (bs, 1H, -NH). ^{13}C -NMR (DMSO- d_6): δ 55.92 (-OCH₃), 87.46, 92.41 (acetylenic carbon), 110.22, 111.58, 111.68, 119.23, 120.71, 122.20, 123.30, 125.15, 127.32, 131.42, 133.57, 134.04, 135.04, 143.10, 143.78, 147.95, 148.31, 160.13 (aromatic carbons). Anal. Calcd. for $\text{C}_{21}\text{H}_{15}\text{N}_3\text{O}$: C, 77.52; H, 4.65; N, 12.91%; Found: C, 77.61; H, 4.58; N, 12.83%. MI-MS: 326.2 (M+1).

2-[6-(Pyrazin-2-ylethynyl)pyridin-3-yl]-1H-benzimidazole (6k). White powder. Mp 272-275 °C. IR (KBr): 3416 (-NH), 3184, 2215 (acetylene), 1620, 1489, 1473, 1424, 1314, 1140, 733 cm^{-1} . ^1H -NMR (DMSO- d_6): δ 7.25-7.46 (m, 2H, Ar-H), 7.56-7.70 (m, 2H, Ar-H), 7.93 (d, J = 7.8 Hz, 1H, Ar-H), 8.56 (d, J = 8.2 Hz, 1H, Ar-H), 8.73 (d, J = 8.5 Hz, 2H, Ar-H), 8.97 (s, 1H, Ar-

H), 9.41 (s, 1H, Ar-H), 13.21 (bs, 1H, -NH). ^{13}C -NMR (DMSO- d_6): δ 86.32, 91.03 (acetylenic carbon), 111.74, 119.32, 122.27, 123.43, 125.25, 128.14, 134.17, 135.04, 138.30, 141.31, 143.75, 144.38, 145.18, 147.90, 147.98, 148.21 (aromatic carbons). Anal. Calcd. for $\text{C}_{18}\text{H}_{11}\text{N}_5$: C, 72.72; H, 3.73; N, 23.56%; Found: C, 72.67; H, 3.59; N, 23.38%. MI-MS: 298.3 (M+1).

(2-{{5-(1H-Benzimidazol-2-yl)pyridin-2-yl}ethynyl}phenyl)methanol (6l). Off white powder. Mp 276-278 °C. IR (KBr): 3409, 3074, 2924, 2218 (acetylene), 1596, 1497, 1433, 1278, 1025, 741 cm^{-1} . ^1H -NMR (DMSO- d_6): δ 4.77 (d, J = 4.5 Hz, 2H, - CH_2), 5.4 (s, 1H, -OH), 7.24-7.35 (m, 3H, Ar-H), 7.46-7.57 (m, 4H, Ar-H), 7.71 (d, J = 7.4 Hz, 1H, Ar-H), 7.83 (d, J = 8.7 Hz, 1H, Ar-H), 8.36 (d, J = 8.1 Hz, 1H, Ar-H), 9.36 (s, 1H, Ar-H), 13.18 (bs, 1H, -NH). ^{13}C -NMR (DMSO- d_6): δ 61.32 (- CH_2), 87.97, 93.41 (acetylenic carbon), 111.73, 118.60, 119.28, 122.28, 123.36, 125.38, 126.62, 127.01, 127.50, 129.74, 132.16, 134.08, 134.08, 142.83, 144.82, 148.02, 148.02, 148.28 (aromatic carbons). Anal. Calcd. for $\text{C}_{21}\text{H}_{15}\text{N}_3\text{O}$: C, 77.52; H, 4.65; N, 12.91%; Found: C, 77.41; H, 4.78; N, 12.79%. MI-MS: 326.5 (M+1).

2-{{6-[(4,4-Dimethyl-3,4-dihydro-2H-thiochromen-6-yl)ethynyl]pyridin-3-yl}-1H-benzimidazole (6m). Pale yellow powder. Mp 255-257 °C. IR (KBr): 3183, 3144, 2221 (acetylene), 1597, 1494, 1429, 1319, 1243, 764 cm^{-1} . ^1H -NMR (CD_3OD): δ 1.37 (s, 6H, - $(\text{CH}_3)_2$), 1.99 (t, J = 6.3 Hz, 2H, - SCH_2), 3.08 (t, J = 6.3 Hz, 2H, - CH_2), 7.09 (d, J = 7.8 Hz, 1H, Ar-H), 7.26 (d, J = 8.1 Hz, 1H, Ar-H), 7.57-7.63 (m, 4H, Ar-H), 7.81-7.84 (m, 2H, Ar-H), 8.54 (m, 1H, Ar-H), 9.26 (s, 1H, Ar-H), 13.21 (bs, 1H, -NH). ^{13}C -NMR (CD_3OD): δ 22.76 (- CH_2), 29.83 (- CH_2), 32.90 (- CH_3), 36.63 (- CH_3), 88.38, 92.93 (acetylenic carbon), 114.37, 114.37, 116.04, 119.81, 125.85, 125.85, 126.76, 127.23, 127.87, 129.28, 130.21, 133.04, 133.04, 135.24, 135.74, 142.54, 145.26, 146.40, 149.09 (aromatic carbons). Anal. Calcd. for $\text{C}_{25}\text{H}_{21}\text{N}_3\text{S}$: C, 75.92; H, 5.35; N, 10.62%; Found: C, 75.81; H, 5.20; N, 10.84%. MI-MS: 396.7 (M+1).

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