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# Synthesis and Characterization of New monocationic pyridine-arylthiophene derivatives

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**Abstract:** Three new monocationic thienylpyridine derivatives **7a-c** were prepared through two sequential steps. First step involved the preparation of carbonitrile derivatives **6a-c** in good yields *via* a Suzuki coupling reaction between the bromothienyl derivative **4** and the appropriate phenylboronic acids **5a-c**. Second step involved treatment of carbonitrile derivatives **6a-c** with lithium bis-trimethylsilylamide, followed by de-protection step and subsequent hydrochloride salt formation. Chemical structures of the newly synthesized thienylpyridines were confirmed based on their spectral data, Infrared FT-IR, $^{1}$H-NMR and mass spectrometry.

**keywords**: Thiophene derivatives, pyridine derivatives, Suzuki reaction, cationic compounds.

## 1.Introduction

Thiophene containing compounds have applications in many fields. They have significant therapeutic activity as antiproliferative agents [1], antidepressant agents [2], anti-atherosclerotic agents [3]. Pyridine derivatives possess a diverse chemotherapeutic profile in anticancer, antimicrobial, or antiprotozoal activity, mostly the pyridine ring has a fundamental role in the pharmacokinetic properties of these biologically active compounds [4-8]. Furthermore, furanylnicotinamidine derivatives have been reported for their potent antiproliferative activity [9]. Dicationic compound furanylnicotinamidine derivative (DB829) has been successfully passed the preclinical studies as antitrypanosomal agent [10,11]. Recently, bithiophene-fluorobenzamidine compound showed a very promising *in vivo* antitumor activity against colorectal cancer in rats without causing hepato- or nephro-toxicity [12]. Conjugated compounds which have thiophene moiety are used in various industrial applications because upon electronic excitation, they absorb ultraviolet light or radiation of lower frequencies. For example, polythiophenes play an important role in semiconductors [13], also they can be used in electro-optic devices [14] and white-light-emitting diodes [15]. In the present study, we report herein preparation and characterization of three new monoamidines of thienylpyridines, along with mass fragmentation pattern for 4-methoxyphenylthienyl derivative.

## 2. Results and discussion

Retrosynthetic analysis is a guide for the design of the target compounds. Synthetic analysis of thienylpyridine derivatives **7a-c** is depicted in **Figure 1**. Disconnection starts with function group interconversion (FGI) of the amidine group to its corresponding carbonitrile group. The disconnection of thienylnicotinonitriles **6a-c** may be done *via* different possible disconnections as follow; (i) 1,4-dicarbonyl interconversion, this interconversion leads to 1,4-dicarbonyl starting material **1a-c** that is difficult to prepare herein, because of unavailability of the starting materials, (ii) Palladium-catalyzed disconnections; this may be possible *via* either Heck coupling disconnection to the easily prepared 6-(thiophen-2-yl)nicotinonitrile (**2**) and commercially available bromophenyl derivatives **3a-c**, or Suzuki coupling disconnection to the easily prepared 6-(5-bromothiophen-2-yl)nicotinonitrile (**4**), and commercially available arylboronic acids **5a-c**.

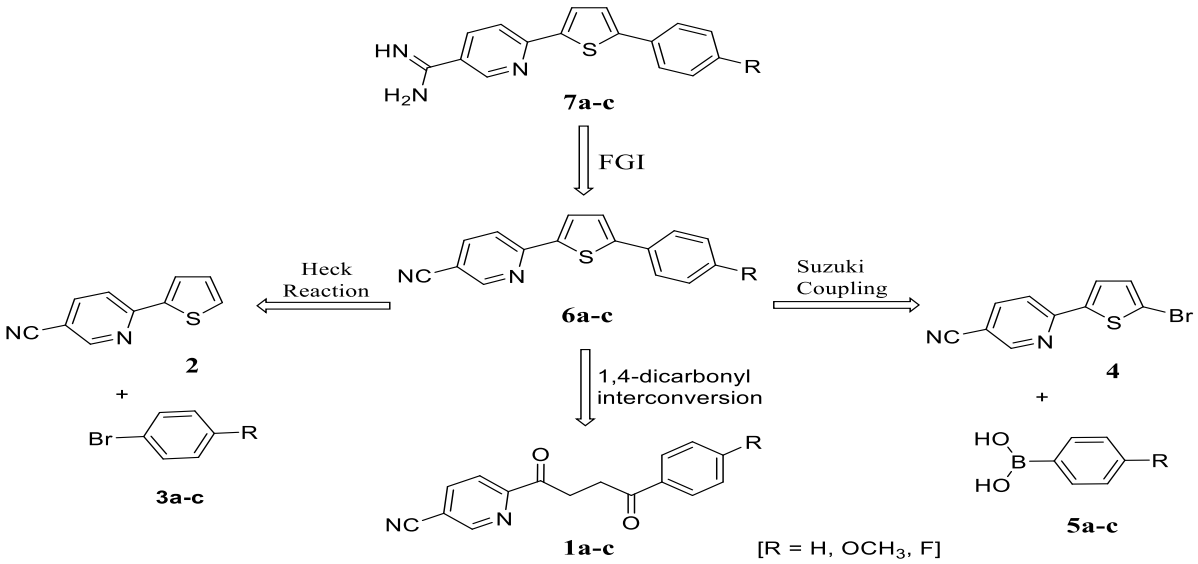


**Fig 1:** Retrosynthetic analyses for the new thiophene derivatives **7a-c & 6a-c**.

The preparation of the new monocationic thienylpyridines **7a-c** (**Figure 2**) begins with Suzuki coupling reaction of bromothienyl derivative **4** with the appropriate phenylboronic acids **5a-c** to furnish the carbonitrile derivatives **6a-c**. The nicotinonitrile derivatives **6a-c** were converted to their corresponding nicotinamidines **7a-c** on treatment with lithium bis-trimethylsilylamide, followed by hydrolysis with HC(gas). After this, the crude products were neutralized with NaOH to furnish the corresponding free bases which were converted to their hydrochloride salts on treatment with hydrogen chloride in ethanol

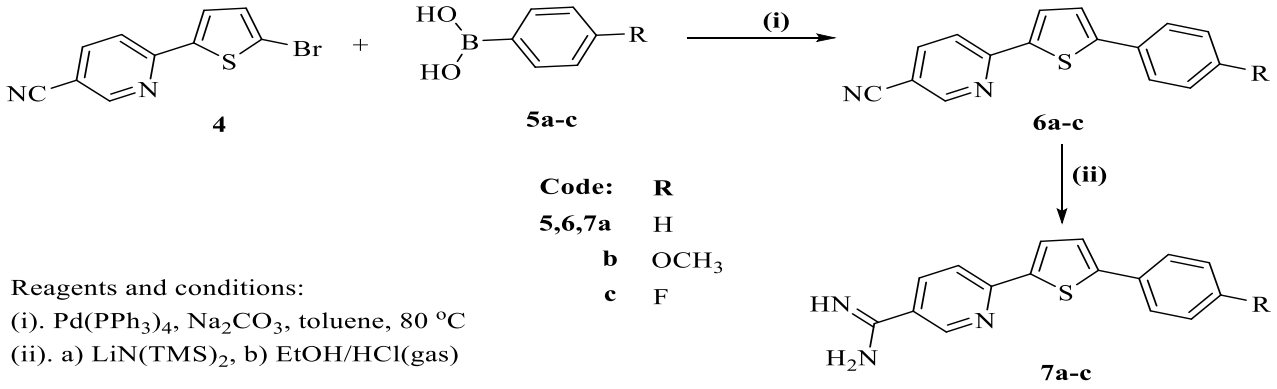


**Fig 2**: Synthesis scheme for the new thiophene derivatives **7a-c**.

The chemical structures of newly synthesized carbonitrile derivatives **6a-c** were confirmed from their spectral and elemental analyses. IR spectra for all mononitriles **6a-c** indicated that appearance of nitrile group in each case with stretching vibrations in the range of 2222 to 2226 $cm^{-1}$. $^1$H-NMR spectrum of the nicotinonitrile **4b** showed splitting pattern corresponding to 2,5-disubstituted pyridyl moiety confirmed by the presence of ABX system (doublet of doublet at δ 8.28 ppm with coupling constants of J = 9.0, & J = 2.5 Hz, two doublet signals, one with large coupling constant J = 9.0 Hz at δ 8.10 ppm and small coupling constant J = 2.5 Hz at δ 8.92), two doublet signals with coupling constant J = 4.0 Hz at δ 7.51 ppm (1H), and 7.97 ppm (1H) refereed to protons of thiophene ring, in addition to three signals of 4-methoxyphenyl moiety, one singlet signal at δ 3.78 ppm integrated for three protons corresponding to the methoxy group, and two doublet signals (AA'BB' system) with coupling constant J = 8.5 Hz at δ 7.00 ppm and 7.68 ppm refereed to 1,4-disubstituted phenyl moiety.The chemical structures of the newly synthesized monocationic thienylpyridine derivatives **7a-c** were confirmed from their spectral and elemental analyses. IR spectra of all monoamidines indicated that disappearance of

nitrile group in each case and displayed new peaks corresponding to N-H stretching vibrations (ν' 3383, 3240 $cm^{-1}$ for compound **7b**). $^1H$ NMR spectrum of all monoamidine derivatives showed the characteristic signals corresponding to the cationic amidine group and were deuterium exchangeable. $^1H$ NMR spectrum of the monocationic compound **7b** showed two singlet signals at δ 9.38 (for $NH_2$) and δ 9.65 (for $^+NH_2$) characteristic for the cationic amidine group, ABX splitting system corresponding for 2,5-disubstituted pyridyl moiety (doublet of doublet signal at δ 8.27 ppm, doublet signal with large coupling constant at δ 8.15 ppm and another doublet signal with small coupling constant at δ 8.95 ppm), two doublet signals one proton each with coupling constant J = 4.0 Hz at δ 7.51 and 7.99 ppm refereed to 2,5-disubstituted thiophene ring, in addition to three signals corresponding to 4-methoxyphenyl moiety, one singlet signal at δ 3.78 ($OCH_3$, 3H), and two doublet signal (AA'BB' system) at δ 7.00 ppm (2H), 7.68 ppm (2H) refereed to 1,4-disubstituted phenyl ring. Additionally, mass spectrum of monoamidine derivative **7b** gave its molecular ion peak at a m/z 309, and m/z peak at 292 corresponding to the fragment that produced from the loss of a molecule of ammonia, and m/z peak at 294 corresponding to the fragment that produced from the loss of a methyl group (**Figure 3**).

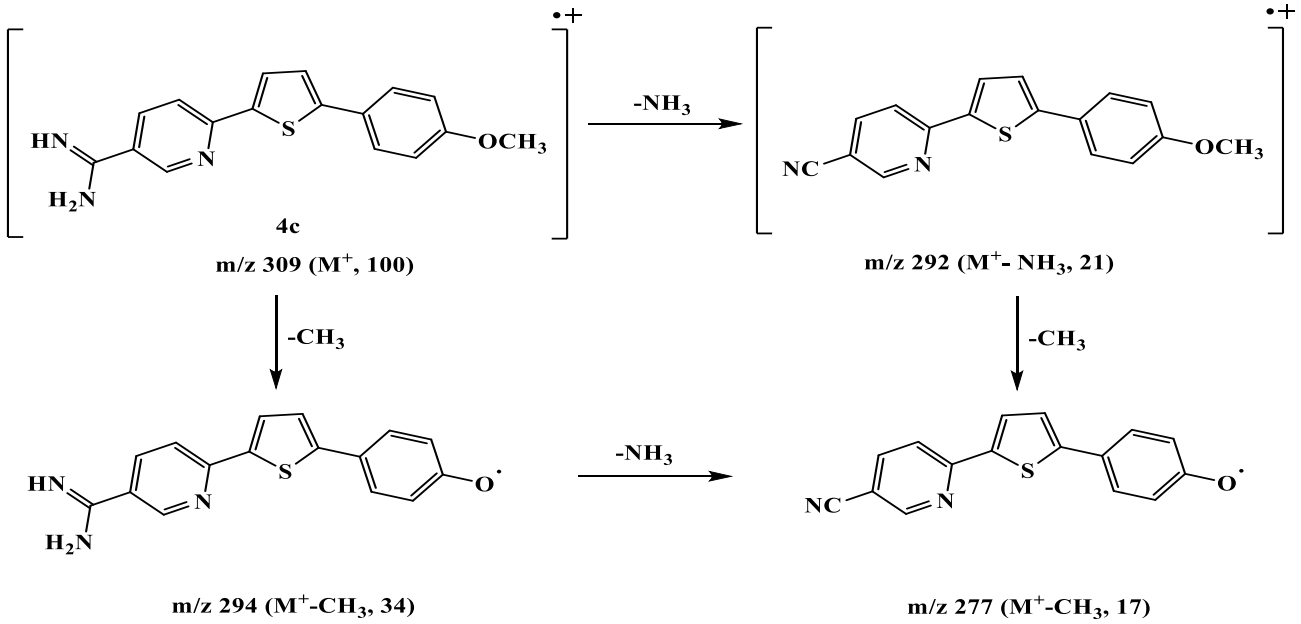


**Fig 3**: Mass fragmentation pattern of monoamidine derivative **7b**.

## 3. Experimental

[1 Melting points were measured in degree centigrade on Gallenkamp apparatus and are uncorrected. The infrared spectra (KBr) were explored on Thermo Scientific Nicolet iS10 FTIR spectrometer. $^1H$ NMR spectra were measured in DMSO-$d_6$ as a solvent using 500 MHz on JEOL's spectrometer. Perkin-Elmer 2400 analyzer has been used to determine the elemental analyses. A Schimadzu Qp-2010 Plus (GC-MS) spectrometer was used for recording Mass spectra

### 3.1. General methodology for preparation of thienylnicotinonitriles 6a-c.

To a strirred solution of bromothienyl derivative (1.052 g, 4 mmol), $Pd(PPh_3)_4$ (160 mg), 4 mL of 2M $Na_2CO_3$ (aqueous) in 16 mL toluene was added the methanolic solution of appropriate arylboronic acid (4.8 mmol). The reaction mixture was heated at 80 $^oC$ with stirring for 12 hours. After this, concentrated ammonia 4 mL was added to the reaction mixture, then it was extracted with ethyl acetate (250 mL, 3x). The organic layer was evaporated to dryness and the solid was filtered off and recrystallized from either ethanol or ethanol/ethyl acetate to furnish the desired thienylnicotinonitrile derivatives **6a-c**.

### 3.1.1.6-(5-Phenylthiophen-2yl)nicotinonitrile (6a)

carbonitrile derivative **6a** was obtained in 72% yield as a yellow solid, m.p. 160-162 $^oC$ (EtOH). $R_f$ = 0.5 (thin layer chromatography, TLC, petroleum ether-EtOAc 8:2). IR (KBr)

ν'/$cm^{-1}$ 3060 (C-H stretching vibrations), 2226 (CN stretching vibrations), 1586, 1547, 1503 (C=N, C=C stretching vibrations). MS (EI) m/e (rel.int.); 262 ($M^+$, 100). $^1$H NMR; δ/ppm = 7.36-7.47 (m. 3H), 7.65 (d, J = 4.0 Hz, 1H; thiophene), 7.74-7.76 (m, 2H), 8.03 (d, J = 4.0 Hz, 1H; thiophene), 8.15 (d, J = 8.5 Hz, 1H; pyridine), 8.32 (dd, J = 8.5, 2.5 Hz, 1H; pyridine), 8.95 (d, J = 2.5 Hz, 1H; pyridine). Anal. Calcd. for: $C_{16}H_{10}N_2S$ (262.33): C, 73.26; H, 3.84; N, 10.68 Found: C, 73.48; H, 3.92; N, 10.49 %.

### 3.1.2. 6-[5-(4-Methoxyphenyl)thiophen-2-yl]nicotinonitrile (6b):

carbonitrile derivative **6b** was obtained in 74% yield as a golden-yellow solid, mp 194-195 $^o$C (EtOH). $R_f$ = 0.4 (TLC), petroleum ether-EtOAc (8:2). IR (KBr) ν'/$cm^{-1}$ 3047, 2927 (C-H stretching vibrations), 2222 (CN stretching vibrations), 1585, 1545, 1512 (C=C stretching vibrations). MS (EI) m/e (rel.int.); 292 ($M^+$, 100). $^1$H NMR; δ/ppm = 3.78 (s, 3H), 7.00 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 4.0 Hz, 1H; thiophene), 7.68 (d, J = 8.5 Hz, 2H), 7.97 (d, J = 4.0 Hz, 1H; thiophene), 8.10 (d, J = 9.0 Hz, 1H; pyridine), 8.28 (dd, J = 9.0, 2.5 Hz, 1H; pyridine). 8.92 (d, J = 2.5 Hz, 1H; pyridine). Anal. Calcd. for: $C_{17}H_{12}N_2OS$ (292.35): C, 69.84; H, 4.14; N, 9.58 Found: C, 69.71; H, 4.25; N, 9.43 %.

### 3.1.3.6-[5-(4-Fluorophenyl)thiophen-2-yl]nicotinonitrile (6c):

carbonitrile derivative **6c** was obtained in 87% yield as a yellow solid, mp 231-232 $^o$C (EtOH/EtOAc). $R_f$ = 0.48 (TLC), petroleum ether (60-80 $^o$C)-EtOAc (7:3). IR (KBr) ν'/$cm^{-1}$ 3057 (C-H stretching vibrations), 2226 (CN stretching vibrations), 1590, 1547 (C=C stretching vibrations). MS (EI) m/e (rel.int.); 280 ($M^+$, 100). $^1$H NMR; δ/ppm = 7.27-7.31 (m, 2H), 7.61 (d, J = 4.0 Hz, 1H; thiophene), 7.78-7.812 (m, 2H), 8.01 (d, J = 4.0 Hz, 1H; thiophene), 8.14 (d, J = 8.5 Hz, 1H; pyridine), 8.31 (dd, J = 8.5, 2.0 Hz, 1H; pyridine), 8.94 (d, J = 2.0 Hz, 1H; pyridine). Anal. Calcd. for: $C_{16}H_9FN_2S$ (280.32): C, 68.56; H, 3.24; N, 9.99 Found: C, 68.71; H, 3.15; N, 10.13 %.

## 3.2. General methodology for preparation of thienylnicotinamidines 7a-c:

The proper thienylcarbonitrile derivative of **6a-c** (1.5 mmol) was allowed to react with lithium bis-trimethylsilylamide (1M solution in THF, 9 mL) with stirring for overnight. After this, ethanolic hydrogen chloride solution (15 mL, 1.25 M) was added dropwise with cooling, until a precipitate was formed. The reaction mixture was left to stir for 6 hr. The precipitate was collected and neutralized with 1N NaOH followed by filtration. Finally, the monoamidine free base was treated with ethanolic-HCl(gas) solution and the resultant solid was triturated with ether and filtered off to furnish the target hydrochloride salts **7a-c**.

### 3.2.1.6(5Phenylthiophen2yl)nicotinamidine hydrochloride salt (7a):

cationic compound **7a** was obtained in 68% yield as an orange solid, mp 286-287 $^o$C. IR (KBr) ν'/$cm^{-1}$ 3356, 3230 (N-H stretching vibrations of $^+NH_2$, $NH_2$), 3062 (C-H stretching vibrations), 1676, 1629, 1593 (C=N & C=C stretching vibrations). MS (EI) m/e (rel.int.); 279 ($M^+$, 100), 262 (30). $^1$H NMR; δ/ppm = 7.35-7.38 (m, 1H). 7.44-7.47 (m, 2H), 7.66 (d, J = 4.0 Hz, 1H; thiophene), 7.75-7.77 (m, 2H), 8.05 (d, J = 4.0 Hz, 1H; thiophene), 8.20 (d, J = 8.0 Hz, 1H; pyridine), 8.29 (dd, J = 8.0, 2.0 Hz, 1H; pyridine), 8.94 (d, J = 2.0 Hz, 1H; pyridine). 9.27 (s, $NH_2$, $D_2O$ exchangeable), 9.56 (s, $^+NH_2$, $D_2O$ exchangeable). Anal. Calcd. for: $C_{16}H_{13}N_3S$-1.0HCl (315.82): C, 60.85; H, 4.47; N, 13.31 Found: C, 60.93; H, 4.57; N, 13.04 %.

### 3.2.2. 6-[5-(4-Methoxyphenyl)thiophen-2-yl]nicotinamidine hydrochloride salt (7b):

cationic compound **7b** was obtained in 69 yield as a brick-red solid, mp 282-283 $^o$C. IR (KBr) ν'/$cm^{-1}$ 3383, 3240 (N-H stretching vibrations of $^+NH_2$, $NH_2$), 3080, 2960 (C-H stretching vibrations), 1677, 1630, 1598 (C=N & C=C stretching vibrations). MS (EI) m/e (rel.int.); 309 ($M^+$, 100), 294 (34). 292 (21). 277 (17). $^1$H NMR; δ/ppm = 3.78 (s, 3H), 7.00 (d, J = 9.0 Hz, 2H), 7.51 (d, J = 4.0 Hz, 1H; thiophene), 7.68 (d, J = 9.0 Hz, 2H), 7.99 (d, J = 4.0 Hz, 1H; thiophene), 8.15 (d, J = 9.0 Hz, 1H; pyridine), 8.27 (dd, J = 9.0, 2.0 Hz, 1H; pyridine). 8.95 (d, J = 2.0 Hz, 1H; pyridine), 9.38 (s, $NH_2$, $D_2O$ exchangeable), 9.65 (s,

$^{+}NH_2$, $D_2O$ exchangeable). Anal. Calcd. for: $C_{17}H_{15}N_3OS$-1.0HCl (345.84): C, 59.04; H, 4.66; N, 12.15 Found: C, 58.87; H, 4.85; N, 12.09 %.

**3.2.3. 6-[5-(4-Fluorophenyl)thiophen-2-yl]nicotinamidine hydrochloride salt (7c):** cationic compound **7c** was obtained in 80% yield as a golden-yellow solid, mp 315-317 $^{o}$C. IR (KBr) ν'/cm$^{-1}$ 3429, 3284 (N-H stretching vibrations of $^{+}NH_2$, $NH_2$), 3085 (C-H stretching vibrations), 1667, 1591 (C=N & C=C stretching vibrations). MS (EI) m/e (rel.int.); 297 ($M^{+}$, 100), 280 (53). $^{1}$H NM R; δ/ppm = 7.28-7.32 (m, 2H), 7.63 (d, J = 4.0 Hz, 1H; thiophene), 7.79-7.82 (m, 2H), 8.04 (d, J = 4.0 Hz, 1H; thiophene), 8.20 (d, J = 9.0 Hz, 1H; pyridine), 8.27 (dd, J = 9.0, 2.0 Hz, 1H; pyridine), 8.94 (d, J = 2.0 Hz, 1H; pyridine), 9.30 (s, $NH_2$, $D_2O$ exchangeable), 9.58 (s, $^{+}NH_2$, $D_2O$ exchangeable). Anal. Calcd. for: $C_{16}H_{12}FN_3S$-1.0HCl (333.81): C, 57.57; H, 3.93; N, 12.59 Found: C, 57.91; H, 4.00; N, 12.32 %.

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