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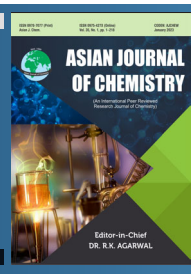

Acetic Acid-Water Mediated Efficient One-Pot Synthesis of Functionalized Isoxazolyl Amino Chromeno[4,3-*b*]pyridine Derivatives

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A simple, efficient, economical and environmentally benign method has been developed for one-pot three component synthesis of isoxazolyl amino chromeno[4,3-*b*]pyridine derivatives from 4-amino-3-methyl-5-styrylisoxazoles, malononitrile and (*E*)-3-benzylidenechroman-4-one by using acetic acid (AcOH) as a promoter and water as a green reaction medium under thermal condition. The interesting features of this method are environmental friendly, metal-free, less reaction time, wide substrate scope, operational simplicity, easy purification of products and good yields.

Keywords: Isoxazolyl amino chromeno[4,3-*b*]pyridine, One-pot reaction, Green chemistry, Water, Acetic acid.

INTRODUCTION

To reduce the usage of volatile, flammable and poisonous organic solvents or to replace them with inexpensive "green solvents" is a common method of green chemistry expression [1]. Due to its low cost, environmental friendliness, easy availability, inflammability and non-toxicity as a reaction medium, water is increasingly being used in organic chemical synthesis as a solvent. Water has been shown to have a significant effect on the rate and selectivity of organic chemical reactions due to its ability to reduce or eliminate hydrophobic interactions and to enhance organic compounds in the aquous environment [2,3]. The development of safe, economical, environmental friendly and scalable synthetic methodologies for the synthesis of large libraries of organic compounds with medicinal themes is an exciting field of study in both academia and the pharmaceutical industry [4,5].

Because of their high efficiency, low waste generation and high yields, multi-component reactions (MCRs) in water have been identified as a reliable technique in the field of organic synthesis. Developing innovative and synthetically valuable multi-component reactions is a problem for both industrial and academic researchers [6,7] in light of the growing interest in the synthesis of heterocyclic scaffolds. Due to their prevalence in both natural and manmade chemical molecules [8-10], nitrogen-containing heterocyclic compounds are of critical importance. The chromenopyridine framework is a molecule that combines the two essential scaffolds, the chromeno and pyridine rings, into a single ring. Antibacterial, anticancer, antifungal, antiinflammatory and α-adrenergic antagonist actions [11-16] are few of the many biological and pharmacological features exhibited by several chromenopyridine derivatives. Similar to the focus on isoxazole ring containing heterocyclic compounds in medicinal chemistry due to their beneficial biological characteristics [17,18]. Isoxazole derivatives have been shown to be effective against a wide range of microorganisms, inflammation, tuberculosis, pain, cancer and COX-2 inhibition [19-21].

The heterocyclic compounds containing isoxazole and chromenopyridine moieties have a variety of biological applications. As a result, the combination of these two heterocyclic molecules into one molecule sparked tremendous interest in the pharmacology and drug design. As a result, both synthetically and biologically, the development of an effective

synthetic process for the synthesis of these heterocyclic scaffolds is remarkable. Diverse techniques for the synthesis of chromenopyridine derivatives employing various starting materials have been devised [22-28]. However, these mentioned processes have a number of drawbacks, including the use of hazardous organic solvents, low yields, employment of an expensive catalyst, multistep synthesis, severe reaction conditions, a long reaction time, difficulty in workup and expensive reagents.

In light of these developments in the synthesis and biological applications of new isoxazole heterocyclic derivatives [29-36], herein an efficient and environmental friendly one-pot protocol for the synthesis of isoxazolylaminochromeno[4,3-*b*]pyridine derivatives using 4-amino-3-methyl-5-styrylisoxazoles, malononitrile and (*E*)-3-benzylidenechroman-4-one using H_2O/AcOH as a reaction media under metal free conditions.

EXPERIMENTAL

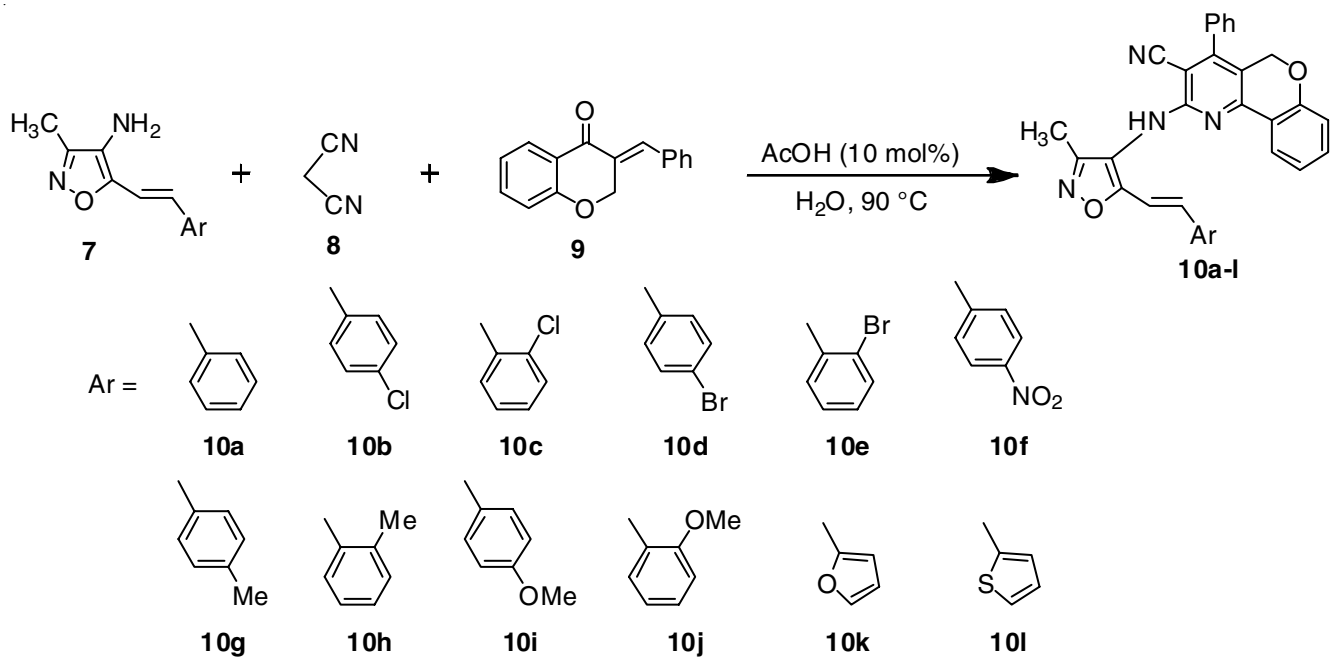
All melting points were recorded using a Fisher-Johns melting point instrument and are uncorrected. Merck precoated 60 mm F_{254} silica gel was used for the TLC analysis, and the plates were analyzed using the *t*-test. Exposure to the iodine vapour facilitated the visualization process. A Perkin-Elmer BX-series FT-IR spectrometer was used to acquire the IR spectra (KBr pellet). A Varian Gemini 300 MHz spectrometer was used to acquire ^{1}H NMR spectra. A Bruker 75 MHz spectrometer was used to acquire the ^{13}C NMR spectra. The Q-TOF Micro mass spectrometer was used to capture the high-resolution mass spectra (HRMS).

General procedure for the synthesis of isoxazolylamino chromeno[4,3-*b*]pyridine derivatives (10a-l and 11a-n): A mixture of 4-amino-3-methyl-5-styrylisoxazoles (**7**, 1 mmol), malononitrile (**8**, 1 mmol) and (*E*)-3-benzylidenechroman-4-ones (9, 1 mmol) in water (5 mL) was stirred at 90 ºC for 3-4 h in the presence of acetic acid (10 mol%). When the reaction was completed (which was checked with TLC), the mixture was cooled to room temperature and then poured into ice-cold water (20 mL). The precipitate that formed was filtered off, washed with distilled water followed by recrystallization from methanol to get desired isoxazolylaminochromeno[4,3-*b*] -pyridine derivatives (**10a-l** and **11a-n**) (**Schemes I** and **II**).

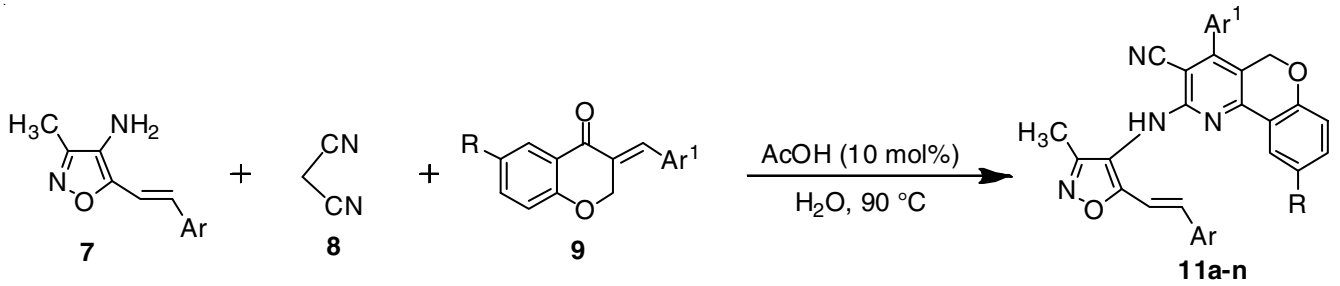
(*E*)-2-((3-Methyl-5-styrylisoxazol-4-yl)amino)-4-phenyl-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (10a): Yield: 88%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3532, 2948, 2840, 2230, 1642, 1051, 740, ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.53 (s, 1H), 8.23 (d, *J* = 7.5 Hz, 1H), 7.81-7.22 (m, 13H), 6.71 (d, *J* = 12 Hz, 1H), 6.62 (d, *J* = 12 Hz, 1H), 4.85 (s, 2H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 164.6, 158.2, 156.2, 154.1, 152.5, 150.8, 136.7, 134.5, 133.4, 129.8, 129.3, 129.1, 128.9, 128.7, 128.3, 127.7, 126.5, 124.5, 122.6, 122.2, 121.2, 115.2, 112.4, 100.5, 82.7, 62.4, 12.4. HRMS (ESI-MS) calcd. for $C_{31}H_{22}N_4NaO_2$ (M+Na)$^+$ 505.1640, found 505.1642.

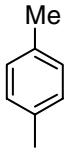
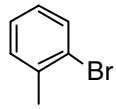
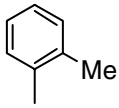
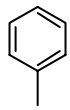
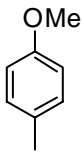
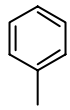
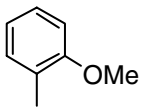
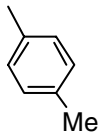
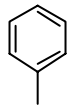
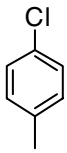
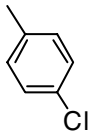
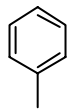
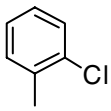
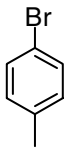
(*E*)-2-((5-(4-Chlorostyryl)-3-methylisoxazol-4-yl)-amino)-4-phenyl-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (10b): Yield: 94%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3524, 2945, 2847, 2224, 1640, 1056, 745, ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.43 (s, 1H), 8.18 (d, *J* = 7.5 Hz, 1H), 7.84-7.20 (m, 12H), 6.70 (d, *J* = 12 Hz, 1H), 6.63 (d, *J* = 12 Hz, 1H), 4.94 (s, 2H), 2.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 162.8, 157.1, 156.9, 154.4, 152.1, 150.5, 138.2, 136.7, 134.3, 133.8, 129.7, 129.3, 128.8, 128.5, 128.1, 127.6, 126.3, 124.2, 122.9, 122.4, 121.5, 115.3, 112.1, 100.8, 82.5, 62.1, 12.8. HRMS (ESI-MS) calcd. for $C_{31}H_{21}ClN_4NaO_2$ (M+Na)$^+$ 539.1251, found 539.1251.

(*E*)-2-((5-(2-Chlorostyryl)-3-methylisoxazol-4-yl)-amino)-4-phenyl-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (10c): Yield: 80%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3520, 2938, 2840, 2235, 1648, 1063, 749, ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.22 (s, 1H), 8.32 (d, *J* = 7.5 Hz, 1H), 7.86-7.21 (m, 12H), 6.72 (d, *J* = 12 Hz, 1H), 6.60 (d, *J* = 12 Hz, 1H), 5.21 (s, 2H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm:



Scheme-I: Acetic acid-water mediated synthetic route of functionalized isoxazolyl amino chromeno[4,3-*b*]pyridine derivatives (**10a-l**)



Compd.	Ar	R	Ar^1	Compd.	Ar	R	Ar^1
11a		H		**11h**		H	
11b		H		**11i**		Me	
11c		H		**11j**		Cl	
11d		H		**11k**		Cl	
11e		H		**11l**		Cl	
11f		H		**11m**		H	
11g		H		**11n**		H	

Scheme-II: Acetic acid-water mediated synthetic route of functionalized isoxazolyl amino chromeno[4,3-*b*]pyridine derivatives (**11a-n**)

163.2, 158.5, 156.1, 154.7, 152.4, 150.2, 137.3, 136.2, 134.8, 133.4, 129.6, 129.4, 129.0, 128.6, 128.3, 128.2, 127.6, 127.3, 126.6, 124.5, 122.3, 122.7, 121.1, 115.7, 112.5, 100.4, 82.2, 62.6, 12.2. HRMS (ESI-MS) calcd. for $C_{31}H_{21}ClN_4NaO_2$ $(M+Na)^+$ 539.1251, found 539.1253.

(*E*)-2-((5-(4-Bromostyryl)-3-methylisoxazol-4-yl)-amino)-4-phenyl-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (10d): Yield: 92%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3484, 2941, 2843, 2231, 1646, 1063, 739, ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.21 (s, 1H), 8.34 (d, *J* = 7.5 Hz, 1H), 7.82-7.22 (m, 12H), 6.72 (d, *J* = 12 Hz, 1H), 6.62 (d, *J* = 12 Hz, 1H), 5.02 (s, 2H), 2.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 161.4, 158.5, 156.3, 154.1, 152.7, 150.2, 136.3, 134.7, 133.3, 131.6, 129.8, 129.2, 128.6, 128.3, 128.0, 127.5, 126.8, 124.6, 122.4, 122.2, 121.1, 115.6, 112.5, 100.2, 82.1, 62.7, 12.3. HRMS (ESI-MS) calcd. for $C_{31}H_{21}BrN_4NaO_2$ $(M+Na)^+$ 583.0746, found 583.0747.

(*E*)-2-((5-(2-Bromostyryl)-3-methylisoxazol-4-yl)-amino)-4-phenyl-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (10e): Yield: 82%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3515, 2933, 2841, 2229, 1643, 1058, 737, ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.18 (s, 1H), 8.25 (d, *J* = 7.5 Hz, 1H), 7.84-7.22 (m, 12H), 6.70 (d, *J* = 12 Hz, 1H), 6.61 (d, *J* = 12 Hz, 1H), 4.88 (s, 2H), 2.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 162.7, 157.1, 156.8, 154.4, 152.1, 150.7, 137.5, 134.2, 133.1, 131.4, 129.7, 129.2, 129.1, 128.8, 128.5, 128.3, 127.5, 127.1,

126.4, 124.2, 122.7, 122.5, 121.3, 115.3, 112.1, 100.6, 82.3, 62.1, 12.3. HRMS (ESI-MS) calcd. for $C_{31}H_{21}BrN_4NaO_2$ (M+Na)$^+$ 583.0746, found 583.0749.

(*E*)-2-((3-Methyl-5-(4-nitrostyryl)isoxazol-4-yl)-amino)-4-phenyl-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (10f): Yield: 90%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3457, 2941, 2843, 2236, 1649, 1065, 740, ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.22 (s, 1H), 8.34 (d, *J* = 7.5 Hz, 1H), 7.85-7.23 (m, 12H), 6.72 (d, *J* = 12 Hz, 1H), 6.61 (d, *J* = 12 Hz, 1H), 4.86 (s, 2H), 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 161.5, 158.6, 156.4, 154.1, 152.5, 150.2, 147.3, 136.3, 134.6, 133.2, 129.9, 129.4, 128.6, 128.3, 128.0, 127.8, 126.5, 124.1, 122.6, 122.2, 121.9, 115.1, 112.4, 100.1, 82.4, 62.8, 12.3. HRMS (ESI-MS) calcd. for $C_{31}H_{21}N_5NaO_4$ (M+Na)$^+$ 550.1491, found 550.1493.

(*E*)-2-((3-Methyl-5-(4-methylstyryl)isoxazol-4-yl)-amino)-4-phenyl-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (10g): Yield: 84%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3514, 2952, 2843, 2221, 1645, 1060, 748, ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.36 (s, 1H), 8.21 (d, *J* = 7.5 Hz, 1H), 7.85-7.23 (m, 12H), 6.71 (d, *J* = 12 Hz, 1H), 6.61 (d, *J* = 12 Hz, 1H), 4.86 (s, 2H), 2.34 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 162.2, 158.5, 156.1, 154.2, 152.6, 150.9, 138.8, 135.2, 134.6, 133.1, 129.8, 129.4, 128.6, 128.4, 128.2, 127.7, 126.4, 124.5, 122.7, 122.1, 121.4, 115.7, 112.4, 100.3, 82.1, 62.9, 23.4, 12.1. HRMS (ESI-MS) calcd. for $C_{32}H_{24}N_4NaO_2$ (M+Na)$^+$ 519.1797, found 519.1797.

(*E*)-2-((3-Methyl-5-(2-methylstyryl)isoxazol-4-yl)-amino)-4-phenyl-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (10h): Yield: 80%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3519, 2942, 2846, 2230, 1642, 1061, 744, ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.32 (s, 1H), 8.28 (d, *J* = 7.5 Hz, 1H), 7.88-7.20 (m, 12H), 6.71 (d, *J* = 12 Hz, 1H), 6.63 (d, *J* = 12 Hz, 1H), 5.08 (s, 2H), 2.35 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 162.5, 158.1, 156.6, 154.4, 152.7, 150.1, 138.6, 136.5, 134.2, 133.1, 129.7, 129.2, 129.1, 128.8, 128.4, 128.1, 127.8, 127.5, 126.4, 124.1, 122.6, 122.4, 121.3, 115.2, 112.8, 100.1, 82.6, 62.1, 24.1, 12.5. HRMS (ESI-MS) calcd. for $C_{32}H_{24}N_4NaO_2$ (M+Na)$^+$ 519.1797, found 519.1799.

(*E*)-2-((5-(4-Methoxystyryl)-3-methylisoxazol-4-yl)-amino)-4-phenyl-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (10i): Yield: 86%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3523, 2950, 2836, 2234, 1641, 1063, 742, ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.21 (s, 1H), 8.25 (d, *J* = 7.5 Hz, 1H), 7.83-7.21 (m, 12H), 6.73 (d, *J* = 12 Hz, 1H), 6.62 (d, *J* = 12 Hz, 1H), 5.12 (s, 2H), 3.63 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 161.6, 157.1, 156.5, 154.6, 153.4, 152.2, 150.5, 136.6, 134.1, 133.7, 129.5, 129.2, 128.7, 128.4, 128.1, 127.8, 126.2, 124.6, 122.5, 122.0, 121.6, 115.1, 112.5, 100.1, 82.7, 62.4, 59.6, 12.6. HRMS (ESI-MS) calcd. for $C_{32}H_{24}N_4NaO_3$ (M+Na)$^+$ 535.1746, found 535.1746.

(*E*)-2-((5-(2-Methoxystyryl)-3-methylisoxazol-4-yl)-amino)-4-phenyl-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (10j): Yield: 82%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3534, 2942, 2852, 2232, 1651, 1060, 744, ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.16 (s, 1H), 8.28 (d, *J* = 7.5 Hz, 1H), 7.88-7.22 (m, 12H), 6.70 (d, *J* = 12 Hz, 1H), 6.61 (d, *J* = 12 Hz, 1H), 5.08 (s, 2H), 3.52 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 162.5, 157.2, 156.5, 155.3, 153.8, 152.1, 150.7, 137.6, 134.2, 133.1, 129.8, 129.5, 129.1, 128.9, 128.4, 128.1, 127.7, 127.4, 126.8, 124.1, 122.5, 122.6, 121.4, 115.4, 112.2, 100.2, 82.5, 62.1, 60.2, 12.3. HRMS (ESI-MS) calcd. for $C_{32}H_{24}ClN_4NaO_3$ (M+Na)$^+$ 535.1746, found 535.1746.

(*E*)-2-((5-(2-(Furan-2-yl)vinyl)-3-methylisoxazol-4-yl)-amino)-4-phenyl-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (10k): Yield: 84%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3513, 2942, 2847, 2238, 1638, 1062, 746, ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.12 (s, 1H), 8.19 (d, *J* = 7.5 Hz, 1H), 7.75-6.93 (m, 11H), 6.73 (d, *J* = 12 Hz, 1H), 6.60 (d, *J* = 12 Hz, 1H), 4.84 (s, 2H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 162.1, 157.7, 155.1, 154.5, 153.6, 152.1, 150.3, 145.6, 134.2, 133.1, 129.7, 129.3, 128.8, 128.5, 127.4, 124.1, 122.4, 122.6, 121.3, 115.7, 113.6, 112.4, 107.6, 100.3, 82.3, 62.1, 12.1. HRMS (ESI-MS) calcd. for $C_{29}H_{20}N_4NaO_3$ (M+Na)$^+$ 495.1433, found 495.1433.

(*E*)-2-((3-Methyl-5-(2-(thiophen-2-yl)vinyl)isoxazol-4-yl)amino)-4-phenyl-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (10l): Yield: 88%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3520, 2946, 2842, 2231, 1642, 1058, 744, ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.23 (s, 1H), 8.24 (d, *J* = 7.5 Hz, 1H), 7.78-7.09 (m, 11H), 6.72 (d, *J* = 12 Hz, 1H), 6.62 (d, *J* = 12 Hz, 1H), 4.92 (s, 2H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 163.2, 158.5, 156.5, 154.3, 152.1, 150.5, 143.6, 134.1, 133.7, 131.4, 129.8, 129.1, 128.7, 128.4, 128.1, 127.6, 126.8, 124.1, 122.3, 122.7, 121.5, 115.1, 112.7, 100.1, 82.3, 62.1, 12.6. HRMS (ESI-MS) calcd. for $C_{29}H_{20}N_4NaO_2S$ (M+Na)$^+$ 511.1205, found 511.1207.

(*E*)-2-((3-Methyl-5-styrylisoxazol-4-yl)amino)-4-(*p*-tolyl)-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (11a): Yield: 80%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3542, 2943, 2852, 2238, 1641, 1058, 745, ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.24 (s, 1H), 8.16 (d, *J* = 7.5 Hz, 1H), 7.83-7.21 (m, 12H), 6.72 (d, *J* = 12 Hz, 1H), 6.63 (d, *J* = 12 Hz, 1H), 5.12 (s, 2H), 2.41 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 164.5, 157.1, 156.6, 153.7, 151.2, 150.4, 138.3, 136.7, 134.1, 132.4, 129.9, 129.2, 128.8, 128.5, 128.1, 127.8, 127.3, 124.1, 123.6, 122.4, 121.6, 116.1, 113.6, 100.6, 82.3, 62.2, 23.1, 12.5. HRMS (ESI-MS) calcd. for $C_{32}H_{24}N_4NaO_2$ (M+Na)$^+$ 519.1797, found 519.1799.

(*E*)-2-((3-Methyl-5-styrylisoxazol-4-yl)amino)-4-(*o*-tolyl)-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (11b): Yield: 78%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3534, 2953, 2841, 2241, 1640, 1055, 749, ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.23 (s, 1H), 8.13 (d, *J* = 7.5 Hz, 1H), 7.85-7.22 (m, 12H), 6.70 (d, *J* = 12 Hz, 1H), 6.61 (d, *J* = 12 Hz, 1H), 5.19 (s, 2H), 2.42 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 163.1, 157.6, 155.1, 154.1, 152.4, 150.3, 137.1, 135.4, 134.6, 132.5, 129.9, 129.4, 129.2, 128.7, 128.3, 128.0, 127.6, 127.2, 126.5, 124.4, 122.1, 122.5, 121.6, 116.6, 113.1, 100.4, 83.2, 63.5, 23.6, 12.2. HRMS (ESI-MS) calcd. for $C_{32}H_{24}N_4NaO_2$ (M+Na)$^+$ 519.1797, found 519.1798.

(*E*)-4-(4-Methoxyphenyl)-2-((3-methyl-5-styrylisoxazol-4-yl)amino)-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (11c): Yield: 84%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3537,

2956, 2843, 2242, 1647, 1060, 749, ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.19 (s, 1H), 8.43 (d, *J* = 7.5 Hz, 1H), 7.82-7.23 (m, 12H), 6.71 (d, *J* = 12 Hz, 1H), 6.61 (d, *J* = 12 Hz, 1H), 5.02 (s, 2H), 3.54 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 162.9, 158.4, 156.1, 154.3, 153.8, 152.5, 150.2, 136.1, 134.7, 132.3, 129.8, 129.3, 128.9, 128.5, 128.2, 127.6, 126.6, 124.3, 122.7, 122.3, 121.2, 116.5, 113.2, 100.5, 82.3, 61.7, 58.6, 12.3. HRMS (ESI-MS) calcd. for $C_{32}H_{24}N_4NaO_3$ $(M+Na)^+$ 535.1746, found 535.1749.

(*E*)-4-(2-Methoxyphenyl)-2-((3-methyl-5-styrylisoxazol-4-yl)amino)-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (11d): Yield: 75%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3521, 2953, 2843, 2240, 1642, 1056, 740, ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.32 (s, 1H), 8.36 (d, *J* = 7.5 Hz, 1H), 7.82-7.20 (m, 12H), 6.72 (d, *J* = 12 Hz, 1H), 6.63 (d, *J* = 12 Hz, 1H), 4.96 (s, 2H), 3.62 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 164.1, 158.8, 156.2, 155.8, 153.2, 152.6, 150.4, 138.3, 134.8, 132.7, 129.6, 129.3, 129.0, 128.8, 128.5, 128.2, 127.9, 127.1, 126.7, 124.4, 122.7, 122.0, 121.2, 116.9, 113.6, 100.4, 82.1, 62.7, 59.5, 12.7. HRMS (ESI-MS) calcd. for $C_{32}H_{24}ClN_4NaO_3$ $(M+Na)^+$ 535.1746, found 535.1746.

(*E*)-4-(4-Chlorophenyl)-2-((3-methyl-5-styrylisoxazol-4-yl)amino)-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (11e): Yield: 90%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3531, 2949, 2837, 2230, 1646, 1061, 749, ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.32 (s, 1H), 8.24 (d, *J* = 7.5 Hz, 1H), 7.82-7.23 (m, 12H), 6.72 (d, *J* = 12 Hz, 1H), 6.61 (d, *J* = 12 Hz, 1H), 5.02 (s, 2H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 163.2, 158.7, 156.1, 154.8, 152.0, 150.7, 137.5, 135.1, 134.5, 132.3, 129.9, 129.2, 128.7, 128.4, 128.2, 127.8, 126.1, 124.5, 122.7, 122.1, 121.8, 116.1, 113.6, 100.3, 82.1, 61.6, 12.3. HRMS (ESI-MS) calcd. for $C_{31}H_{21}ClN_4NaO_2$ $(M+Na)^+$ 539.1251, found 539.1254.

(*E*)-4-(2-Chlorophenyl)-2-((3-methyl-5-styrylisoxazol-4-yl)amino)-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (11f): Yield: 79%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3536, 2947, 2855, 2231, 1652, 1059, 754, ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.12 (s, 1H), 8.26 (d, *J* = 7.5 Hz, 1H), 7.83-7.23 (m, 12H), 6.71 (d, *J* = 12 Hz, 1H), 6.61 (d, *J* = 12 Hz, 1H), 4.97 (s, 2H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 162.6, 157.8, 156.4, 154.1, 152.5, 150.5, 138.7, 136.5, 134.3, 132.1, 129.8, 129.5, 129.2, 128.8, 128.1, 128.0, 127.3, 127.1, 126.9, 124.1, 122.6, 122.4, 121.3, 116.2, 113.8, 100.1, 82.6, 61.3, 12.4. HRMS (ESI-MS) calcd. for $C_{31}H_{21}ClN_4NaO_2$ $(M+Na)^+$ 539.1251, found 539.1252.

(*E*)-4-(4-Bromophenyl)-2-((3-methyl-5-styrylisoxazol-4-yl)amino)-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (11g): Yield: 91%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3521, 2938, 2852, 2224, 1642, 1060, 745, ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.19 (s, 1H), 8.32 (d, *J* = 7.5 Hz, 1H), 7.85-7.21 (m, 12H), 6.70 (d, *J* = 12 Hz, 1H), 6.61 (d, *J* = 12 Hz, 1H), 5.13 (s, 2H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 163.1, 157.8, 156.1, 154.5, 152.3, 150.7, 137.1, 134.4, 133.1, 131.4, 129.7, 129.4, 128.8, 128.3, 128.1, 127.7, 126.3, 124.1, 122.6, 122.8, 121.4, 114.7, 111.1, 100.4, 82.4, 61.5, 12.1. HRMS (ESI-MS) calcd. for $C_{31}H_{21}BrN_4NaO_2$ $(M+Na)^+$ 583.0746, found 583.0746.

(*E*)-4-(2-Bromophenyl)-2-((3-methyl-5-styrylisoxazol-4-yl)amino)-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (11h): Yield: 80%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3524, 2945, 2853, 2235, 1640, 1061, 743, ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.21 (s, 1H), 8.32 (d, *J* = 7.5 Hz, 1H), 7.82-7.21 (m, 12H), 6.72 (d, *J* = 12 Hz, 1H), 6.62 (d, *J* = 12 Hz, 1H), 5.02 (s, 2H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 164.2, 158.3, 156.4, 154.1, 152.4, 150.4, 138.1, 134.4, 132.5, 130.8, 129.9, 129.5, 129.3, 128.7, 128.4, 128.1, 127.7, 127.3, 126.5, 124.5, 122.6, 122.2, 121.1, 116.7, 113.6, 100.6, 82.1, 62.7, 12.1. HRMS (ESI-MS) calcd. for $C_{31}H_{21}BrN_4NaO_2$ $(M+Na)^+$ 583.0746, found 583.0748.

(*E*)-9-Methyl-2-((3-methyl-5-styrylisoxazol-4-yl)amino)-4-phenyl-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (11i): Yield: 81%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3534, 2948, 2850, 2245, 1638, 1061, 741, ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.26 (s, 1H), 8.23 (s, 1H), 7.81-7.22 (m, 12H), 6.71 (d, *J* = 12 Hz, 1H), 6.62 (d, *J* = 12 Hz, 1H), 4.68 (s, 2H), 2.38 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 162.1, 158.5, 155.1, 154.2, 152.6, 150.1, 137.8, 136.3, 134.6, 132.1, 129.8, 129.4, 128.7, 128.3, 128.0, 127.6, 127.4, 124.4, 123.3, 122.1, 121.5, 116.1, 112.4, 100.2, 82.1, 62.5, 23.7, 12.2. HRMS (ESI-MS) calcd. for $C_{32}H_{24}N_4NaO_2$ $(M+Na)^+$ 519.1797, found 519.1797.

(*E*)-9-Chloro-2-((3-methyl-5-styrylisoxazol-4-yl)amino)-4-phenyl-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (11j): Yield: 88%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3532, 2941, 2842, 2235, 1645, 1061, 739, ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.24 (s, 1H), 8.13 (s, 1H), 7.82-7.22 (m, 12H), 6.72 (d, *J* = 12 Hz, 1H), 6.61 (d, *J* = 12 Hz, 1H), 5.02 (s, 2H), 2.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 163.4, 158.4, 156.4, 154.1, 152.5, 150.2, 137.7, 136.1, 134.5, 132.3, 129.9, 129.5, 128.6, 128.3, 128.2, 127.1, 126.5, 124.8, 122.5, 122.1, 121.8, 115.1, 113.7, 100.4, 82.1, 62.4, 12.3. HRMS (ESI-MS) calcd. for $C_{31}H_{21}ClN_4NaO_2$ $(M+Na)^+$ 539.1251, found 539.1253.

(*E*)-9-Chloro-2-((3-methyl-5-(4-methylstyryl)isoxazol-4-yl)amino)-4-phenyl-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (11k): Yield: 85%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3524, 2951, 2849, 2241, 1643, 1059, 743, ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.19 (s, 1H), 8.23 (s, 1H), 7.79-7.23 (m, 11H), 6.71 (d, *J* = 12 Hz, 1H), 6.60 (d, *J* = 12 Hz, 1H), 4.97 (s, 2H), 2.32 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 162.6, 157.1, 156.9, 154.3, 152.1, 150.5, 138.1, 136.5, 134.2, 132.1, 129.8, 129.2, 128.8, 128.4, 128.1, 127.5, 126.1, 124.5, 122.8, 122.3, 121.4, 116.2, 112.6, 100.1, 82.5, 62.1, 23.6, 12.2. HRMS (ESI-MS) calcd. for $C_{32}H_{23}ClN_4NaO_2$ $(M+Na)^+$ 553.1407, found 553.1408.

(*E*)-9-Chloro-2-((5-(4-chlorostyryl)-3-methylisoxazol-4-yl)amino)-4-phenyl-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (11l): Yield: 90%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3529, 2945, 2840, 2226, 1640, 1058, 746, ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.19 (s, 1H), 8.22 (s, 1H), 7.83-7.20 (m, 11H), 6.70 (d, *J* = 12 Hz, 1H), 6.63 (d, *J* = 12 Hz, 1H), 4.97 (s, 2H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 164.4, 157.1, 155.7, 154.4, 152.1, 150.5, 138.1, 136.4, 134.1, 132.6, 129.6, 129.4, 128.8, 128.6, 128.4, 127.7, 126.2, 124.5, 122.4, 122.2, 121.7, 115.4, 112.6, 100.3, 82.4, 61.3,

12.1. HRMS (ESI-MS) calcd. for $C_{31}H_{20}Cl_2N_4NaO_2$ $(M+Na)^+$ 573.0861, found 573.0861.

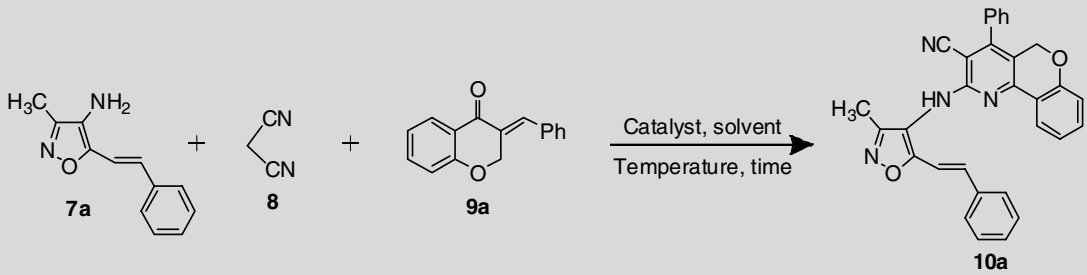
(*E*)-4-(Furan-2-yl)-2-((3-methyl-5-styrylisoxazol-4-yl)-amino)-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (11m): Yield: 82%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3527, 2948, 2842, 2242, 1647, 1056, 739, ^1H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.23 (s, 1H), 8.23 (d, *J* = 7.5 Hz, 1H), 7.73-6.98 (m, 11H), 6.70 (d, *J* = 12 Hz, 1H), 6.61 (d, *J* = 12 Hz, 1H), 5.08 (s, 2H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 164.4, 158.3, 156.4, 154.1, 153.8, 151.4, 150.5, 143.1, 134.5, 132.6, 129.9, 129.2, 128.9, 128.3, 127.1, 124.5, 122.1, 122.4, 121.9, 116.4, 114.1, 111.6, 108.1, 100.4, 82.6, 62.4, 12.8. HRMS (ESI-MS) calcd. for $C_{29}H_{20}N_4NaO_3$ $(M+Na)^+$ 495.1433, found 495.1436.

(*E*)-2-((3-Methyl-5-styrylisoxazol-4-yl)amino)-4-(thiophen-2-yl)-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile (11n): Yield: 80%, m.p.: > 300 ºC. IR (KBr, ν_{max}, cm^{-1}): 3536, 2951, 2856, 2240, 1642, 1063, 742, ^1H NMR (300 MHz, $CDCl_3$) δ, ppm: 10.19 (s, 1H), 8.15 (d, *J* = 7.5 Hz, 1H), 7.75-7.03 (m, 11H), 6.71 (d, *J* = 12 Hz, 1H), 6.61 (d, *J* = 12 Hz, 1H), 5.05 (s, 2H), 2.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm: 164.4, 157.2, 155.3, 153.8, 152.4, 150.1, 144.3, 134.5, 132.5, 130.8, 129.9, 129.4, 128.9, 128.3, 128.0, 127.4, 126.6, 124.4, 122.7, 122.3, 121.2, 116.6, 113.5, 100.4, 82.5, 62.4, 12.3. HRMS (ESI-MS) calcd. for $C_{29}H_{20}N_4NaO_2S$ $(M+Na)^+$ 511.1205, found 511.1205.

RESULTS AND DISCUSSION

Starting with 1 mmol each of 4-amino-3-methyl-5-styryl-isoxazole (**7a**), malononitrile (**8**) and (*E*)-3-benzylidenechroman-4-one (**9a**), a series of experiments was determine to check the feasibility of the reaction [29,35]. The model process was used with and without catalysts in various solvents to determine the optimal reaction conditions. Table-1 shows the outcomes of our experiments. The desired product **10a** was achieved in a 22% yield, after the model reaction was performed in ethanol at 90 ºC for 18 h without a catalyst (Table-1, entry 1). Then, the efficiency of the reaction was examined using a number of catalysts, including *p*-TSA, $ZnCl_2$, $In(OTf)_3$, $InCl_3$, L-proline, TFA, TfOH and AcOH in ethanol (Table-1, entries 2-9). Testing the reaction with AcOH as a catalyst, on the other hand, yielded a better outcome (Table-1, entry 9). After conducting the aforementioned tests, different solvents such CH_3CN, MeOH, THF, toluene and PEG-400 in the presence of AcOH, but still same findings (Table-1, entries 10-14) were obtained. Unexpectedly, using water as a solvent increased the reaction rate and provided an excellent yield of product **10a** when reacted 10 mol% AcOH at 90 ºC (Table-1, entry 15). The yield of the final product did not noticeably improve with further decrease or increase in the amount of catalyst (Table-1, entries,

TABLE-1
OPTIMIZATION OF THE REACTION CONDITIONS OF COMPOUND **10a**[a]



Entry	Solvent	Catalyst (mol%)	Temp. (°C)	Time (h)	Yield[b] (%)
1	EtOH	–	90	18	22
2	EtOH	*p*-TSA (10)	90	12	35
3	EtOH	$ZnCl_2$ (10)	90	12	41
4	EtOH	$In(OTf)_3$ (10)	90	10	47
5	EtOH	$InCl_3$ (10)	90	10	49
6	EtOH	L-Proline (10)	90	10	50
7	EtOH	TFA (10)	90	7	65
8	EtOH	TfOH (10)	90	6	65
9	EtOH	AcOH (10)	90	8	77
10	MeOH	AcOH (10)	90	8	63
11	CH_3CN	AcOH (10)	90	6	52
12	Toluene	AcOH (10)	90	10	55
13	THF	AcOH (10)	90	10	52
14	PEG-400	AcOH (10)	90	6	75
15[c]	**H_2O**	**AcOH (10)**	**90**	**3**	**88**
16	H_2O	AcOH (5)	90	4	78
17	H_2O	AcOH (15)	90	3	88
18	H_2O	AcOH (10)	80	6	77
19	H_2O	AcOH (10)	100	5	84
20	H_2O	AcOH (10)	25	24	28
21	H_2O	–	90	24	Trace

[a]All the reactions were performed with **7a** (1 mmol), **8** (1 mmol) and **9a** (1 mmol) in 5 mL of indicated solvent at heating conditions. [b]Isolated yields. [c]Bold values are highest yields obtained.

16 and 17). The use of AcOH (10 mol%) in water at 80 ºC and 100 °C (Table-1, entries 18 and 19) did not increase the yield of the product. Therefore, it was determined that 90 ºC and 10 mol% AcOH in water provided the optimal reaction conditions for obtaining a high yield of isoxazolyl amino chromeno[4,3-*b*]-pyridine (**10a**). Even after 24 h, the results were not satisfactory when the reaction was carried out at lower temperatures (Table-1, entry 20). Only minute quantities of the desired product were produced when the reaction mixture was carried out in water at 90 ºC without the presence of AcOH (Table-1 entry 21). From these optimization results, it was found that acetic acid-water combination at 90 ºC is the most effective catalyst and solvent media for this one-pot reaction.

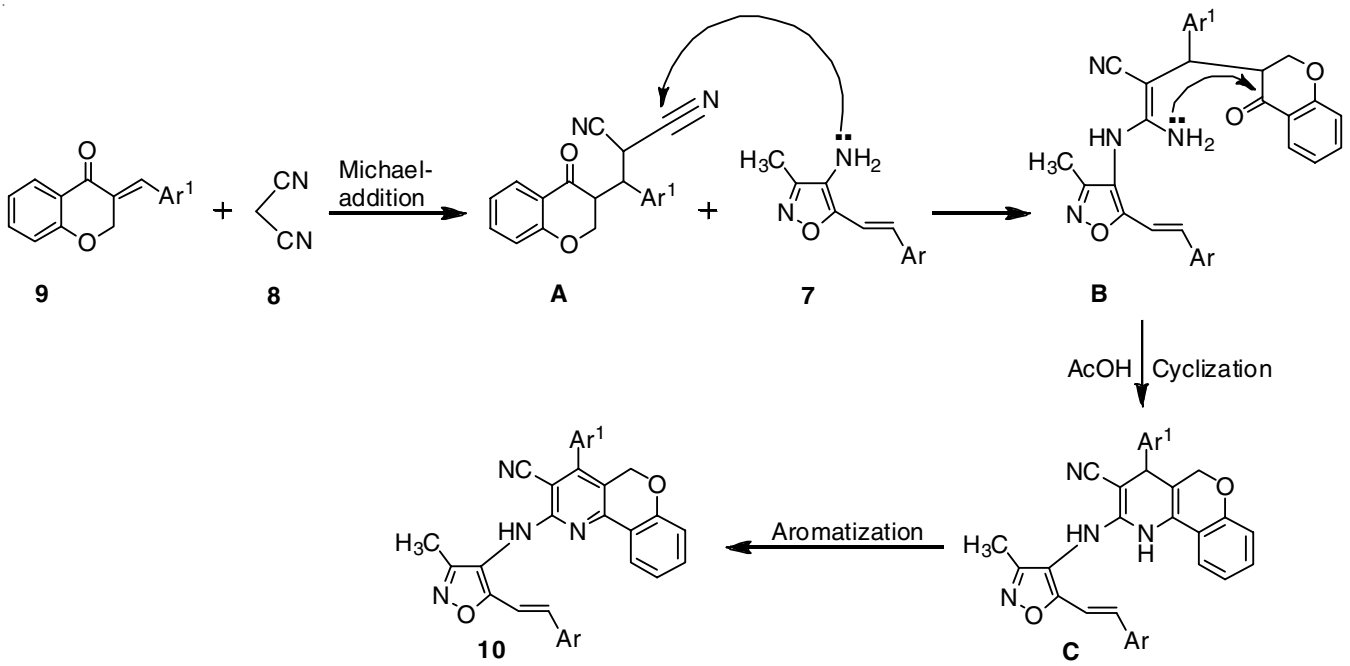
Under the optimized conditions, the synthetic method was used to make different isoxazolylaminochromeno[4,3-*b*]-pyridine derivatives by reacting different substrates together in different manners. The generality of the reaction was established using various 4-amino-3-methyl-5-styrylisoxazoles (**7**) (1 mmol), malononitrile (**8**) (1 mmol) and (*E*)-3-benzylidene-chroman-4-one (**9a**) (1 mmol) to afford the title products **10a-l** in good yields (80-94%). In particular, under the optimized reaction conditions, the final products were obtained in good to excellent yields, when phenyl group contains either electron-withdrawing groups (*e.g*. chloro, bromo and nitro groups) or electron-donating groups (*e.g.* methyl and methoxy groups in the moiety of aminostyrylisoxazoles (**7**). Thus, 4-amino-3-methyl-5-styryl-isoxazoles (**7**) consisting *p*-substitutants and that too electron-withdrawing groups showed greater reactivity and resulted in higher yields than those with electron-donating groups, which may be attributed to the electronic effects. In case of *o*-substituted substrates, irrespective of either electron donating groups or electron-withdrawing groups, obtained the corresponding isoxazolylaminochromeno[4,3-*b*]pyridine (**10**) derivatives in relatively a little bit lower yields, which is attributed due to the steric hindrance. Furthermore, when a hetero-aromatic nucleus like furan and thiophene was introduced in aminostyrylisoxazoles (**7**), the reaction progressed well and obtained the desired scaffolds in 84-88% yields.

Next, the substrate scope of different (*E*)-3-benzylidene-chroman-4-ones (**9**) with 4-amino-3-methyl-5-styrylisoxazoles (**7**) and malononitrile (**8**) was also investigated. As observed, the reaction with different (*E*)-3-benzylidenechroman-4-ones bearing ether electron donating group or electron withdrawing group, the substitutents on phenyl ring progressed smoothly to give the final products **11a-n** in 75-91% yield. Meanwhile, it was also observed that (*E*)-3-benzylidenechroman-4-ones having electron withdrawing group *e.g*. chloro and bromo exhibited better reactivity and gave good yields than those having electron donating group groups such as methyl and methoxy. In all of these cases, the products were filtered and recrystallized from methanol, instead of conventional chromatographic purification. The structures of all the newly synthesized compounds **10a-l** and **11a-n** were characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS analysis.

A plausible mechanism for the formation of isoxazolyl amino chromeno[4,3-*b*]pyridines (**10**) is proposed in **Scheme-III** based on the experimental results. First, the Michael addition between compounds **8** and **9** to give intermediate **A**, which react with compound **7** to afford intermediate **B**, in which an intramolecular cyclization protocol is occured in the presence of an acid catalyst to yield the intermediate **C**, which further upon aromatization to obtain target product **10**.

Conclusion

In conclusion, an efficient, cost-effective, environmentally begnin protocol for the synthesis of new isoxazolyl amino chromeno[4,3-*b*]pyridine derivatives from a one-pot reaction of 4-amino-3-methyl-5-styrylisoxazoles, malononitrile and



Scheme-III: Plausible mechanism

(*E*)-3-benzylidenechroman-4-one has been reported. As a straightforward one-pot three-component reaction in an aqueous media catalyzed by acetic acid, which does not requires any means of purification like column chromatography, this synthetic protocal contributes significantly to the needs of green chemistry. Further ongoing study aims to investigate the versatility of this reaction technique by investigating it out on a variety of substrates, synthesizing more complexed type products and evaluating their biological characteristics.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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