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ARTICLE TYPE

Synthesis of 1-amino-2-aroyl/acetylnaphthalenes through base mediated one pot inter and intramolecular C-C bond formation strategy

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A new precursor 2-(1-cyano-2,2-bis(methylthio)vinyl)benzonitrile has been synthesized by reaction of 2-cyanomethylbenzonitrile, carbon disulfide and methyl iodide under basic conditions. Reaction of 2-(1-cyano-2,2-bis(methylthio)vinyl)benzonitrile with various functionalized aryl/heteroaryl methyl ketones or acetone under basic condition afforded 4-amino-3-aroyl/heteroaroyl/acetyl-2-methylsulfanylnapthalene-1-carbonitriles in good yields through (5C+1C) annulations strategy which involves sequential intermolecular followed by intramolecular C-C bond formation reactions. Structure of the product was confirmed by single crystal X-ray crystallography.

Introduction

Ketenedithioacetals are known as versatile precursors, for their broad synthetic applications.[1] Their synthetic utility has been widely explored for the construction of various aromatic and heteroaromatic along with nonaromatic ring systems of medicinal and synthetic importance.[2] A large variety of ketenedithiacetals are reported for their application in substitution, elimination and addition reactions;[1] synthesis of various functionalized 2*H*-pyran-2-ones;[3] partially reduced coumarin;[3] pyrazoles;[3] oxazoles;[3] thiophenes;[3] pyridines;[3] pyrimidines[3] and fluorescent[4] compounds. The broad synthetic potential of these synthons gave us enthusiasm to further investigate their chemistry.

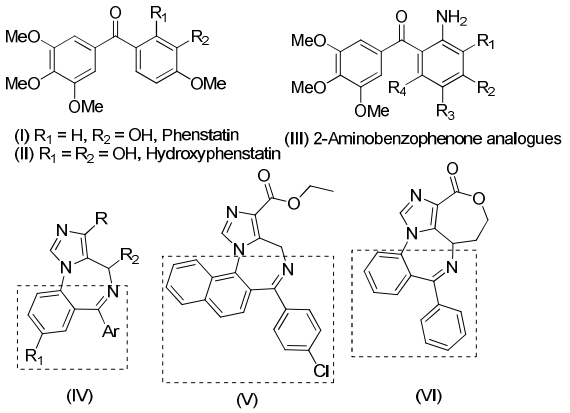
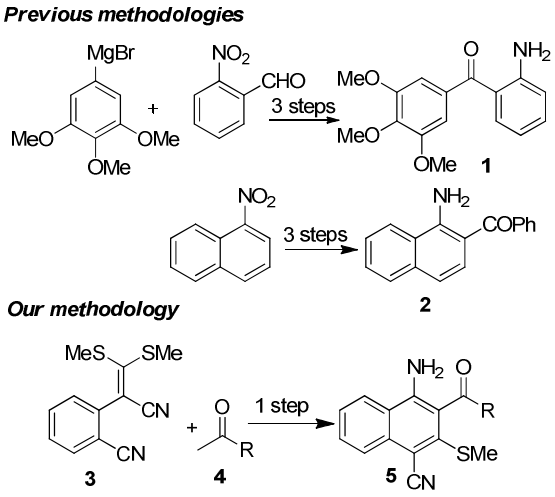


Fig. 1: Structure of phenstatin **I**, hydroxyphenstatine **II**, 2-aminobenzophenone analogues **III** 3-substituted 6-aryl-4*H*-imidazo-[1,5-*a*]benzodiazepines and related compound (**IV-VI**).

Functionally loaded diaryl ketones are present as the structural motif in various synthetically and biologically important molecules and natural products.[5] α-Aminodiaryl ketones and molecules embedded with these molecular skeletons found application as antitubulin agents, e.g. Phenstatin **I**,[6] Hydroxyphenstatine[6] (**II**) and 2-aminobenzophenone analogues (**III**).[7] 2-Amino-1-aroylnaphthalene and 2-hydroxy-1-aroylnaphthalene also exhibit good anti proliferative activity against human cancer cell, comparable to the potency of colchine (Fig. 1).[8]

3-Substituted 6-phenyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepines (**IV**) and related compounds (**V-VI**) embedded with o-aminatedphenyl aryl ketones are reported as central benzodiazepine receptor (CBR) ligands as shown in Figure 1.[9]



Scheme 1: Reported methodologies versus our methodology.

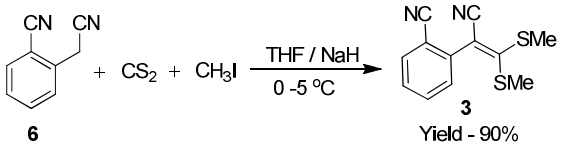
Extensive literature survey, concluded that very limited methodologies are available for the synthesis of *o*-aminoaryl aryl ketones. 2-Aminobenzophenone analogues have been prepared in three steps by Liou *et al.*[7] The first step was synthesis of benzhydrol derivatives via coupling of (3,4,5-

trimethoxyphenyl)magnesium bromide with various substituted 2-nitrobenzaldehydes, which, on oxidation with pyridinium dichromate (PDC), followed by nitro group reduction, provided functionalized α-aminobenzophenones. Synthesis of the α-aminonaphthophenones was also reported by Zhang *et al*.[10] The required precursor 1-amino-2-naphthonitrile for the synthesis of α-aminonaphthophenones has been synthesized by regioselective cyanation of l-nitronaphthalene.[11] Reaction of aryl magnesium halides with 1-amino-2-naphthonitrile followed by hydrolysis provided the α-nitronaphthophenones, which, upon concomitant reduction, gave α-aminonaphthophenones in overall poor yield.

Most of the previously reported methodologies required a multistep reaction approach, use of expensive reagents, harsh reaction conditions, naphthyl ring containing precursors and provided overall low yields. [10,11] 5+1 Annulation strategy for the construction of various kind of nuclei has been reported earlier.[11] Zhang *et al* have reported the 5C+1C/N cyclization strategy for the synthesis of benzene nucleus from ketenedithioacetals.[11b] Liu and co-worker have also used 5C+1C cyclization for the synthesis of highly crowded cyclohexenone.[11] We have made first attempt to synthesized naphthalene nucleus using 5C+1C cyclization strategy.

Results and Discussion

We have chosen 2-(1-cyano-2,2-bis(methylthio)vinyl)benzonitrile as a synthetic key precursor for the construction of multifunctional naphthalene rings. This was synthesized by reaction of 2-cyanomethylbenzonitrile, carbon disulfide and methyl iodide under basic conditions (Scheme 2). We have screened some alkaline solvent combinations such as NaH/THF, K_2CO_3/DMF, NaOEt/Ethanol and KO^{t}Bu/THF for the synthesis of the desired precursor and NaH/THF was found to be the best combination.



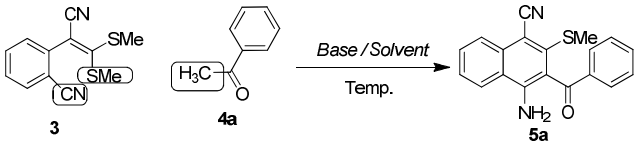
Scheme 2: Synthesis of 2-(1-cyano-2,2-bis(methylthio)vinyl)benzonitrile

Earlier report[3] shows that methylthio group of ketenedithioacetals act as excellent leaving group, can be employed for the development of new molecular make-ups. We wish to use carbon nucleophiles to replace the methylthio group of 2-(1-cyano-2,2-bis(methylthio)vinyl)benzonitrile followed by utilization of the nitrile group at the ortho position in the benzene ring for concomitant cyclization.

Taking into account the above concept, we have used 2-(1-cyano-2,2-bis(methylthio)vinyl)benzonitrile and acetophenone as model substrates to screen various reaction conditions (Table 1). We have started the screening with use of sodium hydride in THF and isolated the desired compound with 55% yield upon reacting for 20 hours at room temperature (entry 1). We shifted to a polar solvent, DMF, in lieu of THF in combination of NaH, but little change was observed (entry 2). We have also tested potassium hydroxide and sodamide in DMF under similar reaction conditions and got better results in the case of potassium hydroxide than sodamide. For further improvement, we carried out the reaction in DMSO with KOH at room temperature, and surprisingly the reaction completed in 2 hours with 81 % yield (entry 5). This result proves that DMSO is best solvent for screening of various bases. Probably the presence of CHO group in DMF hindered the formation of desired product due some side reactions with acetophenone. We screened sodium hydride, sodamide and sodium hydroxide in DMSO, but no base was better than potassium hydroxide (entry 6, 7 and 8). We have checked the influence of temperature using potassium hydroxide as a base in dimethyle sulfoxide and no exciting results were obtained (entry 9 and 10). We have also evaluated the effect of excess of potassium hydroxide on the reaction, and observed the lower yield of desired product (entry 11 and 12). We proposed that, excess of base enhances the possibility of side reactions of the product and lower the yield. Thus stirring of one equivalent of 2-(1-cyano-2,2-bis(methylthio)vinyl)benzonitrile **3** with 1.1 equivalent of aryl methyl ketones **4** and two equivalent of potassium hydroxide in DMSO at room temperature, followed by proper work-up and purification provides multifunctional naphthalenes **5** in good yield.

With these optimized reaction conditions, we have synthesized various highly functionalized aryl naphthyl ketones (Scheme 3). We have used various acetophenones **4** containing electron donor and acceptor groups. It has been observed that the presence of these groups in the aryl ring negatively affects the yields of the desired product. Interestingly, we observed that use of *p*-chloro/fluoroacetophenone, provides the desired product 4-amino-3-(4-chloro/fluoro-benzoyl)-2-(methylthio)-1-naphthonitrile as a major product and 4-amino-2-(methylthio)-3-(4-(methylthio)benzoyl)-1-naphthonitrile as a minor product

Table 1: Optimization of reaction conditions[a]



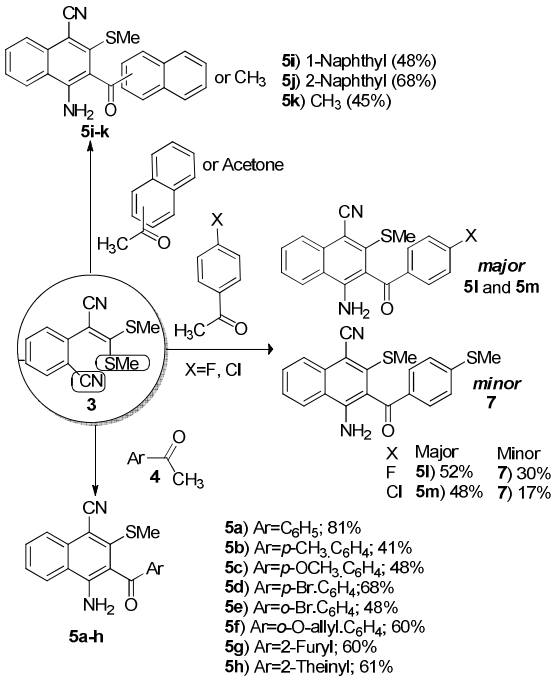
Entry	Base	Solvent	Temp(°C)[c]	Time(hrs)	Yield(%)[b]
1	NaH	THF	RT	20	55
2	NaH	DMF	RT	20	65
3	KOH	DMF	RT	20	70
4	$NaNH_2$	DMF	RT	20	26
5	KOH	DMSO	RT	2	81
6	NaH	DMSO	RT	2	70
7	$NaNH_2$	DMSO	RT	2	70
8	NaOH	DMSO	RT	2	65
9	KOH	DMSO	60	2	65
10	KOH	DMSO	90	1.5	55
11	KOH	DMSO	RT	2	70[d]
12	KOH	DMSO	RT	2	66[e]

a). All the reactions were carried out by using **3** (0.5 mmol), **4a** (0.55 mmol), base (1.0 mmol) and 4.0 mL of solvent; b) Yield reported are after purification through column chromatography; c) RT is room temperature and it was ranging from 25-30 °C; d) Reaction was carried out using base KOH 3 equivalent (1.5 mmol); e) Reaction was carried out using base KOH 4 equivalent (2.0 mmol).

by an unusual nucleophilic substitution of fluoro/chloro in the aryl ring due to *in situ* generated methylthio nucleophile, while use of *o/p*-bromoacetophenone afforded the only desired product without any formation of product **7**. Probably, bigger size of bromein prevents the nucleophilic attack of methylthio group.

Use of *o*-substituted acetophenone gave low to moderate yield of aryl naphthyl ketone, probably due to steric hindrance. We tried 2-hydroxyacetophenone as a nucleophile source and ended up with a complex reaction mixture, but use of 2-allyloxyacetophenone yielded the desired product in moderate yield. Apart from functionalized acetophenones, we have also used 2-acetylfuran and 2-acetylthiophene as a nucleophile source and isolated the desired product in moderate yield. We have successfully synthesized dinaphthyl ketone by using acetonaphthone as a nucleophile source in good yield. Interestingly, we have also used acetone as a nucleophile source and successfully synthesized highly functionalized acetonaphthone, which is a very interesting precursor and very difficult to synthesized by reported literature procedures.

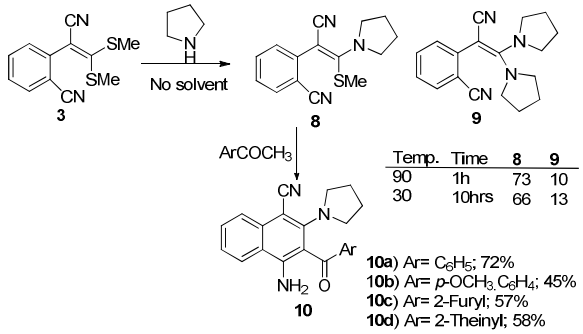
In order to further enhance the scope of this reaction, we have planned to replace the methylthio group with a secondary amine,



Scheme 3: Synthesis of various 4-amino-3-aroyl/heteroaroyl/acetyl-2-methylsulfanylnapthalene-1-carbonitriles (**5a-m** and **7**)

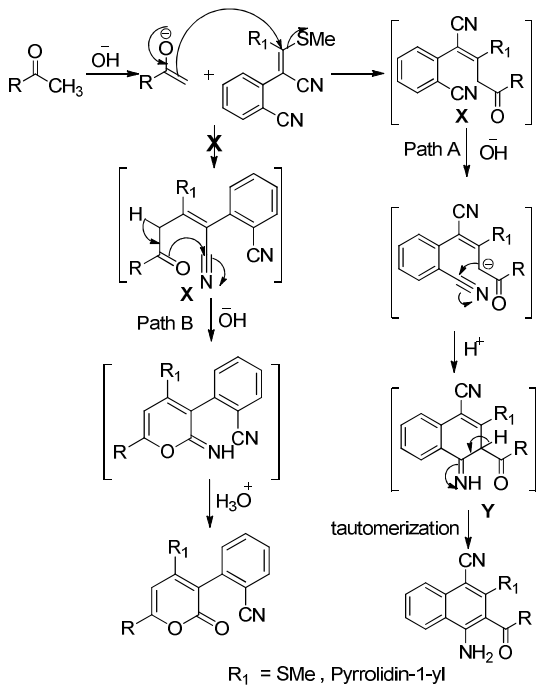
before 5C+1C annulations. We have tested various reaction conditions for the synthesis of 2-(1-cyano-2-(methylthio)-2-(pyrrolidin-1-yl)vinyl)benzonitrile, but failed to obtained a selective route to monoamination. Reaction of 2-(1-cyano-2,2-bis(methylthio)vinyl)benzonitrile and excess of pyrrolidine at 30 °C yielded a mixture of 2-(1-cyano-2-(methylthio)-2-(pyrrolidin-1-yl)vinyl)benzonitrile as a major product and 2-(1-cyano-2,2-di(pyrrolidin-1-yl)vinyl)benzonitrile as a minor product (Scheme 3). At 90ºC, the monoaminated product was isolated in 73% yield, while continuation of the reaction for longer provided the diaminated product in excess. Six membered secondary amines yielded a major diaminated product due to more nucleophilic nature of nitrogen, which was not a suitable precursor for the synthesis of naphthalene.

We have taken 2-(1-cyano-2-(methylthio)-2-(pyrrolidin-1-yl)vinyl)benzonitrile as a precursor and preformed the reaction with various functionalized aryl/heteroaryl methyl ketones, using KOH as a base in DMSO at room temperature and successfully obtained naphthalene bearing a pyrrolidine group in lieu of the methylthio group.



Scheme 4: Synthesis of 2-(1-cyano-methylsulfanyl-2-pyrrolidine-1-1yl-vinyl)-benzonitrile, 2-(1-cyano-methylsufanyl-2,2-di-pyrrolidine-1-yl-vinyl)-benzonitrile and 4-amino-3-aroyl/heteroaroyl/acetyl-2-pyrrolidin-1-yl-1-carbonitriles

Mechanistically, the reaction is possibly initiated by a nucleophilic substitution at C-2 of 2-(1-cyano-2,2-bis(methylthio)vinyl)benzonitrile by an *in situ* generated nucleophile from acetophenone with loss of the methylthio group, which leads to the formation of intermediate **X** (Scheme 5). In presence of excess base, the carbanion generated in α position to the carbonyl group, which attacks intramolecularly at the nitrile group present in ortho position, with formation of intermediate **Y** (Path A). Intermediate **Y** undergoes tautomerisation to yield the desired product. Mechanistically, there was also the possibility for the formation of 2-pyranone (Path B), but the aryl naphthyl ketone has been regioselectively isolated. We proposed that C-C bond formation by attack of the carbanion at the nitrile group present in the aryl ring is more facile than C-O bond formation due to reaction of the enolate oxygen with the other nitrile group.



Scheme 5: Proposed mechanism for synthesis of 4-amino-3-aroyl/heteroaroyl/acetyl-2-methylsulfanylnapthalene-1-carbonitriles.

In order to prove the mechanism, we have made various attempt to isolate the intermediate X, but failed. We performed the reaction using a ketone/base ratio of 2:1, but we got a mixture of products with the starting material and without any trace of intermediate. This concludes that, as soon as intermediate X forms in the reaction mixture, it immediately undergoes cyclization due to the formation of activated methylene group, which is more reactive the methyl group and cannot be isolated. We have also attempted the reaction to check that proton on amino group is coming from methyl group of aryl methyl ketone or after acidic work-up. We have performed two parallel reactions of **3** and acetone-d6 and acetone in DMSO-d6 in presence of potassium hydroxide. Reaction containing acetone shows additional peak at ~5.98 ppm in comparison to the mixture containing acetone-d6, which confirms that proton on amino group is coming from methyl group of aryl methyl ketone (See SI; Figure 1).

X-ray structural analysis

The structure of one of the products 4-amino-3-(4-methoxybenzoyl)-2-(pyrrolidin-1-yl)-1-naphthonitrile **10b** have been confirmed by X-ray crystallography (Fig. 3).[§] Compound **10b** crystallized in *P*-1 space group having two molecules in the triclinic unit cell. The naphthalene and the anisole rings are planar and the dihedral angle between the planes formed by the fused naphthalene and anisyl rings is 52.47°. The five membered pyrrolidine ring adopts a puckered half-chair conformation to relieve the strain resulting from the eclipsed orientation of the hydrogens and substituents on the adjacent carbon atoms. The proton H1b forms an intramolecular hydrogen bond with carbonyl oxygen O1 having an H1b···O1 interaction length of 1.891 Å with N1–H1b···O1 bond angle of 138.35°.

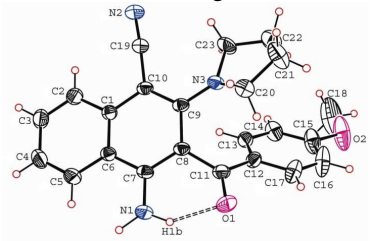


Fig. 2. ORTEP diagram of **10b** at 30% probability with atom numbering scheme. Only one molecule of the asymmetric unit comprising of two molecules is presented.

The compound displayed intermolecular N–H···N≡C interaction (Fig. 3) to form a one dimensional chain having an N···H interaction distance of 2.091 Å and interaction angle of 159.39° (symm. op. -1+*x,y,z*). Quantum chemical DFT calculations for the dimer held by N–H···N≡C interaction yielded the interaction energy of -8.18 kcal mol^{-1}. Additionally the atoms-in-molecules (AIM) theory calculations indicated the bond critical points between the H and N atoms, which also confirm the presence of this interaction between two molecules (see SI). The values of electron density (ρ) +0.019733; Laplacian (∇^2ρbcp) +0.059176; bond ellipticity (ε) +0.018129 and total energy density (H) +0.014103 at the bond critical point indicated the real interaction. The bond ellipticity (ε) measuring the extent to which the density is preferentially accumulated in a given plane of the bond path indicated that these N–H···N≡C interactions are not cylindrically symmetrical in nature.

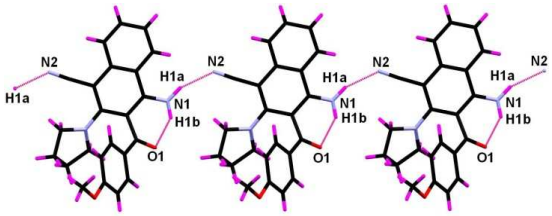


Fig. 3 One dimensional chain held by intermolecular N–H···N≡C interactions (symm. op. -1+*x,y,z*).

Conclusion

In conclusion, we have developed an economical, metal free one step (5+1) annulation strategy for the synthesis of 4-amino-3-aroyl/acetyl-2-methylsulfanyl/secamino-napthalene-1-carbonitriles. The precursor required for the synthesis of 4-amino-3-aroyl/acetylnapthalenes is easily accessible in one step in moderate to good yield. This synthesis is also atomically economical. We have not used any harsh reaction conditions and the structure was confirmed unambiguously by X-ray crystallography.

Experimental section

General remarks: We have used commercially available reagents without purification. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz NMR and 100MHz NMR spectrometer and $CDCl_3$ was used as solvent. Chemical shifts are reported in parts per million shift (δ-value) from ($CDCl_3$) (δ 7.24 ppm for ^{1}H) or based on the middle peak of the solvent ($CDCl_3$) (δ 77.00 ppm for ^{13}C NMR) as an internal standard. Signal patterns are indicated as s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; bs, broad singlet and bm, broad multiplet. Coupling constants (*J*) are given in hertz (Hz). Infrared (IR) spectra was recorded on a Perkin-Elmer AX-1 spectrophotometer and reported in wave number (cm^{-1}). HRMS reported are showing the peak for M+H$^+$. Room temperature was ranging from 25-30 ºC during the reactions.

General procedure for the synthesis of 2-(1-cyano-2,2-bismethylsulfanylvinyl)benzonitrile 3: To a well dried 100 mL RB flask added THF (40.0 mL) and sodium Hydride [60% dispersion in mineral oil] (30.0 mmol, 1.20 g) and cooled on ice-bath. 2-Cyanomethyl-benzonitrile (15.0 mmol, 2.130 g) was added drop wise to the pre-cold basic solution. After complete addition, stirred the reaction mixture for one hour followed by drop-wise addition of carbondisulphide (16.5 mmol, 0.995mL) at 0-5 ^{0}C. Reaction mixture was further stirred for another hour followed by drop-wise addition of methyl iodide (33.0 mmol, 2.055 mL) over a period of 30 minutes. The reaction mixture was stirred for one hour. After completion, excess of THF was removed under reduced pressure. The mixture was poured onto ice-water with vigorous stirring, filtered the obtained precipitate and dried under vacuum. Compound was purified by recrystallization from 2% acetone in hexane.

2-(1-cyano-2,2-bis-methylsufanyl-vinyl)-benzonitrile 3: Yield: 90% (3.321 g) ; 0.42 R_f (20% ethylacetate-hexane), light yellow solid, mp: 82-84 ^{0}C; IR (KBr): 2925, 2853, 2226, 2200 cm^{-1}; ^{1}H NMR (400 MH_Z , $CDCl_3$): δ 2.41 (s, 3H, -SCH_3), 2.64 (s, 3H, -

SCH_3), 7.43-7.49 (m, 2H, ArH), 7.61-7.66 (m, 1H, ArH), 7.70 (d, J = 8.0 Hz, 1H, Ar-H); ^{13}C NMR (100 MH_Z, $CDCl_3$): δ 18.0, 18.8, 107.1, 112.8, 116.9, 117.1, 129.1, 130.5, 133.2, 133.3, 137.8, 165.1; HRMS (ESI) calculated for $C_{12}H_{10}N_2S_2$, 247.0358 ($M+H^+$); found for *m/z*, 247.0358.

General procedure for the synthesis of 4-amino-3-aroyl-2-methylsulfanyl-napthalene-1-carbonitrile: To a 25 mL RB flask, a mixture of 2-(1-cyno-2,2-bismethylsulfanyl-vinyl)-benzonitrile (0.5 mmol, 0.123g), aryl/alkyl methyl ketone (0.55 mmol), and powdered KOH (1 mmol, 0.056g) in dry DMSO (4.0 mL) was stirred at room temperature for 2 h under dry condition. After completion (monitored by TLC) of reaction, the mixture was poured onto ice-water with constant stirring followed by neutralization with 10% HCl. The obtained precipitate was filtered off and dried. The crude product was purified by silica gel column chromatography using 15% ethylacetate in hexane as an eluent.

4-Amino-3-benzoyl-2-methylsulfanyl-napthalene-1-carbonitrile 5a: Yield: 81% (0.129 g); 0.28 R_f (20% ethylacetate-hexane), light brown solid mp: 166-168 ^{0}C; IR (KBr): 3372, 2921, 2205, 1638, 1248, 763 cm^{-1}; ^{1}H NMR (400 MH_Z, $CDCl_3$): δ 2.35 (s, 3H, -SCH_3), 5.37 (s, 2H, -NH_2), 7.39-7.47 (m, 2H, ArH), 7.53-7.63 (m, 2H, ArH), 7.69-7.76 (m, 3H, ArH), 7.84 (d, J = 8.0 Hz, 1H, ArH), 8.21 (d, J = 8.0 Hz, 1H, ArH); ^{13}C NMR (100 MH_Z, $CDCl_3$): δ 20.5, 104.6, 117.2, 120.5, 121.6, 121.6, 126.0, 127.0, 128.7, 129.1, 130.0, 133.5, 134.5, 138.5, 140.6, 145.3, 196.8; HRMS (ESI) calculated for $C_{19}H_{14}N_2OS$, 319.0900 ($M+H^+$); found for *m/z*, 319.0889.

4-Amino-3-(4-methyl-benzoyl)-2-methylsulfanyl-napthalene-1-carbonitrile 5b: Yield: 41% (0.068 g); 0.27 R_f (20% ethylacetate-hexane), light yellow, mp: 170-172 ^{0}C; IR (KBr): 3367, 2926, 2854, 2206, 1627, 1242, 752 cm^{-1}; ^{1}H NMR (400 MH_Z, $CDCl_3$): δ 2.37 (s, 3H, -SCH_3), 2.40 (s, 3H, -CH_3), 5.27 (s, 2H, -NH_2), 7.21-7.25 (m, 2H, ArH), 7.53-7.61 (m, 1H, ArH), 7.63 (d, J = 8.0 Hz, 2H, ArH), 7.69-7.75 (m, 1H, ArH), 7.83 (d, J = 8.0 Hz, 1H, ArH), 8.20 (d, J = 8.0 Hz, 1H, ArH); ^{13}C NMR (100 MH_Z, $CDCl_3$): δ 20.5, 21.7, 104.3, 117.3, 120.9, 121.6, 125.9, 126.9, 129.3, 129.4, 129.9, 134.4, 135.7, 140.3, 144.8, 145.0, 196.3; HRMS (ESI) calculated for $C_{20}H_{16}N_2OS$, 333.1056 ($M+H^+$); found for *m/z*, 333.1044.

4-Amino-3-(4-methoxy-benzoyl)-2-methylsulfanyl-napthalene-1-carbonitrile 5c: Yield: 48% (0.084 g); 0.24 R_f (20% ethylacetate-hexane), Brown solid, mp: 131-133^{0}C; IR (KBr): 3362, 2933, 2207, 1630, 1594, 1259, 752 cm^{-1}; ^{1}H NMR (400 MH_Z, $CDCl_3$): δ 2.40 (s, 3H, -SCH_3), 3.85 (s, 3H, -OCH_3), 5.19 (s, 2H, -NH_2), 6.90 (d, J = 8.8 Hz, 2H, Ar-H), 7.54-7.62 (m, 1H, ArH), 7.67-7.76 (m, 3H, ArH), 7.82 (d, J = 8.0 Hz, 1H, ArH), 8.20 (d, J = 8.0 Hz, 1H, ArH); ^{13}C NMR (100 MH_Z, $CDCl_3$): δ 20.6, 55.5, 104.4, 114.0, 117.3, 121.3, 121.5, 121.6, 126.0, 126.9, 129.8, 130.9, 131.8, 134.4, 140.2, 144.7, 164.2, 195.1; HRMS (ESI) calculated for $C_{20}H_{16}N_2O_2S$, 349.1005 ($M+H^+$); found for *m/z*, 349.0990.

4-Amino-3-(4-bromo-benzoyl)-2-methylsulfanyl-napthalene-1-carbonitrile 5d: Yield: 68% (0.135 gm); 0.26 R_f (20% ethylacetate-hexane); light yellow solid, mp: 152-154 ^{0}C; IR (KBr): 3361, 2924, 2207, 1638, 1249, 749 cm^{-1}; ^{1}H NMR (400 MH_Z, $CDCl_3$): δ 2.37 (s, 3H, -SCH_3), 5.45 (s, 2H, -NH_2), 7.51-7.69 (m, 5H, ArH), 7.70-7.78 (m, 1H ,ArH), 7.83 (d, J = 8.0 Hz, 1H, ArH), 8.21 (d, J = 8.0 Hz, 1H, ArH); ^{13}C NMR (100 MH_Z, $CDCl_3$): δ 20.6, 104.7, 117.1, 119.6, 121.6, 121.6, 126.1, 127.2, 128.7, 130.2, 130.5, 132.0, 134.5, 137.5, 140.5, 145.6, 195.7; HRMS (ESI) calculated for $C_{19}H_{13}BrN_2OS$, 397.0005 ($M+H^+$); found for *m/z*, 396.9983.

4-Amino-3-(2-bromo-benzoyl)-2-methylsulfanyl-napthalene-1-carbonitrile 5e: Yield 48% (0.095 g); 0.26 R_f (20% ethylacetate-hexane); yellow solid, mp: 188-190 ^{0}C; IR (KBr): 3369, 2925, 2211, 1609, 1245, 757 cm^{-1}; ^{1}H NMR (400 MH_Z , $CDCl_3$): δ 2.23 (s, 3H, -SCH_3), 6.56 (s, 2H, -NH_2), 7.15-7.20 (m, 1H, ArH), 7.23-7.29 (m, 2H, ArH), 7.57-7.67 (m, 2H, ArH), 7.74 (t, J = 7.7 Hz, 1H, ArH), 7.90 (d, J = 8.0 Hz, 1H, ArH), 8.17 (d, J = 8.8 Hz, 1H, ArH); ^{13}C NMR (100 MH_Z, $CDCl_3$): δ 20.4, 105.2, 117.1, 118.0, 121.3, 121.8, 121.9, 126.1, 126.9, 127.2, 130.1, 130.8, 131.7, 134.2, 134.6, 142.4, 142.6, 148.9, 196.7; HRMS (ESI) calculated for $C_{19}H_{13}BrN_2OS$, 397.0005 ($M+H^+$); found for *m/z*, 397.0007.

3-(2-Allyloxy-benzoyl)-4-amino-2-methylsulfanyl-napthalene-1-carbonitrile 5f: Yield: 60% (0.112 g); 0.37 R_f (40% ethylacetate-hexane), light yellow, mp: 165-167 ^{0}C; IR (KBr): 3372, 2929, 2208, 1610, 1240, 757 cm^{-1}; ^{1}H NMR (400 MH_Z, $CDCl_3$): δ 2.26 (s, 3H, -SCH_3), 4.29-4.33 (m, 2H , -CH_2-), 4.78-4.86 (dd, J = 1.4 Hz, 1H, CH), 4.96-5.06 (m, 1H, CH), 5.32-5.46 (m, 1H, CH), 5.88 (s, 2H, -NH_2), 6.85 (d, J = 8.0 Hz, 1H, ArH), 6.99 (t, J = 7.7 Hz, 1H, ArH), 7.38-7.47 (m, 1H, ArH), 7.56 (t, J = 7.7 Hz, 1H, ArH), 7.60-7.64 (m, 1H, ArH), 7.69 (t, J = 7.7 Hz, 1H, ArH), 7.84 (d, J = 8.8 Hz, 1H, ArH), 8.15 (d, J = 8.8 Hz, 1H, ArH); ^{13}C NMR (100 MH_Z, $CDCl_3$): δ 20.2, 69.1, 104.2, 112.7, 117.4, 117.7, 120.7, 121.7, 122.0, 122.2, 125.9, 126.7, 129.9, 130.0, 130.9, 131.8, 133.7, 134.3, 141.6, 146.1, 157.4, 196.0; HRMS (ESI) calculated for $C_{22}H_{18}N_2O_2S$, 375.1162 ($M+H^+$); found for *m/z*, 375.1161.

4-Amino-3-(furan-2-carbonyl)-2-methylsulfanyl-napthalene-1-carbonitrile 5g: Yield: 60% (0.092 g); 0.30 R_f (40% ethylacetate-hexane), dark green solid, mp: 196-98 ^{0}C; IR (KBr): 3371, 2925, 2209, 1618, 1298, 756 cm^{-1}; ^{1}H NMR (400 MH_Z, $CDCl_3$): δ 2.46 (s, 3H, -SCH_3), 5.46 (s, 2H, -NH_2), 6.53-6.57 (dd, J = 1.4 Hz, 1H, ArH), 7.03 (d, J = 3.6 Hz, 1H, ArH), 7.55-7.64 (m, 2H, ArH), 7.69-7.76 (m, 1H, ArH), 7.83 (d, J = 8.0 Hz, 1H, ArH), 8.19 (d, J = 8.05 Hz, 1H, ArH); ^{13}C NMR (100 MH_Z, $CDCl_3$): δ 20.0, 100.0, 112.9, 117.6. 119.5, 120.6, 121.4, 123.8, 124.4, 126.3, 130.2, 134.1, 139.2, 146.6, 148.6, 152.8, 182.1; HRMS (ESI) calculated for $C_{17}H_{12}N_2O_2S$, 309.0692 ($M+H^+$); found for *m/z*, 309.0677.

4-Amino-2-methylsulfanyl-3-(thiophene-2-carbonyl)-napthalene-1-carbonitrile 5h: Yield: 61% (0.099 g); 0.31 R_f (30% ethylacetate-hexane), yellow solid mp: 173-175 ^{0}C; IR (KBr): 3362, 2929, 2207, 1624, 1271, 727 cm^{-1}; ^{1}H NMR (400 MH_Z, $CDCl_3$): δ 2.47 (s, 3H, -SCH_3), 5.24 (s, 2H, -NH_2), 7.06-7.10 (m, 1H, ArH), 7.32-7.37 (m, 1H, ArH), 7.56-7.63 (m, 1H, ArH), 7.69-7.76 (m, 2H, ArH), 7.82 (d, J = 8.8 Hz, 1H, ArH), 8.21 (d, J = 8.0 Hz,1H, ArH); ^{13}C NMR (100 MH_Z, $CDCl_3$): δ 20.9, 104.5, 117.2, 121.2, 121.5, 121.6, 126.0, 127.0, 128.3, 130.0, 134.4, 134.8, 135.5, 140.2, 144.7, 145.1, 188.3; HRMS (ESI) calculated for $C_{17}H_{12}N_2OS_2$, 325.0464 ($M+H^+$); found for *m/z*, 325.0450.

4-Amino-2-methylsulfanyl-3-(naphthalene-1-carbonyl)-napthalene-1-carbonitrile 5i: Yield: 48% (0.088 g); 0.25 R_f

(20% ethylacetate-hexane), orange solid, mp: 187-189 ^{0}C; IR (KBr): 3372, 2925, 2210, 1609, 1240, 759 cm^{-1}; ^{1}H NMR (400 MH$_Z$, CDCl$_3$): δ 2.12 (s, 3H, -SCH$_3$), 5.95 (s, 2H, -NH$_2$), 7.22-7.35 (m, 2H, ArH), 7.55-7.71 (m, 4H ,ArH), 7.90 (d, *J* = 8.0 Hz, 2H, ArH), 7.95 (d, *J* = 8.0 Hz, 1H, ArH), 8.19 (d, *J* = 8.0 Hz, 1H, ArH), 8.78 (d, *J* = 8.0 Hz, 1H, ArH); ^{13}C NMR (100 MH$_Z$, CDCl$_3$): δ 20.3, 104.9, 117.2, 121.1, 121.6, 121.8, 124.0, 126.0, 126.7, 127.1, 128.2, 128.5, 128.8, 130.3, 130.7, 133.1, 134.0, 134.6, 137.6, 141.9, 146.8, 198.9; HRMS (ESI) calculated for $C_{23}H_{16}N_2OS$, 369.1056 (M+H$^+$); found for *m/z*, 369.1038.

4-Amino-2-methylsulfanyl-3-(naphthalene-2-carbonyl)-napthalene-1-carbonitrile 5j: Yield: 68% (0.125 g); 0.25 R$_f$ (20% ethylacetate-hexane), yellow solid, mp: 192-193 ^{0}C; IR (KBr): 3372, 2925, 2208, 1617, 1291, 754 cm^{-1}; ^{1}H NMR (400 MH$_Z$, CDCl$_3$): δ 2.34 (s, 3H, -SCH$_3$), 5.38 (s, 2H, -NH$_2$), 7.47-7.53 (m, 1H, ArH), 7.55-7.66 (m, 2H ,ArH), 7.75 (t, *J* = 7.3 Hz, 1H, ArH), 7.82 (d, *J* = 8.0 Hz, 1H, ArH), 7.85-7.90 (m, 2H, ArH), 7.90-7.96 (m, 2H, ArH), 8.07 (s, 1H, ArH), 8.25 (d, *J* = 8.0Hz, 1H, ArH); ^{13}C NMR (100 MH$_Z$, CDCl$_3$): δ 20.6, 104.7, 117.2, 120.8, 121.6, 121.7, 124.3, 126.1, 126.9, 127.0, 127.8, 128.8, 129.6, 130.0, 131.1, 132.4, 134.5, 135.8, 135.9, 140.6, 145.4, 196.7; HRMS (ESI) calculated for $C_{23}H_{16}N_2OS$, 369.1056 (M+H$^+$); found for *m/z*, 369.1033.

3-Acetyl-4-amino-2-methylsulfanyl-napthalene-1-carbonitrile 5k: Yield: 45% (0.058 gm); 0.35 R$_f$ (20% ethylacetate-hexane), light brown solid, mp: 140-142 ^{0}C; IR (KBr): 3373, 2925, 2854, 2210, 1611, 1234, 757 cm^{-1}; ^{1}H NMR (400 MH$_Z$, CDCl$_3$): δ 2.56 (s, 3H, -SCH$_3$), 2.70 (s, 3H, -CH$_3$), 6.04 (s, 2H, -NH$_2$), 7.48-7.60 (m, 1H, ArH), 7.65-7.72 (m, 1H, ArH), 7.83 (d, *J* = 8.8 Hz, 1H, ArH), 8.14 (d, *J* = 8.0 Hz, 1H, ArH); ^{13}C NMR (100 MH$_Z$, CDCl$_3$): δ 20.7, 32.6, 104.5, 117.2, 120.9, 121.7, 122.0, 126.0, 127.0, 130.3, 134.1, 140.5, 145.7, 204.1; HRMS (ESI) calculated for $C_{14}H_{12}N_2OS$, 257.0743 (M+H$^+$); found for *m/z*, 257.0730.

4-Amino-3-(4-fluoro-benzoyl)-2-methylsulfanyl-napthalene-1-carbonitrile 5l: Yield: 52% (0.087 g); 0.30 R$_f$ (20% ethylacetate-hexane), yellow solid, mp: 144-146 ^{0}C; IR (KBr): 3328, 2929, 2209, 1611, 1228, 757 cm^{-1}; ^{1}H NMR (400 MH$_Z$, CDCl$_3$): δ 2.37 (s, 3H, -SCH$_3$), 5.49 (s, 2H, -NH$_2$), 7.10 (t, *J* = 8.79Hz, 2H, ArH), 7.60 (t, *J* = 7.3 Hz, 1H, ArH), 7.70-7.78 (m, 3H, ArH), 7.83 (d, *J* =8.0 Hz, 1H, ArH), 8.21 (d, *J* = 8.8 Hz, 1H, ArH); ^{13}C NMR (100 MH$_Z$, CDCl$_3$): δ 20.5, 104.6, 115.6 (d, $J_{C\text{-}F}$ = 22.0 Hz), 117.1, 120.1, 121.6, 126.6, 127.1, 130.1, 131.8 (d, $J_{C\text{-}F}$ = 9.6 Hz), 134.4, 134.8, 134.9, 140.4, 145.3, 166.0 (d, $J_{C\text{-}F}$ = 253.9Hz), 195.2; HRMS (ESI) calculated for $C_{19}H_{13}FN_2OS$, 337.0805 (M+H$^+$); found for *m/z*, 337.0789.

4-Amino-3-(4-chloro-benzoyl)-2-methylsulfanyl-napthalene-1-carbonitrile 5m: Yield: 48% (0.085 g); 0.31 R$_f$ (20% ethylacetate-hexane), orange solid, mp: 135-137 ^{0}C; IR (KBr): 3377, 2925, 2210, 1620, 1261, 757 cm^{-1}; ^{1}H NMR (400 MH$_Z$, CDCl$_3$): δ 2.37 (s, 3H, -SCH$_3$), 5.42 (s, 2H, -NH$_2$), 7.39 (d, *J* = 8.8 Hz, 2H, ArH), 7.57-7.67 (m, 3H ,ArH), 7.71-7.77 (m, 1H, ArH), 7.83 (d, *J* = 8.8 Hz, 1H, ArH), 8.21 (d, *J* = 8.0 Hz, 1H, ArH); ^{13}C NMR (100 MH$_Z$, CDCl$_3$): δ 20.5, 104.4, 117.1, 119.6, 121.6, 121.6, 126.0, 127.1, 129.0, 130.2, 130.4, 134.4, 136.9, 139.9, 140.4, 145.6, 195.6; HRMS (ESI) calculated for $C_{19}H_{13}ClN_2OS$, 353.0510 (M+H$^+$); found for *m/z*, 353.0490.

4-Amino-2-methylsulfanyl-3-(4-methylsulfanyl-benzoyl)-napthalene-1-carbonitrile 7: Yield: 30% (0.055 g); 0.30 R$_f$ (30% ethylacetate-hexane), yellow solid, mp: 137-139 ^{0}C; IR (KBr): 3375, 2919, 2206, 1636, 1248, 755 cm^{-1}; ^{1}H NMR (400 MH$_Z$, CDCl$_3$): δ 2.40 (s, 3H, -SCH$_3$), 2.50 (s, 3H, -SCH$_3$), 5.28 (s, 2H, -NH$_2$), 7.20-7.26 (m, 2H, ArH), 7.56-7.68 (m, 3H ,ArH), 7.70-7.77 (m, 1H, ArH), 7.83 (d, *J* = 8.8 Hz, 1H, ArH) , 8.22 (d, *J* = 8.8 Hz, 1H, ArH); ^{13}C NMR (100 MH$_Z$, CDCl$_3$): δ 14.6, 20.6, 104.4, 117.2, 120.7, 121.5, 124.9, 126.0, 127.0, 129.6, 129.9, 134.3, 134.4, 140.3, 145.0, 147.1, 195.6; HRMS (ESI) calculated for $C_{20}H_{16}N_2OS_2$, 365.0777 (M+H$^+$); found for *m/z*, 365.0780.

General procedure synthesis of 2-(1-cyano-2-methylsulfanyl-2-pyrrolidine-1-yl-vinyl)-benzonitrile. A mixture of 2-(1-cyno-2,2-bismethylsulfanyl-vinyl)-benzonitrile (1 mmol, 0.246g), pyrrolidine (as a solvent 5.0 mL) was stirred at 90 °C temperature for 1h. After completion (monitored by TLC) of reaction, the mixture was poured onto ice-water with constant stirring followed by neutralization with 10% HCl. The obtained precipitate was filtered off and dried over Na_2SO_4. Crude contains both mono and diaminated product. The crude product was purified by silica gel column chromatography using 20% ethylacetate-hexane as an eluent for monoaminated product and 25% ethyl acetate in hexane as an eluent for diaminated product.

2-(1-Cyano-2-methylsulfanyl-2-pyrrolidine-1-yl-vinyl)-benzonitrile 8: 2-(1-Cyano-2-methylsulfanyl-2-pyrrolidine-1-yl-vinyl)-benzonitrile 8: Yield: 73% (0.196 gm); red, 0.32 R$_f$ (20% ethylacetate-hexane), mp: 191-193 ^{0}C; IR (KBr) 2924, 2853, 2220, 2181, 1514, 1252, 761 cm^{-1}; ^{1}H NMR (400 MH$_Z$, CDCl$_3$): δ 1.83-1.93 (bm, 4H , -CH$_2$-), 2.56 (s, 3H , -SCH$_3$), 3.10-3.60 (bm, 4H, -CH$_2$-), 7.15-7.22 (m, 1H, ArH), 7.45-7.58 (m, 3H, ArH); ^{13}C NMR (100 MH$_Z$ CDCl$_3$): δ 18.9, 25.3, 52.6, 111.7, 118.0, 122.1, 125.7, 129.6, 132.6, 132.8, 141.4, 165.6; HRMS (ESI) calculated for $C_{15}H_{15}N_3S$, 270.1059 (M+H$^+$); found for *m/z*, 270.1059.

2-(1-Cyano-2,2-di-pyrrolidine-1-yl-vinyl)-benzonitrile 9: Yield: 10% (0.029 gm); 0.30 R$_f$ (10% ethylacetate-hexane), light red, mp: 120-122 ^{0}C; IR (KBr): 2925, 2869, 2181, 1537, 1295, 756, cm^{-1}; ^{1}H NMR (400 MH$_Z$, CDCl$_3$): δ 1.92-2.00 (m, 8H , -CH$_2$-), 3.76-3.87 (m, 8H, -CH$_2$-), 7.00-7.08 (m, 1H, ArH), 7.40-7.50 (m, 1H, ArH), 7.78 (d, *J* = 8.0 Hz, 1H, ArH), 7.96 (d, *J* = 8.0, 1H, ArH); ^{13}C NMR (100 MH$_Z$, CDCl$_3$): δ 25.5, 25.8, 48.7, 51.2, 69.2, 113.7, 120.5, 121.8, 122.5, 126.2, 130.6, 141.9, 155.5, 157.1.

General procedure synthesis of 4-amino-3-aroyl-2-pyrrolidin-1-yl-napthalene-1-carbonitriles: A mixture of 2-(1-cyano-2-methylsulfanyl-2-pyrrolidine-1-yl-vinyl)-benzonitrile (0.5 mmol, 0.134 g), ketone (0.55 mmol), and powdered KOH (1 mmol, 0.056 g) in dry DMSO (4.0 mL) was stirred at room temperature for 2 h. After completion (monitored by TLC) of reaction, the mixture was poured onto ice-water with constant stirring followed by neutralization with 10% HCl. The obtained precipitate was filtered, dried and purified by silica gel column chromatography using 20% ethylacetate-hexane as an eluent.

4-Amino-3-benzoyl-2pyrrolidin-1-yl-napthalene-1-carbonitrile 10a: Yield: 72% (0.123 g); 0.32 R$_f$ (20% ethylacetate-hexane), brown solid, mp: 192-194 ^{0}C; IR (KBr): 3325, 2925, 2855, 2192, 1608, 1256, 755 cm^{-1}; ^{1}H NMR (400 MH$_Z$, CDCl$_3$): δ 1.32-1.37 (m, 4H ,-CH$_2$-), 3.39-3.45 (m, 4H, -CH$_2$-), 6.42 (s, 2H, -NH$_2$), 7.31-7.39 (m, 3H, ArH), 7.44-7.51 (m, 1H ,ArH), 7.54-7.65 (m, 3H, ArH), 7.73 (d, *J* = 8.0 Hz, 1H, ArH),

8.03 (d, *J* = 8.0 Hz, 1H, ArH); ^{13}C NMR (100 MH_Z, $CDCl_3$): δ 25.2, 51.8, 109.2, 118.7, 120.4, 121.6, 123.7, 124.8, 128.0, 128.7, 130.6, 132.2, 136.7, 139.9, 149.2, 153.4, 197.0; HRMS (ESI) calculated for $C_{22}H_{19}N_3O$, 342.1601 ($M+H^+$); found for *m/z*, 342.1601.

4-Amino-3-(4-methoxy-benzoyl)-2-pyrrolidin-1-yl-napthalene-1-carbonitrile 10b: Yield: 45% (0.083 g); 0.31 R_f (20% ethylacetate-hexane), light yellow, mp: 197-199 ^{0}C; IR (KBr): 3351, 2924, 2191, 1594, 1251, 763 cm^{-1}; ^{1}H NMR (400 MH_Z , $CDCl_3$): δ 1.42-1.47(m, 4H , $-CH_2-$), 3.44-3.50 (m, 4H, $-CH_2-$), 3.83 (s, 3H, $-OCH_3$), 6.17 (s, 2H, $-NH_2$) , 6.84 (d, *J* = 8.8 Hz, 2H, ArH), 7.29-7.35 (m, 1H ,ArH), 7.57-7.63 (m, 3H, ArH), 7.70 (d, *J* = 8.0 Hz, 1H, ArH), 8.03 (d, *J* = 8.8 Hz, 1H, ArH); ^{13}C NMR (100 MH_Z, $CDCl_3$): δ 25.4, 51.9, 55.4, 82.8, 109.3, 113.3, 118.7, 120.6, 121.6, 123.5, 124.7, 130.4, 131.2, 132.0, 136.6, 148.5, 153.1, 163.1, 195.8; HRMS (ESI) calculated for $C_{23}H_{21}N_3O_2$, 372.1707 ($M+H^+$); found for *m/z*, 372.1684.

4-Amino-3-(furan-2-carbonyl)-2-pyrrolidin-1-yl-napthalene-1-carbonitrile 10c: Yield: 57% (0.094 g); 0.21 R_f (20% ethylacetate-hexane), orange solid, mp: 170-172 ^{0}C; IR (KBr): 2926, 2225, 1618, 1227, 757 cm^{-1}; ^{1}H NMR (400 MH_Z , $CDCl_3$): δ 1.62-1.67 (m, 4H , $-CH_2-$), 3.58-3.64 (m, 4H,- CH_2-), 6.23 (s, 2H, $-NH_2$), 6.45-6.48 (dd, *J* = 2.2 Hz, 1H, ArH), 6.91 (d, *J* = 2.9 Hz, 1H, ArH), 7.26-7.33 (m, 1H, ArH), 7.52-7.62 (m, 2H, ArH), 7.68 (d, *J* = 8.8 Hz, 1H, ArH), 8.00 (d, *J* = 8.8 Hz, 1H, ArH); ^{13}C NMR (100 MH_Z, $CDCl_3$): δ 25.7, 52.2, 82.3, 108.0, 112.1, 117.8, 118.3, 120.7, 121.6, 123.4, 124.7, 130.7, 137.0, 146.2, 148.7, 152.7, 153.6, 183.5; HRMS (ESI) calculated for $C_{20}H_{17}N_3O_2$, 332.1394 ($M+H^+$); found for *m/z*, 332.1396 .

4-Amino-2-pyrrolidin-1-yl-3-(thiophene-2-carbonyl)-napthalene-1-carbonitrile 10d: Yield: 58% (0.101 g); 0.30 R_f (20% ethylacetate-hexane), yellow solid, mp: 171-173 ^{0}C; IR (KBr): 3349, 2925, 2854, 2190, 1597, 1253, 759 cm^{-1}; ^{1}H NMR (400 MH_Z, $CDCl_3$): δ 1.57-1.67 (m, 4H , $-CH_2-$), 3.59-3.65 (m, 4H, $-CH_2-$), 6.09 (s, 2H, $-NH_2$), 6.99-7.04 (m, 1H, ArH), 7.27-7.36 (m, 2H, ArH), 7.56-7.62 (m, 2H, ArH), 7.68 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.02 (d, *J* = 8.0 Hz, 1H, ArH); ^{13}C NMR (100 MH_Z, $CDCl_3$): δ 25.6, 52.2, 82.5, 109.0, 118.3, 120.6, 121.6, 123.4, 124.6, 127.6, 130.5, 133.0, 133.3, 136.8, 145.3, 148.0, 152.2, 188.5; HRMS (ESI) calculated for $C_{20}H_{17}N_3OS$, 348.1165 ($M+H^+$); found for *m/z*, 348.1147.

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§ Crystal data for **10b** (CCDC 967742): $C_{23}H_{21}N_3O_2$, FW= 371.43, Triclinic, P -1, *a* = 9.094(5) Å, *b* = 13.650(5) Å, *c* = 16.253(5) Å, α = 80.99(3), β = 85.10(3), γ = 72.87(4) V = 1902.6(14) $Å^3$, T = 298(2) K, Z = 4, μ, mm^{-1} = 0.084, d_{calc}, g cm^{-3} = 1.297, R_1 [$I > 2\sigma(I)$] = 0.0787, wR_2 = 0.1529, R_1 [all data] = 0.1815, wR_2 = 0.2068, S = 1.010.

† Electronic Supplementary Information (ESI) available: Crystallographic and Computations details and CIF file for **10b**. See DOI: 10.1039/b000000x/

† Electronic Supplementary Information (ESI) available: [All the proton and ^{13}C NMR spetra are given in SI]. See DOI: 10.1039/b000000x/

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