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A diversity oriented synthesis of highly functionalized unsymmetrical biaryls through carbanion induced ring transformation of 2*H*-pyran-2-ones☆

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Abstract—A new route for the synthesis of unsymmetrical biaryls endowed with electron withdrawing and donating substituents is delineated through base catalyzed ring transformation of 2*H*-pyran-2-ones with malononitrile in a single step. This procedure offers the flexibility of introducing desired functionalities in aromatic rings, which are difficult to obtain by other classical routes.

Biaryls with electron donating and withdrawing substituents occupy a unique place in various classes of organic compounds not only due to their prevalence as the core framework of numerous natural products[1] but also their use as chiral reagents,[2] as chiral phases for chromatography[3] and as a building block of chiral liquid crystals.[4] Although the synthesis of symmetrical and unsymmetrical biaryls has been extensively investigated by various groups, the key step in such syntheses is almost always the inter- or intramolecular cross-coupling of two aromatic rings in the presence of metal complexes. However, the process of achieving symmetrical and unsymmetrical biaryls endowed with electronegative or electropositive groups is still a major problem in the synthesis of natural products.

The reductive dimerization of aryl halides is one of the oldest methods for the preparation of biaryl compounds. The classical Ullmann reaction[5] has commonly been employed to generate biaryls with electronegative groups. The most commonly used process to obtain symmetrical and unsymmetrical biaryls is through Suzuki cross-coupling reactions.[6] A recent improvement of the Suzuki coupling is the introduction of phosphine-free catalytic systems.[7]

Recently, Pd-catalyzed cross-coupling of aromatic halides with organometallic complexes has been found to be a versatile route for C–C bond formation.[8] Although these procedures have acquired wide popularity in synthetic chemistry, most of them suffer with limitations to harsh reaction conditions or functional group intolerance and/or difficulty in obtaining various metal complexes.[9]

4-Aryl-3-cyanoanthranilate and 4-arylanthranilodinitrile may be considered as biaryls in which one of the two-phenyl rings is endowed either with carbomethoxy, amino and nitrile functionalities or amino groups flanked with dinitrile substituents. There are reports in the literature where biaryl compounds with an amino function juxtaposed with nitrile groups have been either synthesized by the reaction of α,β-unsaturated carbonyl compounds with malononitrile[10] or by the reaction of hydroxy methylene ketones and enaminoketones with malononitrile[11] separately, but they suffer from low yield of the desired product. Thus, there is increasing demand to develop an efficient and convenient synthesis of highly functionalized biaryls particularly those with electron donor and acceptor substituents. Here, we describe an expeditious route for the synthesis of suitably functionalized biaryls through carbanion induced ring transformation of 2*H*-pyran-2-ones using malononitrile as a source of the carbanion.

1. Results and discussion

Our strategy to synthesize 4-aryl-3-cyanoanthranilate is based on the carbanion induced ring transformation of 6-aryl-3-carbomethoxy-4-methylsulfanyl-2*H*-pyran-2-ones[12] (**1**) with malononitrile (**2**). These 2*H*-pyran-2-ones may be considered as cyclic ketene hemithioacetals and have been prepared by the reaction of methyl 3,3′-dimethylthioacrylate with acetophenones as described earlier.[12] The reaction of **1** with malononitrile at room

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Keywords: biaryls; 2*H*-pyran-2-ones; carbanion; coupling reaction; ring transformation.

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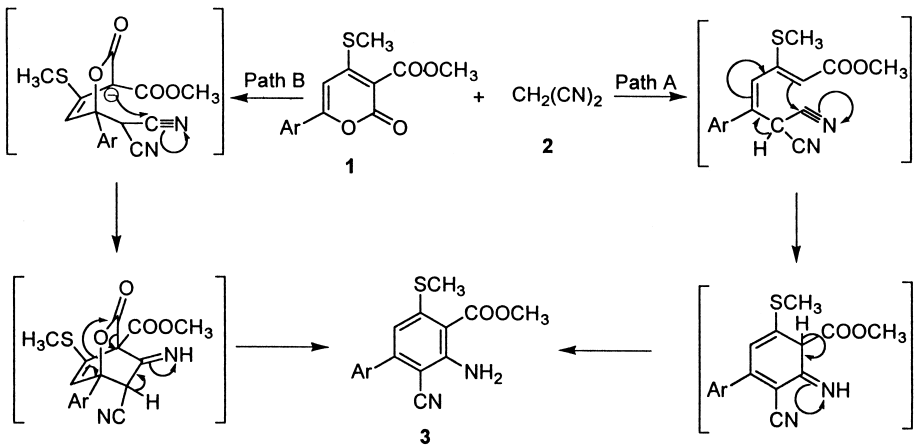


3	Ar	Yield (%)
a	C_6H_5	40
b	4-FC_6H_4	47
c	3-ClC_6H_4	40
d	4-ClC_6H_4	48
e	4-BrC_6H_4	45
f	4-$CH_3C_6H_4$	45
g	2-pyridyl	40
h	3-pyridyl	50
i	4-pyridyl	44
j	2-thienyl	49

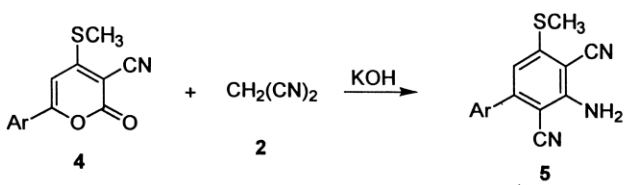
Scheme 1.

temperature under an inert atmosphere led to the formation of the ring transformed products methyl 3-amino-2-cyano-5-methylsulfanyl[1,1′-biphenyl]-4-carboxylates (**3**) in moderate yield. The results are shown in Scheme 1.

To study the influence of electron withdrawing substituents at position 3 of the pyran ring by replacing carbomethoxy group with cyano functionality a reaction of 6-aryl-3-cyano-4-methylsulfanyl-2*H*-pyran-2-one (**4**) with malononitrile in presence of base was carried out and the product isolated, characterized as 3-amino-5-methylsulfanyl-4′-substituted[1,1′-biphenyl]-2,4-dicarbonitriles (**5**) in good yields (Scheme 2).

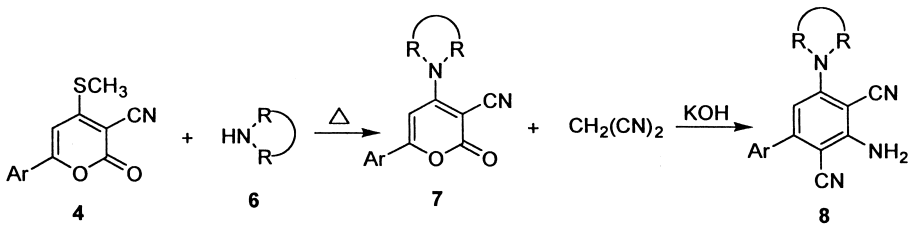
The reaction was further exploited for the construction of unsymmetrical biaryls in which one of the phenyl rings is substituted with amino and cyano groups. The precursors 6-aryl-3-cyano-4-*sec*-amino-2*H*-pyran-2-ones (**7**) used for the ring transformation reactions were prepared by the reaction of **4** with secondary amines (**6**) at reflux temperature. Thus, reaction of **7** with malononitrile in the presence of alkali at room temperature afforded highly functionalized biaryls such as 3-amino-5-*sec*-amino-4′-substituted[1,1′-biphenyl]-2,4-dicarbonitriles (**8**) in moderate yields (Scheme 3).

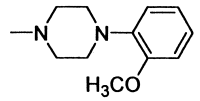
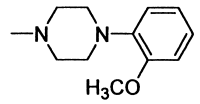
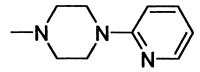
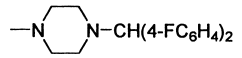
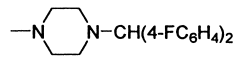
A plausible mechanism for the formation of these products may be the initial attack of the carbanion generated in situ from malononitrile at position C_6 of the pyran ring, a highly electropositive center, followed by ring opening,



5	Ar	Yield (%)
a	C_6H_5	40
b	4-$CH_3C_6H_4$	45
c	4-$CH_3OC_6H_4$	43
d	4-BrC_6H_4	51
e	4-ClC_6H_4	50
f	3-Cl,4-FC_6H_4	32
g	4-$NO_2C_6H_4$	51
h	1-naphthyl	32

Scheme 2.



8	—N(R)R	Ar	Yield (%)
a	$N(CH_3)_2$	4-FC_6H_4	48
b	$N(CH_3)_2$	4-$CH_3C_6H_4$	55
c		4-ClC_6H_4	45
d		4-BrC_6H_4	44
e		4-ClC_6H_4	52
f		4-BrC_6H_4	48
g		4-FC_6H_4	39
h		4-ClC_6H_4	39
i		4-$CH_3OC_6H_4$	42

Scheme 3.

decarboxylation and re-cyclization to yield unsymmetrical biaryls (Path A, Scheme 1). This reaction may also proceed via an inverse electron demand Diels–Alder type cycloaddition reaction with malononitrile, followed by elimination of carbon dioxide to yield biaryl compounds (Path B, Scheme 1). Since the reaction is performed at ambient temperature (~25°C) under very mild reaction conditions, Path A seems to be highly probable. The beauty of the procedure lies in the creation of molecular diversity by synthesizing highly functionalized cyanoanthranilates and anthranilo-1,3-dinitriles, which are difficult to obtain in a single step from easily accessible precursors.

In summary, our synthetic approach is superior to the existing procedures in many ways such as (a) mild reaction conditions, (b) use of inexpensive reagents, (c) versatility and compatibility of functional groups, and (d) easy work-up process. Hence, this methodology should prove to be of value in the preparation of highly functionalized biaryls in which concurrent or systematic variation in an aryl ring is required.

2. Experimental

Mps were determined on Büchi-530 apparatus in an open capillary and are uncorrected. The reagent grade reaction solvent DMF was further purified and dried following the literature procedure. Malononitrile was purchased from Aldrich. TLC was performed on precoated silica gel plastic plates and visualized by UV irradiation, exposure to iodine vapors or spraying with $KMnO_4$ solution. IR spectra of liquid samples were run neat, and solids as KBr pellets on a Perkin–Elmer AC-1 instrument. ^1H NMR spectra were recorded at 200 MHz (Brucker WM-200) in $CDCl_3$ with tetramethylsilane as internal reference. Chemical shifts and coupling constants J are reported in δ (ppm) and Hz, respectively. Mass spectra were collected at 70 eV using Jeol JMS-300 spectrometer. Elemental analyses (C, H, and N) were determined on a Carlo Erba EA-1108 at RSIC, Central Drug Research Institute, Lucknow 226001, India.

2.1. Synthesis of methyl 3-amino-2-cyano-5-(methylsulfanyl)[1,1′-biphenyl]-4-carboxylates (3), general procedure

A mixture of 6-aryl-3-carbomethoxy-4-methylsulfanyl-2*H*-pyran-2-one **1** (1 mmol), malononitrile (0.08 g, 1.2 mmol) and KOH (0.07 g, 1.2 mmol) in dry DMF (12 mL) was stirred at room temperature for 20 h. After completion of the reaction, mixture was poured into ice water with vigorous stirring and finally neutralized with 10% HCl. The solid thus obtained was filtered and purified on a silica gel column using chloroform as eluent.

2.1.1. Methyl 3-amino-2-cyano-5-(methylsulfanyl)[1,1′-biphenyl]-4-carboxylate (3a). White solid; mp 169–170°C;

[Found: C, 64.54; H, 4.77; N, 9.44. $C_{16}H_{14}N_2O_2S$ requires C, 64.41; H, 4.73; N, 9.39%]; ν_{max} (KBr) 3444, 2209, 1672 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.45 (s, 3H, SCH_3), 3.98 (s, 3H, OCH_3), 6.41 (brs, 2H, NH_2), 6.55 (s, 1H, ArH), 7.51 (m, 5H, ArH); *m/z* (EI) 298 (M^+), 266.

2.1.2. Methyl 3-amino-2-cyano-4′-fluoro-5-(methylsulfanyl)[1,1′-biphenyl]-4-carboxylate (3b). White solid; mp 185–186°C; [Found: C, 60.81; H, 4.21; N, 8.93. $C_{16}H_{13}FN_2O_2S$ requires C, 60.75; H, 4.14; N, 8.85%]; ν_{max} (KBr) 3425, 2212, 1670 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.44 (s, 3H, SCH_3), 3.97 (s, 3H, OCH_3), 6.42 (brs, 2H, NH_2), 6.53 (s, 1H, ArH), 7.18 (m, 2H, ArH), 7.82 (m, 2H, ArH); *m/z* (EI) 316 (M^+), 288.

2.1.3. Methyl 3-amino-3′-chloro-2-cyano-5-(methylsulfanyl)[1,1′-biphenyl]-4-carboxylate (3c). White solid; mp 169–170°C; [Found: C, 57.89; H, 3.97; N, 8.58. $C_{16}H_{13}ClN_2O_2S$ requires C, 57.74; H, 3.94; N, 8.41%]; ν_{max} (KBr) 3444, 2209, 1672 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.45 (s, 3H, SCH_3), 3.98 (s, 3H, OCH_3), 6.42 (brs, 2H, NH_2), 6.55 (s, 1H, ArH), 7.44 (m, 3H, ArH), 7.49 (s, 1H, ArH); *m/z* (EI) 332 (M^+), 299, 176.

2.1.4. Methyl 3-amino-4′-chloro-2-cyano-5-(methylsulfanyl)[1,1′-biphenyl]-4-carboxylate (3d). White solid; mp 184–186°C; [Found: C, 57.83; H, 3.98; N, 8.52. $C_{16}H_{13}ClN_2O_2S$ requires C, 57.74; H, 3.94; N, 8.41%]; ν_{max} (KBr) 3422, 2208, 1680 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.44 (s, 3H, SCH_3), 3.98 (s, 3H, OCH_3), 6.42 (brs, 2H, NH_2), 6.50 (s, 1H, ArH), 7.47 (s, 4H, ArH); *m/z* (EI) 332 (M^+), 300, 176.

2.1.5. Methyl 3-amino-4′-bromo-2-cyano-5-(methylsulfanyl)[1,1′-biphenyl]-4-carboxylate (3e). White solid; mp 210–211°C; [Found: C, 51.11; H, 3.52; N, 7.48. $C_{16}H_{13}BrN_2O_2S$ requires C, 50.93; H, 3.47; N, 7.42%]; ν_{max} (KBr) 3448, 2203, 1670 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.43 (s, 3H, SCH_3), 3.97 (s, 3H, OCH_3), 6.41 (brs, 2H, NH_2), 6.49 (s, 1H, ArH), 7.41 (d, 2H, *J*=8.2 Hz, ArH), 7.62 (d, 2H, *J*=8.2 Hz, ArH); *m/z* (EI) 377 (M^+), 345.

2.1.6. Methyl 3-amino-2-cyano-4′-methyl-5-(methylsulfanyl)[1,1′-biphenyl]-4-carboxylate (3f). White solid; mp 209–210°C; [Found: C, 65.43; H, 5.23; N, 9.03. $C_{17}H_{16}N_2O_2S$ requires C, 65.35; H, 5.18; N, 8.96%]; ν_{max} (KBr) 3440, 2212, 1687 cm^1; δ_H (200 MHz, $CDCl_3$) 2.43 (s, 6H, SCH_3, CH_3), 3.97 (s, 3H, OCH_3), 6.40 (brs, 2H, NH_2), 6.53 (s, 1H, ArH), 7.28 (d, 2H, *J*=8.0 Hz, ArH), 7.43 (d, 2H, *J*=8.0 Hz, ArH); *m/z* (EI) 312 (M^+), 280.

2.1.7. Methyl 2-amino-3-cyano-6-(methylsulfanyl)-4-(2-pyridinyl)benzoate (3g). Yellow solid; mp 180–181°C; [Found: C, 60.25; H, 4.42; N, 14.20. $C_{15}H_{13}N_3O_2S$ requires C, 60.19; H, 4.38; N, 14.04%]; ν_{max} (KBr) 3431, 2206, 1668 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.48 (s, 3H, SCH_3), 3.97 (s, 3H, OCH_3), 6.44 (brs, 2H, NH_2), 6.89 (s, 1H, ArH), 7.38 (m, 1H, PyH), 7.79 (m, 2H, PyH), 8.76 (d, 1H, *J*=7.2 Hz, PyH); *m/z* (FAB) 300 (M^++1).

2.1.8. Methyl 2-amino-3-cyano-6-(methylsulfanyl)-4-(3-pyridinyl)benzoate (3h). Yellow solid; mp 208–209°C; [Found: C, 60.26; H, 4.45; N, 14.20. $C_{15}H_{13}N_3O_2S$ requires C, 60.19; H, 4.38; N, 14.04%]; ν_{max} (KBr) 3408, 2205, 1665 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.45 (s, 3H, SCH_3), 3.99 (s, 3H, OCH_3), 6.44 (brs, 2H, NH_2), 6.53 (s, 1H, ArH), 7.45 (m, 1H, PyH), 7.92 (d, 1H, *J*=7.2 Hz, PyH), 8.71 (d, 1H, *J*=7.2 Hz, PyH), 8.77 (s, 1H, PyH); *m/z* (EI) 299 (M^+), 267, 219.

2.1.9. Methyl 2-amino-3-cyano-6-(methylsulfanyl)-4-(4-pyridinyl)benzoate (3i). Yellow solid; mp 210–211°C; [Found: C, 60.23; H, 4.48; N, 14.26. $C_{15}H_{13}N_3O_2S$ requires C, 60.19; H, 4.38; N, 14.04%]; ν_{max} (KBr) 3416, 2214, 1670 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.45 (s, 3H, SCH_3), 3.99 (s, 3H, OCH_3), 6.44 (brs, 2H, NH_2), 6.51 (s, 1H, ArH), 7.46 (d, 2H, *J*=7.2 Hz, PyH), 8.74 (d, 2H, *J*=7.2 Hz, PyH); *m/z* (EI) 299 (M^+), 267.

2.1.10. Methyl 2-amino-3-cyano-6-(methylsulfanyl)-4-(2-thienyl)benzoate (3j). Yellow solid; mp 204–206°C; [Found: C, 55.32; H, 4.10; N, 9.31. $C_{14}H_{12}N_2O_2S_2$ requires C, 55.24; H, 3.97; N, 9.20%]; ν_{max} (KBr) 3447, 2208, 1670 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.42 (s, 3H, SCH_3), 3.80 (s, 3H, OCH_3), 6.42 (brs, 2H, NH_2), 6.51 (s, 1H, ArH), 7.21 (m, 1H, CH), 7.32 (d, 1H, *J*=7.2 Hz, CH), 7.58 (d, 1H, *J*=7.2 Hz, CH); *m/z* (EI) 304 (M^+), 271.

2.2. Synthesis of 3-amino-5-(methylsulfanyl)[1,1′-biphenyl]-2,4-dicarbonitriles (5), general procedure

To a mixture of 6-aryl-3-cyano-4-methylsulfanyl-2*H*-pyran-2-one **4** (1 mmol) in dry DMF (12 mL), malononitrile (0.08 g, 1.2 mmol) and KOH (0.07 g, 1.2 mmol) was added and stirred at room temperature for 20–30 h. After completion of the reaction, mixture was poured into ice water with vigorous stirring and finally neutralized with 10% HCl. The solid thus obtained was filtered and purified on a silica gel column using chloroform/hexane (3:1) as eluent.

2.2.1. 3-Amino-5-(methylsulfanyl)[1,1′-biphenyl]-2,4-dicarbonitrile (5a). White solid; mp 243–244°C (Rep.[13] 242–244°C); [Found: C, 67.78; H, 4.31; N, 15.79. $C_{15}H_{11}N_3S$ requires C, 67.90; H, 4.17; N, 15.83%]; ν_{max} (KBr) 3343, 2216 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.56 (s, 3H, SCH_3), 5.24 (brs, 2H, NH_2), 6.56 (s, 1H, ArH), 7.49–7.53 (m, 5H, ArH); *m/z* (EI) 265 (M^+).

2.2.2. 3-Amino-4′-methyl-5-(methylsulfanyl)[1,1′-biphenyl]-2,4-dicarbonitrile (5b). White solid; mp 230–231°C; [Found: C, 68.50; H, 4.56; N, 15.24. $C_{16}H_{13}N_3S$ requires C, 68.79; H, 4.69; N, 15.04%]; ν_{max} (KBr) 3370, 2212 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.42 (s, 3H, CH_3), 2.55 (s, 3H, SCH_3), 5.22 (brs, 2H, NH_2), 6.55 (s, 1H, ArH), 7.30 (d, 2H, *J*=8.1 Hz, ArH), 7.43 (d, 2H, *J*=8.1 Hz, ArH); *m/z* (EI) 279 (M^+).

2.2.3. 3-Amino-4′-methoxy-5-(methylsulfanyl)[1,1′-biphenyl]-2,4-dicarbonitrile (5c). White solid; mp 212–213°C; [Found: C, 65.36; H, 4.10; N, 13.94. $C_{16}H_{13}N_3OS$ requires C, 65.06; H, 4.43; N, 14.22%]; ν_{max} (KBr) 3336, 2217 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.56 (s, 3H, SCH_3), 3.88 (s, 3H, OCH_3), 5.22 (brs, 2H, NH_2), 6.54 (s, 1H, ArH), 7.01 (d, 2H, *J*=8.6 Hz, ArH), 7.49 (d, 2H, *J*=8.6 Hz, ArH); *m/z* (EI) 295 (M^+).

2.2.4. 3-Amino-4′-bromo-5-(methylsulfanyl)[1,1′-biphenyl]-2,4-dicarbonitrile (5d). Yellow solid; mp 260–261°C; [Found: C, 52.02; H, 2.71; N, 11.94. $C_{15}H_{10}BrN_3S$ requires C, 52.33; H, 2.92; N, 12.20%]; ν_{max} (KBr) 3372, 2213 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.56 (s, 3H, SCH_3), 5.26 (brs, 2H, NH_2), 6.51 (s, 1H, ArH), 7.37 (d, 2H, J=8.2 Hz, ArH), 7.65 (d, 2H, J=8.2 Hz, ArH); m/z (EI) 344 (M^+).

2.2.5. 3-Amino-4′-chloro-5-methylsulfanyl[1,1′-biphenyl]-2,4-dicarbonitrile (5e). White solid; mp 210–211°C; [Found: C, 60.20; H, 3.45; N, 14.18. $C_{15}H_{10}ClN_3S$ requires C, 60.09; H, 3.36; N, 14.10%]; ν_{max} (KBr) 3435, 2213 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.56 (s, 3H, SCH_3), 5.26 (s, 2H, NH_2), 6.52 (s, 1H, CH), 7.26 (d, 2H, J=8.2 Hz, ArH), 7.47 (d, 2H, J=8.2 Hz, ArH); m/z (EI) 299 (M^+), 266.

2.2.6. 3-Amino-3′-chloro-4′-fluoro-5-(methylsulfanyl)-[1,1′-biphenyl]-2,4-dicarbonitrile (5f). White solid; mp 218–219°C; [Found: C, 56.42; H, 2.63; N, 13.41. $C_{15}H_9ClFN_3S$ requires C, 56.69; H, 2.85; N, 13.22%]; ν_{max} (KBr) 3342, 2218 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.57 (s, 3H, SCH_3), 5.27 (brs, 2H, NH_2), 6.49 (s, 1H, ArH), 7.53–7.56 (m, 3H, ArH); m/z (EI) 317 (M^+).

2.2.7. 3-Amino-5-(methylsulfanyl)-4′-nitro[1,1′-biphenyl]-2,4-dicarbonitrile (5g). Yellow solid; mp 270–271°C; [Found: C, 58.25; H, 3.48; N, 17.88. $C_{15}H_{10}N_4O_2S$ requires C, 58.05; H, 3.24; N, 18.05%]; ν_{max} (KBr) 3364, 2213 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.56 (s, 3H, SCH_3), 5.24 (brs, 2H, NH_2), 6.54 (s, 1H, ArH), 7.46 (d, 2H, J=8.6 Hz, ArH), 7.64 (d, 2H, J=8.6 Hz, ArH); m/z (EI) 310 (M^+).

2.2.8. 2-Amino-4-(methylsulfanyl)-6-(1-naphthyl)isophthalonitrile (5h). Colorless oil; [Found: C, 72.60; H, 4.20; N, 13.41. $C_{19}H_{13}N_3S$ requires C, 72.35; H, 4.15; N, 13.32%]; ν_{max} (neat) 3349, 2206 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.49 (s, 3H, SCH_3), 5.25 (brs, 2H, NH_2), 6.62 (s, 1H, ArH), 7.46–7.57 (m, 5H, ArH), 7.92–7.95 (m, 2H, ArH); m/z (EI) 315 (M^+).

2.3. Synthesis of 3-amino-5-*sec*-amino-4′-substituted-[1,1′-biphenyl]-2,4-dicarbonitriles (8a–i), general procedure

A mixture of **7** (1 mmol), malononitrile (0.08 g, 1.2 mmol) and KOH (0.07 g, 1.2 mmol) in dry DMF (10 mL) was stirred at room temperature in nitrogen atmosphere for 28 h. On completion, the reaction mixture was poured into ice water and neutralized with 10% HCl. Crude product was filtered and purified on silica gel column by using $CHCl_3$/hexane (1:1) as eluent.

2.3.1. 3-Amino-4′-fluoro[1,1′-biphenyl]-5-dimethylamino-2,4-dicarbonitrile (8a). Yellow solid; mp 210–211°C; [Found: C, 68.31; H, 4.75; N, 20.22. $C_{16}H_{13}FN_4$ requires C, 68.56; H, 4.67; N, 19.99%]; ν_{max} (KBr) 2205, 3432 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.22 (s, 6H, NCH_3), 5.22 (s, 2H, NH_2), 6.07 (s, 1H, CH), 7.14–7.45 (m, 4H, ArH); m/z (EI) 280 (M^+), 266, 237.

2.3.2. 3-Amino-5-dimethylamino-4′-methyl[1,1′-biphenyl]-2,4-dicarbonitrile (8b). Yellow solid; mp 185–186°C; [Found: C, 73.99; H, 6.02; N, 20.58. $C_{17}H_{16}N_4$ requires C, 73.82; H, 5.83; N, 20.34%]; ν_{max} (KBr) 2212, 3428 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.43 (s, 3H, CH_3), 3.22 (s, 6H, NCH_3), 5.44 (s, 2H, NH_2), 7.26–7.38 (m, 4H, ArH); m/z (EI) 276 (M^+), 262, 250.

2.3.3. 3-Amino-4′-chloro-5-(1-pyrrolidinyl)[1,1′-biphenyl]-2,4-dicarbonitrile (8c). Pale yellow solid; mp 200–201°C; [Found: C, 67.21; H, 4.87; N, 17.66. $C_{18}H_{15}ClN_4$ requires C, 66.92; H, 4.68; N, 17.42%]; ν_{max} (KBr) 2216, 3430 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.04 (t, 4H, J=6.6 Hz, NCH_2), 3.69 (t, 4H, J=6.6 Hz, NCH_2), 5.20 (s, 2H, NH_2), 5.95 (s, 1H, CH), 7.26 (d, 2H, J=8.2 Hz, ArH), 7.42 (d, 2H, J=8.2 Hz, ArH); m/z (EI) 322 (M^+), 296, 268.

2.3.4. 3-Amino-4′-bromo-5-(1-pyrrolidinyl)[1,1′-biphenyl]-2,4-dicarbonitrile (8d). Yellow solid; mp >260°C; [Found: C, 58.99; H, 4.32; N, 15.60. $C_{18}H_{15}BrN_4$ requires C, 58.81; H, 4.11; N, 15.31%]; ν_{max} (KBr) 2215, 3430 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.04 (t, 4H, J=6.6 Hz, NCH_2), 3.69 (t, 4H, J=6.6 Hz, NCH_2), 5.20 (s, 2H, NH_2), 5.95 (s, 1H, CH), 7.26–7.32 (m, 2H, ArH), 7.38–7.45 (m, 2H, ArH); m/z (EI) 367 (M^+), 335, 297.

2.3.5. 3-Amino-4′-chloro-5-[4-(2-methoxyphenyl)-1-piperazinyl][1,1′-biphenyl]-2,4-dicarbonitrile (8e). Yellow solid; mp 181–182°C; [Found: C, 67.72; H, 5.12; N, 16.04. $C_{25}H_{22}ClN_5O$ requires C, 67.58; H, 4.99; N, 15.83%]; ν_{max} (KBr) 2212, 3392 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.15 (t, 2H, J=4.8 Hz, NCH_2), 3.25 (t, 2H, J=4.8 Hz, NCH_2), 3.61 (t, 2H, J=4.8 Hz, NCH_2), 3.73 (t, 2H, J=4.8 Hz, NCH_2), 3.98 (s, 3H, OCH_3), 5.23 (s, 2H, NH_2), 6.28 (s, 1H, CH), 6.91–6.97 (m, 4H, ArH), 7.01–7.26 (m, 4H, ArH); m/z (EI) 443 (M^+).

2.3.6. 3-Amino-4′-bromo-5-[4-(2-methoxyphenyl)-1-piperazinyl][1,1′-biphenyl]-2,4-dicarbonitrile (8f). Yellow solid; mp 215–216°C; [Found: C, 61.66; H, 4.78; N, 14.52. $C_{25}H_{22}BrN_5O$ requires C, 61.42; H, 4.53; N, 14.39%]; ν_{max} (KBr) 2215, 3424 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.29 (t, 4H, J=4.8 Hz, NCH_2), 3.65 (t, 4H, J=4.8 Hz, NCH_2), 3.92 (s, 3H, OCH_3), 5.27 (s, 2H, NH_2), 6.32 (s, 1H, CH), 6.95–7.05 (m, 4H, ArH), 7.30 (d, 2H, J=8.2 Hz, ArH), 7.45 (d, 2H, J=8.2 Hz, ArH); m/z (EI) 488 (M^+), 473, 393.

2.3.7. 3-Amino-4′-fluoro[1,1′-biphenyl]-5-[4-(2-pyridinyl)-1-piperazinyl-2,4-dicarbonitrile (8g). Yellow solid; mp 219–220°C; [Found: C, 69.45; H, 4.92; N, 21.33. $C_{23}H_{19}FN_6$ requires C, 69.27; H, 4.80; N, 21.15%]; ν_{max} (KBr) 2216, 3435 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.53 (t, 4H, J=4.9 Hz, NCH_2), 3.78 (t, 4H, J=4.9 Hz, NCH_2), 5.23 (s, 2H, NH_2), 6.25 (s, 1H, CH), 7.12–7.26 (m, 4H, ArH), 7.48–7.53 (m, 2H, PyH), 8.20–8.25 (m, 2H, PyH); m/z (EI) 398 (M^+), 323, 307.

2.3.8. 3-Amino-5-{4-[bis-(4-fluorophenyl)methyl]-1-piperazinyl}-4′-chloro[1,1′-biphenyl]-2,4-dicarbonitrile (8h). Colorless oil; [Found: C, 69.12; H, 4.59; N, 13.24. $C_{31}H_{24}ClF_2N_5$ requires C, 68.90; H, 4.47; N, 13.02%]; ν_{max} (neat) 2212, 3495 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.29 (t, 2H, J=4.8 Hz, NCH_2), 2.42 (t, 2H, J=4.8 Hz, NCH_2), 2.84 (t, 2H, J=4.8 Hz, NCH_2), 3.59 (t, 2H, J=4.8 Hz, NCH_2), 4.38 (s, 1H, CH), 5.79 (s, 2H, NH_2), 6.89 (s, 1H, CH), 6.95–7.10

(m, 8H, ArH), 7.32–7.41 (m, 4H, ArH); *m/z* (FAB) 540 (M^++1).

2.3.9. 3-Amino-5-{4-[bis-(4-fluorophenyl)methyl]-1-piperazinyl}-4′-methoxy[1,1′-biphenyl]-2,4-dicarbonitrile (8i). Colorless oil; [Found: C, 71.98; H, 5.23; N, 13.30. $C_{32}H_{27}F_2N_5O$ requires C, 71.71; H, 5.07; N, 13.12%]; ν_{max} (neat) 2205, 3432 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.42 (t, 2H, *J*=4.8 Hz, NCH_2), 2.63 (t, 2H, *J*=4.8 Hz, NCH_2), 3.38 (t, 2H, *J*=4.8 Hz, NCH_2), 3.48 (t, 2H, *J*=4.8 Hz, NCH_2), 3.88 (s, 3H, OCH_3), 4.28 (s, 1H, CH), 5.18 (s, 2H, NH_2), 5.90 (s, 1H, CH), 6.94–7.08 (m, 8H, ArH), 7.27–7.39 (m, 4H, ArH); *m/z* (EI) 535 (M^+), 473, 393.

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