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**SYNTHESIS AND REACTIVITY OF 2-[1-(5-BROMOBENZOFURAN-2-YL)-ETHYLIDENE]MALONONITRILE IN SYNTHESIS OF HETEROCYCLIC SYSTEMS; A CONVENIENT ROUTE FOR SYNTHESIS OF SOME PYRAZOLE, THIOPHENE, THIENOPYRIMIDINE, ISOBENZOFURAN AND BENZENE DERIVATIVES INCORPORATING BENZOFURAN MOIETY**

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**Abstract**

A facile route to some pyrazole, thiophene, thienopyrimidine, phthalic anhydride and benzene derivatives incorporating benzofuran moiety is reported.

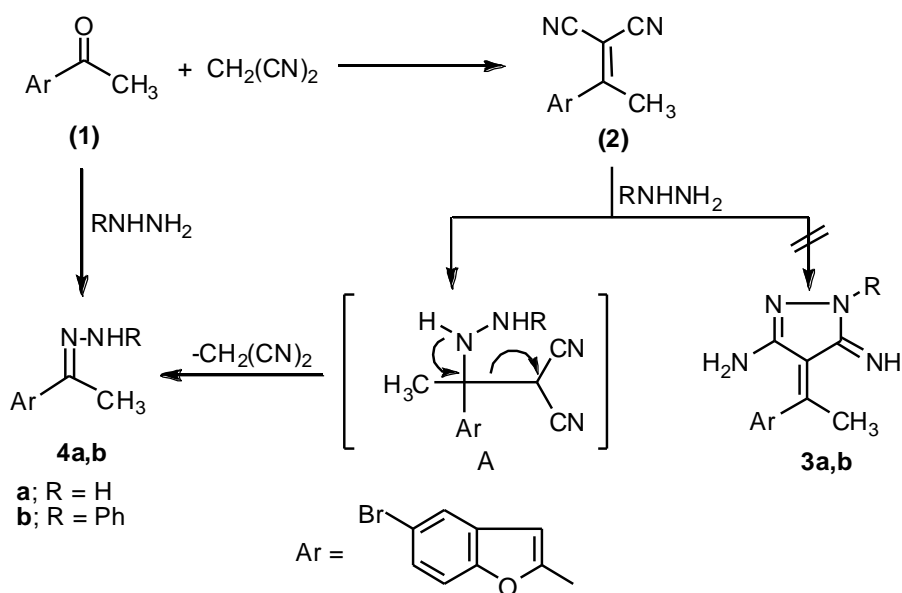
**Keyword** : allylidene, thiophene, benzofuran, theinopyrimidine

**Results and Discussion**

Benzofuran derivatives have been associated with diverse pharmacological activities, such as insecticidal,<sup>1</sup> anticancer,<sup>2</sup> antihistaminic,<sup>3</sup> antiallergic<sup>4</sup> and antitumor agents,<sup>5</sup> in addition to their natural occurrence,<sup>6-9</sup> antimicrobial,<sup>10,11</sup> anticonvulsant and anti-inflammatory activities.<sup>12,13</sup> Our approach to the target new heterocyclic compounds was achieved by the synthesis of 2-[1-(5-bromobenzofuran-2-yl)-ethylidene]malononitrile (**2**) from condensation of 2-acetyl-5-bromo benzofuran (**1**) with malononitrile in boiling benzene containing ammonium acetate and acetic acid. (**Scheme 1**).

In contrast to the anticipated formation of pyrazoline derivatives<sup>14-16</sup> (**3a,b**), the reaction of **2** with hydrazine hydrate or phenylhydrazine in boiling ethanol gave the imino compounds **4a** and **4b** respectively, and is assumed to proceed via elimination of malononitrile from the intermediate (**A**).

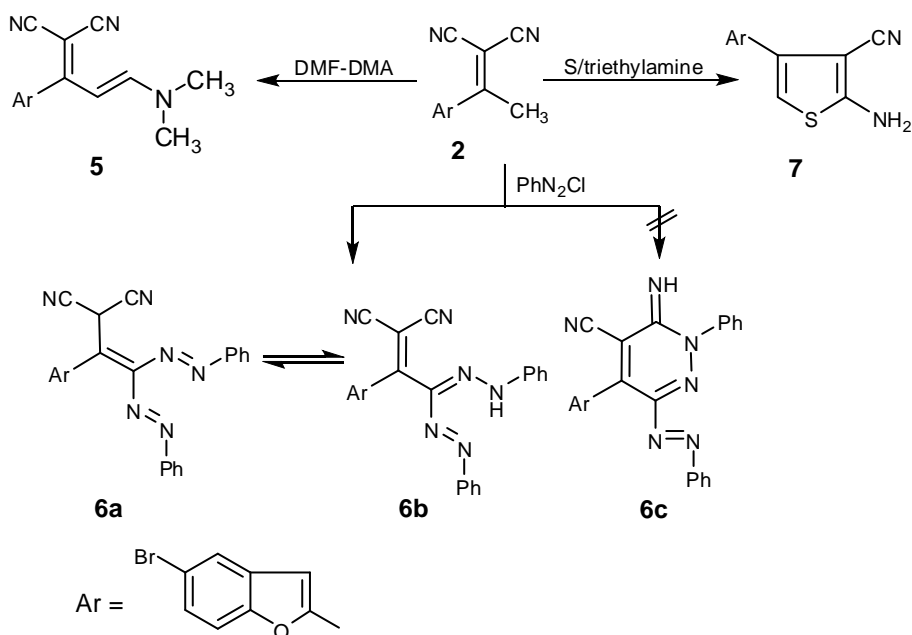
A final evidence for the proposed structures comes from synthesizing compounds **4a** and **4b** via another reaction route. Thus, when compound **1** was condensed with hydrazine hydrate or phenyl hydrazine in ethanol under reflux afforded a products identical in all aspects (m.p., mixed m.p. and IR spectrum) with compounds **4a** and **4b**, respectively, (**Scheme 1**).



Scheme 1

The high reactivity of ethylidene malonitrile derivative (**2**) attracted the author to investigate its chemical uses in organic synthesis. Thus, interaction of 2-[1-(5-bromo-benzo-furan-2-yl)-ethylidene]malonitrile (**2**) with dimethylformamide dimethylacetal in refluxing benzene afforded 2-[1-(5-bromo-benzofuran-2-yl)-3-dimethylamino-allylidene]-malonitrile (**5**), (**Scheme 2**).

On the other hand, Interaction of **2** with benzene diazonium chloride afforded the open chain product **6b** instead of the expected closed product 5-(5-bromo-benzofuran-2-yl)-3-imino-2-phenyl-6-phenylazo-2,3-dihydro-pyridazine-4-carbonitrile (**6c**). The proposed open chain structure **6a** was ruled out on the bases of spectroscopic data and the bases of spectroscopic data supported the open chain product **6b**, (**Scheme 2**).

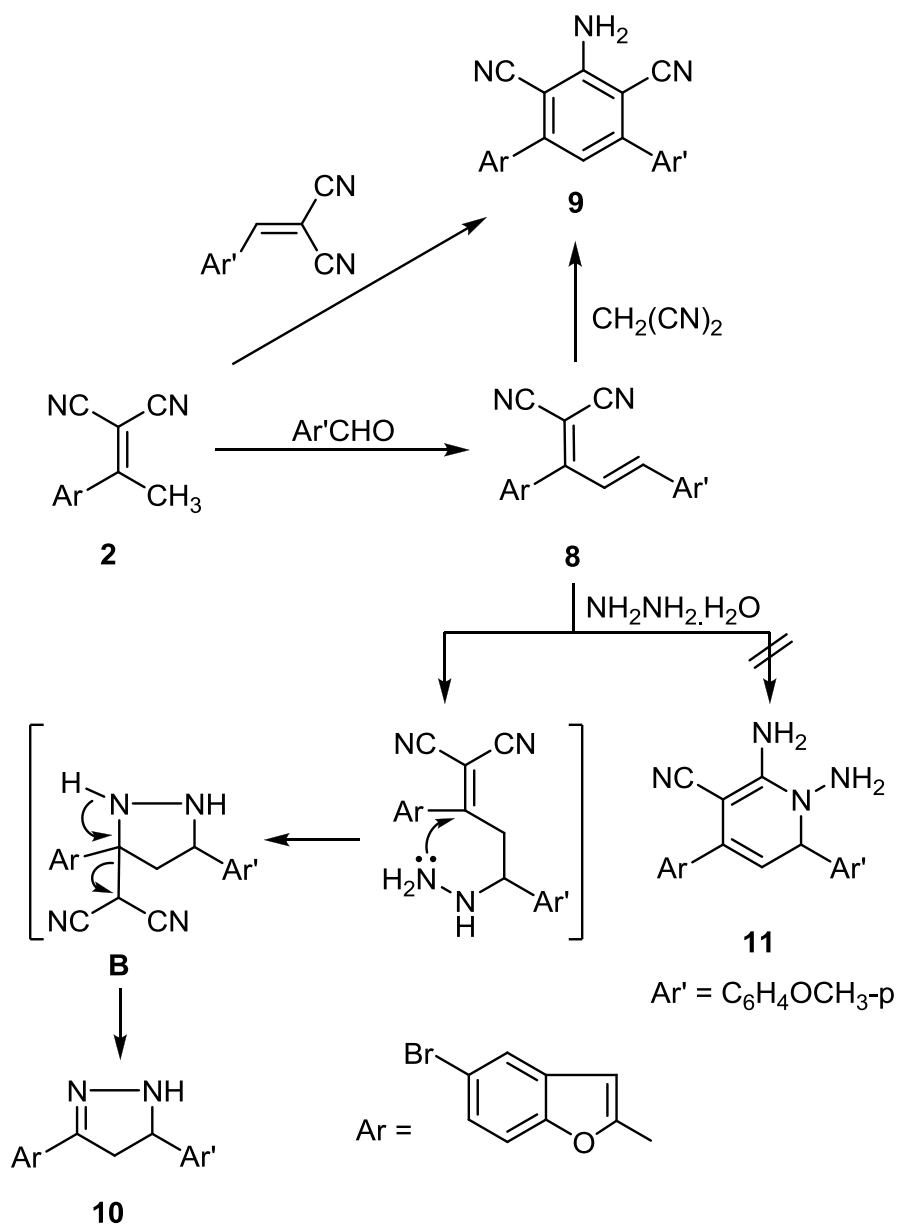


Also, interaction of compound **2** with sulfur *via* Gewald reaction<sup>17</sup> produced 2-amino-4-(5-bromo-benzofuran-2-yl)-thio phen-3-carbonitrile (**7**), (**Scheme 2**).

Condensation of 2-[1-(5-bromo-benzofuran-2-yl)-ethylidene]-malononitrile (**2**) with aromatic aldehyde as *p*-methoxy benzaldehyde gave the corresponding allylidene malononitrile derivative **8**, (**Scheme 3**).

Reaction of the allylidene malononitrile (**8**) with malono-nitrile in ethanol in the presence of piperidine as a catalyst afforded 3-amino-5-(5-bromo-benzofuran-2-yl)-4'-methoxy-bi-phenyl-2,4-dicarbonitrile (**9**), (**Scheme 3**).

A final evidence for the proposed structure **9** was obtained through its synthesis *via* one step synthesis. Thus, the direct condensation of compound **2** with *p*-methoxy- $\alpha$ -cyanocinnam-onitrile in refluxing ethanol/piperidine afforded a product which was found to be identical with compound **9** (m.p., mixed m.p. and IR spectrum) (**Scheme 3**).

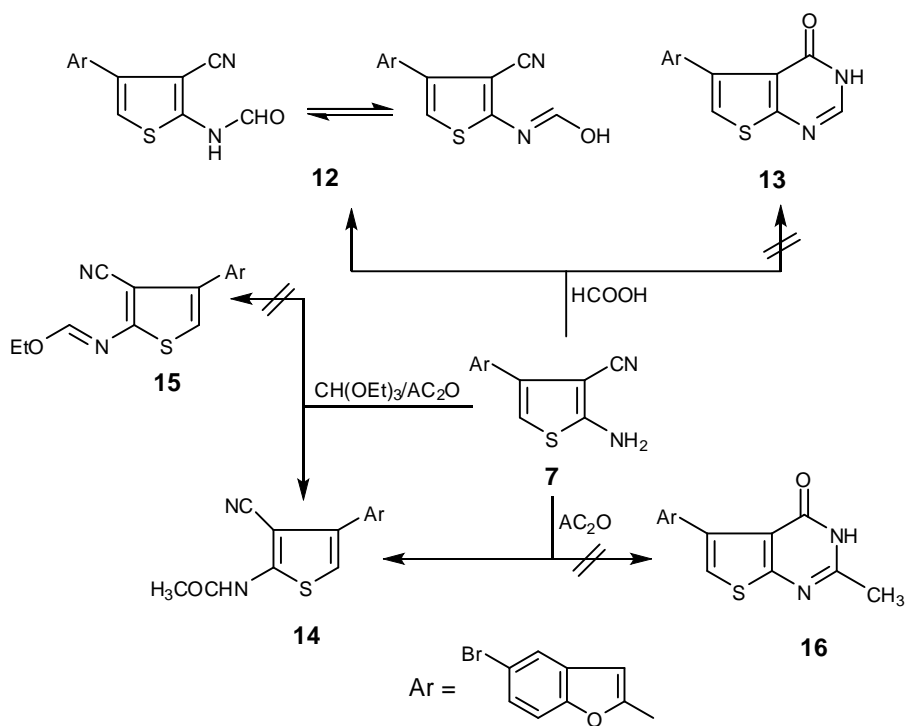


Scheme 3

In contrast to the anticipated formation of pyridine derivative **11**, the reaction of **8** with hydrazine hydrate in boiling ethanol afforded 3-(5-bromobenzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole (**10**), which was assumed to proceed

via addition of hydrazine hydrate to the activated double bond in compound **8** to give the non isolable intermediate (**B**) which underwent intramolecular cyclization followed by elimination of malononitrile to afforded the pyrazole derivative (**10**), (**Scheme 3**).

The high reactivity of 2-aminothiophene-3-carbonitrile derivative (**7**) allows the author to use it as precursor in the synthesis of some new heterocyclic derivatives. Thus, when 2-amino-4-(5-bromo-benzofuran-2-yl)-thiophene-3-carbo-nitrile (**7**) was refluxed in boiling formic acid it gives *N*-(4-(5-bromobenzofuran-2-yl)-3-cyanothiophen-2-yl)formamide (**12**) instead of the thienopyrimidine derivative (**13**), (**Scheme 4**).



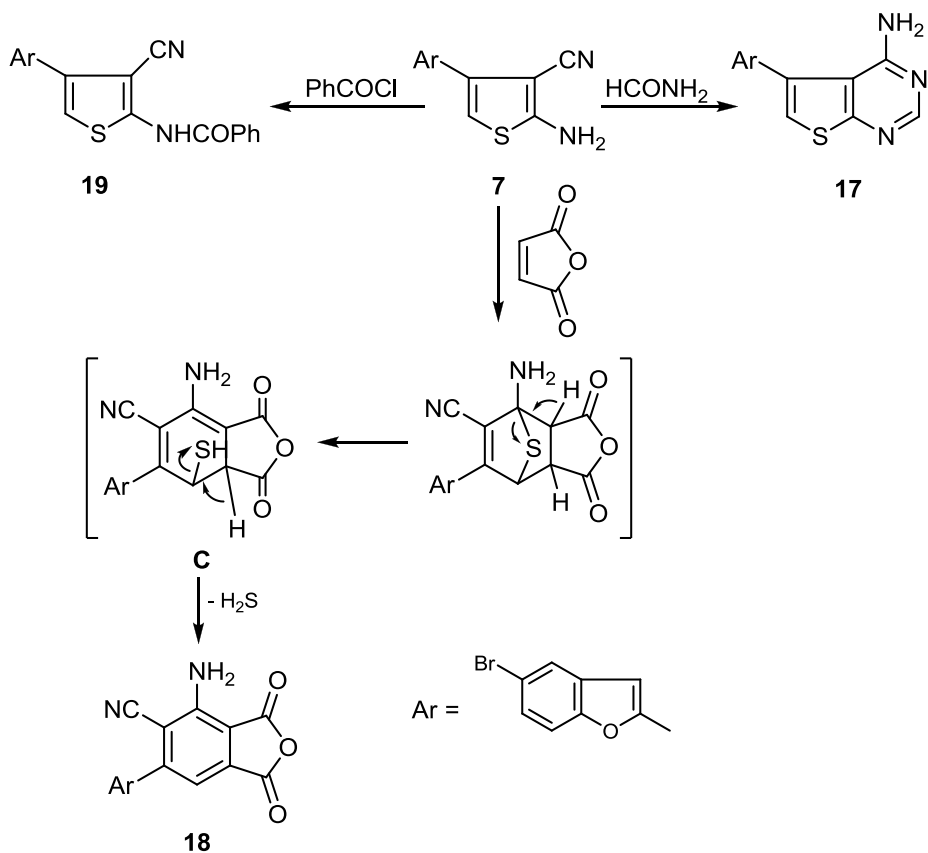
**Scheme 4**

Treatment of 2-aminothiophene-3-carbonitrile derivative (**7**) with triethyl orthoformate in boiling acetic anhydride afforded the *N*-acetylamino derivative (**14**) instead of the *N*-[4-(5-bromo-benzofuran-2-yl)-3-cyano-thiophen-2-yl]-3-cyano-thiophen-2-yl]-formimidic acid ethyl ester (**15**), (**Scheme 4**).

Also, reaction of 2-aminothiophene-3-carbonitrile derivative (**7**) with boiling acetic anhydride afforded *N*-acetyl derivative (**14**) instead of 5-(5-bromobenzofuran-2-yl)-2-methylthieno[2,3-d]pyrimidin-4(3H)-one (**16**), (**Scheme 4**).

Interaction of 2-aminothiophene-3-carbonitrile derivative (**7**) with formamide afforded a product which defined as: 4-amino-5-(5-bromobenzofuran-2-yl)thieno[2,3-d]pyrimidine (**17**), (**Scheme 5**).

Also, interaction of 2-aminothiophene-3-carbonitrile derivative (**7**) with maleic anhydride under Diels-Alder reaction conditions afforded the non isolable intermediate (**C**), which extrude  $H_2S$  and furnished 4-amino-6-(5-bromobenzofuran-2-yl)-1,3-dihydro-1,3-dioxoisobenzofuran-5-carbonitrile (**18**), (**Scheme 5**).



**Scheme 5**

Finally, benzylation of 2-aminothiophene-3-carbonitrile derivative (**7**) was easily obtained and afforded *N*-(4-(5-bromo benzofuran-2-yl)-3-cyanothiophen-2-yl)benzamide (**19**), (**Scheme 5**).

## Experimental

All melting points and antimicrobial activities are uncorrected. IR spectra (KBr) were recorded on FT-IR 5300 spectrometer and Perkin Elmer spectrum RXIFT-IR system ( $\nu$ ,  $\text{cm}^{-1}$ ). The  $^1\text{H}$ NMR spectra were recorded in ( $\text{CDCl}_3$  &  $\text{DMSO-d}_6$ ) at (300) MHz on a Varian Mercury VX-300 NMR spectrometer ( $\delta$ , ppm) using TMS as an internal standard. Mass spectra were obtained on GC Ms-QP 1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out by the Microanalytical Research Center, Faculty of Science, Cairo University and Al-Azhar University.

### 2-[1-(5-Bromo-benzofuran-2-yl)-ethylidene]-malononitrile (**2**)

A solution of 2-acetyl-5-bromobenzofuran (**1**) (0.01 mol) in dry benzene (100 ml) was added to a mixture of malononitrile (0.01 mol), ammonium acetate (2g) and acetic acid (2 ml). The reaction mixture was refluxed using a Dean and Stark water separator until water ceased to be collected. The product obtained was recrystallized from EtOH, yield (88%), m. p. 203-204, ir;  $2220\text{ cm}^{-1}$  (CN).  $^1\text{H}$  NMR ( $\delta$  ppm) spectrum ( $\text{CDCl}_3$ ) indicated signals at : 2.69 (s, 3H,  $\text{CH}_3$ ), 7.36 (s, 1H, CH furan), 7.23-7.76(m, 3H, Ar-H), ms,  $m/z$  (intensity %) 286 (62.1)288(100). M.F.  $\text{C}_{13}\text{H}_7\text{BrN}_2\text{O}$  calculated; C, 54.38, H, 2.46, N, 9.76. Found; C, 54.30, H, 2.40, N, 9.67.

### [1-(5-Bromo-benzofuran-2-yl)-ethylidene]-hydrazones (**4**)

#### Method (A):

A mixture of 2-[1-(5-Bromo-benzofuran-2-yl)-ethylidene]-malononitrile (**2**) (0.01mol) and hydrazine hydrate (0.01 mol) in ethanol (30 ml) was refluxed for 3hrs. the separated solid on heating was filtered off and recrystallized from EtOH-benzene.

#### Method (B):

A solution of 2-acetyl-5-bromobenzofuran (**1**) (0.01 mol) in ethanol (30 ml) and hydrazine hydrate (0.012 mol) was refluxed for 2hrs. the solid formed was filtered

off and recrystallized from the proper solvent to give the hydrazone (**4**). m.p. and mixed m.p. determined with authentic sample gave no depression.

**4a**; recrystallized from EtOH-benzene.(yield 87%),m.p.164-165, ir; 3364, 3270  $\text{cm}^{-1}$  ( $\text{NH}_2$ ), ms,  $m/z$  (intensity %) 252 (100.0)254(99.3). M.F.  $\text{C}_{10}\text{H}_9\text{BrN}_2\text{O}$ , calculated; C, 47.46 H ,3.58, N, 11.07 found; C,47.45, H,3.45, N, 11.10.

**4b**;recrystallized from EtOH-benzene.(yield 78%),m.p.167-169, ir; 3340  $\text{cm}^{-1}$  (NH),ms,  $m/z$  (intensity %) 328 (31.9)330(100). M.F.  $\text{C}_{16}\text{H}_{13}\text{BrN}_2\text{O}$  calculated. C, 58.38 H, 3.98, N, 8.51 found. C 58.33, H, 3.89, N, 8.46.

### **2-[1-(5-Bromo-benzofuran-2-yl)-3-dimethylamino-allylidene]-malononitrile (5)**

A mixture of (**2**) (0.01mol) and N,N-dimethylformamide dimethylacetal (0.01 mol) in benzene (20 ml) was refluxed for 2hrs. the solvent was removed under reduced pressure the residue was collected and recrystallized from EtOH-benzene .(yield 77%), m.p.230-231,ir; 2924 (CH-aliph.) and 2200  $\text{cm}^{-1}$  (CN) ,  $^1\text{H}$  NMR ( $\delta$  ppm) spectrum ( $\text{CDCl}_3$ ) indicated signals at : 3.07 and 3.19 (2s, 6H,  $\text{N}(\text{CH}_3)_2$ ), 5.73 and 7.51 (dd, 2H, olefinic  $\text{CH}=\text{CH}$ ;  $J= 12.6$  Hz), 7.27 (s, 1H, CH furan), 7.21-7.80 (m, 3H, Ar-H),M.F.  $\text{C}_{16}\text{H}_{12}\text{BrN}_3\text{O}$ . calculated; C,56.16 H,3.53, N 12.28 found; C,56.10, H,3.45, N,12.23.

### **2-[1-(5-Bromo-benzofuran-2-yl)-2-phenylazo-2-(phenyl-hydrazono)-ethylidene]-malononitrile (6b)**

To a cold solution of (**2**) (0.01 mol) in pyridine (20 ml) was added benzenediazonium chloride (0.01 mol) [prepared by diazotization of aniline (0.01 mol) in HCl (6M, 6 ml) with sodium nitrite (0.7g) at 0-5°C] portionwise over 30 min with constant stirring. After complete addition, the reaction mixture was stirred for a further 2h at 0-5°C. The solid product was filtered off, washed with water, dried and finally recrystallized from EtOH-benzene.(yield 80%),m.p210-212,ir; 3306 (NH) and 2232  $\text{cm}^{-1}$  (CN),  $^1\text{H}$  NMR ( $\delta$  ppm) spectrum (DMSO) indicated signals at : 7.36 (s, 1H, CH furan), 7.47-7.75 (m, 13H, Ar-H), 8.12 (s, 1H, NH),ms,  $m/z$  (intensity %) 494 (12.9)496(14.5).M.F.  $\text{C}_{25}\text{H}_{15}\text{BrN}_6\text{O}$  calculated; .C,60.62 H,3.05, N, 16.97 found; C,60.55, H,3.00, N,16.92.

### **2-Amino-4-(5-bromo-benzofuran-2-yl)-thiophene-3-carbonitrile (7)**

A mixture of (**2**) (0.01 mol) and elemental sulfur in ethanol (40ml) were treated with a few drops of triethylamine. was refluxed for 3h. The obtained product was filtered off and recrystallized from dioxane.(yield 85%), m.p.254-255,ir; 3318, 3214



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(NH<sub>2</sub>) and 2206 cm<sup>-1</sup> (CN), <sup>1</sup>H NMR (δ ppm) spectrum (DMSO) indicated a signals at : 7.37 (s, 1H, CH furan), 7.44-7.75 (m, 3H, Ar-H), 7.87 (s, 1H, CH thiophene), 8.61 (br, 2H, NH<sub>2</sub>), ms, *m/z* (intensity %) 318 (99.0)320(100) and showed other peaks at : 212 (16.1), 105 (6.8) and 69 (4.3).M.F. C<sub>13</sub>H<sub>7</sub>BrN<sub>2</sub>OS. Calculated; .C,48.92 H,2.21 N, 8.78 found; C,48.85, H,2.17, N,8.70.

### 2-((E)-1-(5-bromobenzofuran-2-yl)-3-(4-methoxyphenyl)allylidene)malononitrile (8)

A mixture of (2) (0.01 mol), and p-methoxy benzaldehyde (0.01 mol) in ethanol (30 ml) and few drops of piperidine was refluxed for 3h, the separated solid on heating was filtered off and recrystallized from EtOH-benzene.(yield 72%), m.p.235-236,ir; 2924 (CH-aliph.), 3024 (CH-arom.) and 2212 cm<sup>-1</sup> (CN), <sup>1</sup>H NMR (δ ppm) spectrum (CDCl<sub>3</sub>) indicated signals at : 3.88 (s, 3H, OCH<sub>3</sub>), 6.94 and 7.58 (dd, 2H, olefinic CH=CH), 7.27 (s, 1H, CH furan), 7.24-7.86 (m, 7H, Ar-H),M.F. C<sub>21</sub>H<sub>13</sub>BrN<sub>2</sub>O<sub>2</sub>, calculated; C,62.24 H,3.23, N, 6.91 found; C,62.18, H,3.19, N, 6.87.

### 3-Amino-5-(5-bromo-benzofuran-2-yl)-4'-methoxybiphenyl-2,4-dicarbonitrile (9)

#### Method (A):

A mixture of (8) (0.01 mol) and malononitrile (0.01 mol) in ethanol (40 ml), few drops of piperidine was added as catalyst. The reaction mixture was refluxed for 3h. The isolated product was collected and recrystallized from dioxane.

#### Method (B):

A solution of (2) (0.01mol) and p-methoxy α-cyano- cinnamionitrile (0.01 mol) in ethanol (40 ml), few drops of piperidine was added as catalyst. The reaction mixture was refluxed for 3h. The isolated product was collected and recrystallized from the proper solvent to give the compound (9). m.p. and mixed m.p. determined with authentic sample gave no depression. (yield 79%), m.p.333-335,ir; 3460, 3354 (NH<sub>2</sub>) and 2212 cm<sup>-1</sup> (CN), <sup>1</sup>H NMR (δ ppm) spectrum (DMSO) indicated a signals at : 3.83 (s,3H, OCH<sub>3</sub>) 7.34 (s, 1H, CH furan), 7.54-7.95 (m, 9H, Ar-H, CH thiophene), 8.74 (br, 2H, NH<sub>2</sub>), ms, *m/z* (intensity %) 443 (100.0)445(91.3).M.F. C<sub>23</sub>H<sub>14</sub>BrN<sub>3</sub>O<sub>2</sub>, calculated; C,62.18 H,3.18, N, 9.46 found; C,62.11, H,3.12, N,9.40 .

### 3-(5-bromobenzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole (10)

A mixture of (8) (0.01 mol) in ethanol (30 ml) and hydrazine hydrate (0.012 mol) was refluxed for 2hrs. the separated solid on heating was filtered off and recrystallized from ETOH-benzene.(yield 69%), m.p.155-156,ir; 3428 cm<sup>-1</sup>

(NH),ms,  $m/z$  (intensity %) 370 (100.0)372(93.2). M.F.  $C_{18}H_{15}BrN_2O_2$ , calculated; C,58.56 H,3.55, N, 7.59 found; C, 58.49, H,3.47, N,7.54 .

**N-(4-(5-bromobenzofuran-2-yl)-3-cyanothiophen-2-yl) formamide (12)**

A mixture of (7) (0.01 mol), with formic acid (0.01 mol) (20ml) was heated under reflux for 3h. The obtained product was filtered off and recrystallized from dioxane.(yield 90%), m.p.280-282,ir; 3268 (NH), 2214 (CN) and  $1700\text{ cm}^{-1}$  (C=O),  $^1\text{H NMR}$  ( $\delta$  ppm) spectrum (DMSO) indicated a signals at : 7.33 (s, 1H, CH furan), 7.47-7.70 (m, 3H, Ar-H), 7.97 (s, 1H, CH thiophene), 8.51 (s, 1H, CHO), 12.25 (s, 1H, NH), M.F.  $C_{14}H_7BrN_2O_2S$ . calculated; C,48.43, H,2.03, N, 8.07 found; C,48.38, H,2.06, N,8.02 .

**N-(4-(5-bromobenzofuran-2-yl)-3-cyanothiophen-2-yl) acetamide (14)**

A mixture of (7) (0.01 mol), with triethyl orthoformate (0.01 mol) in acetic anhydride (20ml) and / or acetic anhydride was heated under reflux for 3h. the solvent was evaporated till dryness, after cooling the obtained product was filtered off and recrystallized from dioxane (yield 78%), m.p.243-245,ir; 3262 (NH), 2230 (CN) and  $1696\text{ cm}^{-1}$  (C=O),  $^1\text{H NMR}$  ( $\delta$  ppm) spectrum (DMSO) indicated signals at: 2.25 (s, 3H,  $\text{CH}_3$ ), 7.30 (s, 1H, CH furan), 7.45-7.62 (m, 3H, Ar-H), 7.94 (s, 1H, CH thiophene), 11.85 (s, 1H, NH) .M.F.  $C_{15}H_9BrN_2O_2S$  calculated; C,49.88, H,2.51, N, 7.76 found; C ,49.82, H , 2.46, N,7.71

**4-amino-5-(5-bromobenzofuran-2-yl)thieno[2,3-d]pyrimidine (17)**

A mixture of (7) (0.01 mol) and formamide (10ml) was heated under reflux for 8h. the solvent was removed under vacuum, the solid obtained was filtered off and recrystallized from DMF (yield 82%), m.p.235-236,ir; 3380,  $3314\text{ cm}^{-1}$  ( $\text{NH}_2$ ),ms,  $m/z$  (intensity %) 345 (65.4)347(100).M.F.  $C_{14}H_8BrN_3OS$ , calculated; C,48.57, H,2.33, N, 12.14 found; C,48.50, H,2.27, N,12.09.

**4-amino-6-(5-bromobenzofuran-2-yl)-1,3-dihydro-1,3-dioxiso benzofuran-5-carbonitrile (18)**

A mixture of (7) (0.01 mol), maleic anhydride (0.01 mol) and 1,4-dioxane (30ml) was heated under reflux for 3h. after cooling the obtained product was filtered off and recrystallized from EtOH-benzene (yield 72%), m.p.224-225,ir; 3414, 3320 ( $\text{NH}_2$ ), 2208 (CN) and 1732,  $1646\text{ cm}^{-1}$  ( $2\text{C=O}$ ),  $^1\text{H NMR}$  ( $\delta$  ppm) spectrum (DMSO) indicated a signals at : 7.32 (s, 1H, CH furan), 7.56-7.87 (m, 4H,

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Ar-H), 8.78 (br, 2H, NH<sub>2</sub>), ms, *m/z* (intensity %) 382 (16.2)384(27.1). M.F. C<sub>17</sub>H<sub>7</sub>BrN<sub>2</sub>O<sub>4</sub>, calculated; C,53.29, H,1.84, N, 7.31 found; C,53.23, H,1.78, N,7.26.

### **N-(4-(5-bromobenzofuran-2-yl)-3-cyanothiophen-2-yl) benzamide (19)**

A mixture of (7) (0.01mol) and benzoyl chloride (10 ml) was refluxed for 2hrs. then allowed to cool and treated with petroleum ether (60~80°C) (50 ml), the solid product was separated, collected by filtration and washed with petroleum ether (60~80 °C) several times, dried and recrystallized from EtOH-benzene (yield 78%), m.p.230-232,ir;3274 (NH), 2212 (CN) and 1660 cm<sup>-1</sup> (C=O),ms, *m/z* (intensity %) 422 (100.0)424(88.4).M.F. C<sub>20</sub>H<sub>11</sub>BrN<sub>2</sub>O<sub>2</sub>S, calculated; C,56.75 H,2.62 N, 6.62 found; C,56.70, H,2.57, N,6.55.

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