Research Paper

# A Facile Synthesis, *In vitro* Antiinflammatory and Antioxidant activity of Novel Benzimidazolylpyrano[2,3-*d*][1,3]thiazolocarbonitriles

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**The synthesis benzimidazolylpyrano[2,3-*d*][1,3]thiazolocarbonitriles (5a-j) were achieved by cyclocondensation of arylidene amino-benzo[*d*]imidazole-2-thiols (3a-j) with mercaptoacetic acid followed by cyclization with 2-(phenylmethylene)malononitrile. Further more, the present study aimed at the evaluation of *in vitro* antiinflammatory activity and antioxidant activity of synthetic compounds. All tested compounds showed appreciable activity against the standard drugs.**

**Key words: Benzimidazolylpyrano[2,3-*d*][1,3]thiazolocarbonitrile, mercaptoacetic acid, Michael addition, cyclo condensation, antiinflammatory activity, antioxidant activity**

Pyrano[2,3-*d*]thiazoles are biologically interesting compounds with diabetes, obesity, hyperlipidemia, and atherosclerotic diseases[1]. They are also known to show antimicrobial, bactericidal, fungicidal and molluscicidal activities[2,3]. Furthermore, benzimidazole a nitrogen containing heterocyclic provides an interesting building block for the synthesis of various biologically active compounds[4-6]. There are several classic examples of benzimidazole derivatives which possess useful pharmaceutical properties and they are marketed as commercial drugs. Fuberidazole and Benomyl can be used as antifungal agents. Benzimidazole derivatives are also reported to possess analgesic[7], anthelminthic[8], antiinflammatory[9], antiarthritic, and anti HIV activities[10].

Glycosidase inhibitors (GIs) have been isolated from plants and microorganisms. The importance of the glycosidases in the living organisms has been identified by the changing the biochemical processes using glycosidase inhibitors. Glycosidase inhibitors have many potential applications as agrochemicals, viral infection, cancer and genetic disorders[11]. Tetrahydro-3a*H*-pyrano [3,2,-*d*] thiazoles are found to be better glycosidase inhibitors (fig. 1)[12].

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Based on biological activity of pyrano[2,3-*d*] thiazoles compounds and benzimidazoles, it seemed that introduction of benzimidazole, pyrano[2,3-*d*] thiazoles rings in a single molecular frame work may enhance the pharmacological activity of these compounds. As a sequel to our research on the design and synthesis of biologically active and pharmacologically important new heterocycles[13-16], it was thought worth while to synthesize the novel title compounds (5a–j) and to have them evaluated for their *in vitro* antiinflammatory and antioxidant activities.

## MATERIALS AND METHODS

All the melting points were determined on a Cintex melting point apparatus and are uncorrected. Analytical TLC was performed on Merck precoated 60 $F_{254}$ silica gel plates. Visualization was done by exposing to iodine vapour. IR spectra (KBr pellet) were recorded on a PerkinElmer BX series FT-IR spectrometer. $^{1}H$ NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer. $^{13}C$ NMR spectra were recorded on a Bruker 75 MHz spectrometer. Chemical shift values are given in ppm (δ) with tetramethylsilane as an internal standard. Mass spectral measurements were carried out by the EI method on a Joel JMC-300 spectrometer at 70 eV. The synthesis of compounds

5a-j was accomplished by synthetic route shown in scheme 1.

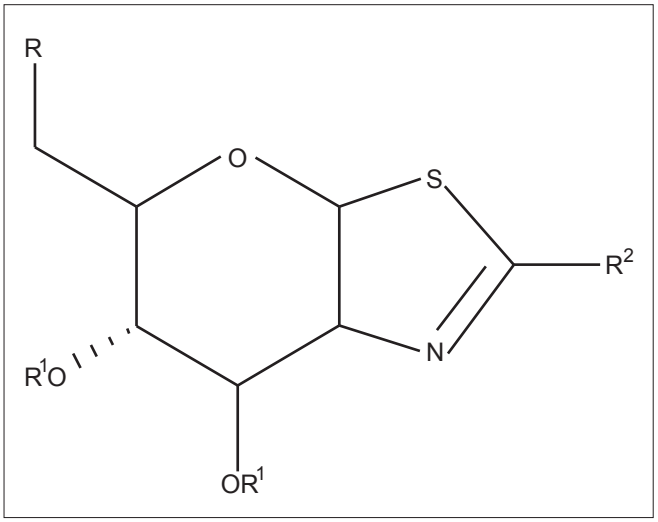
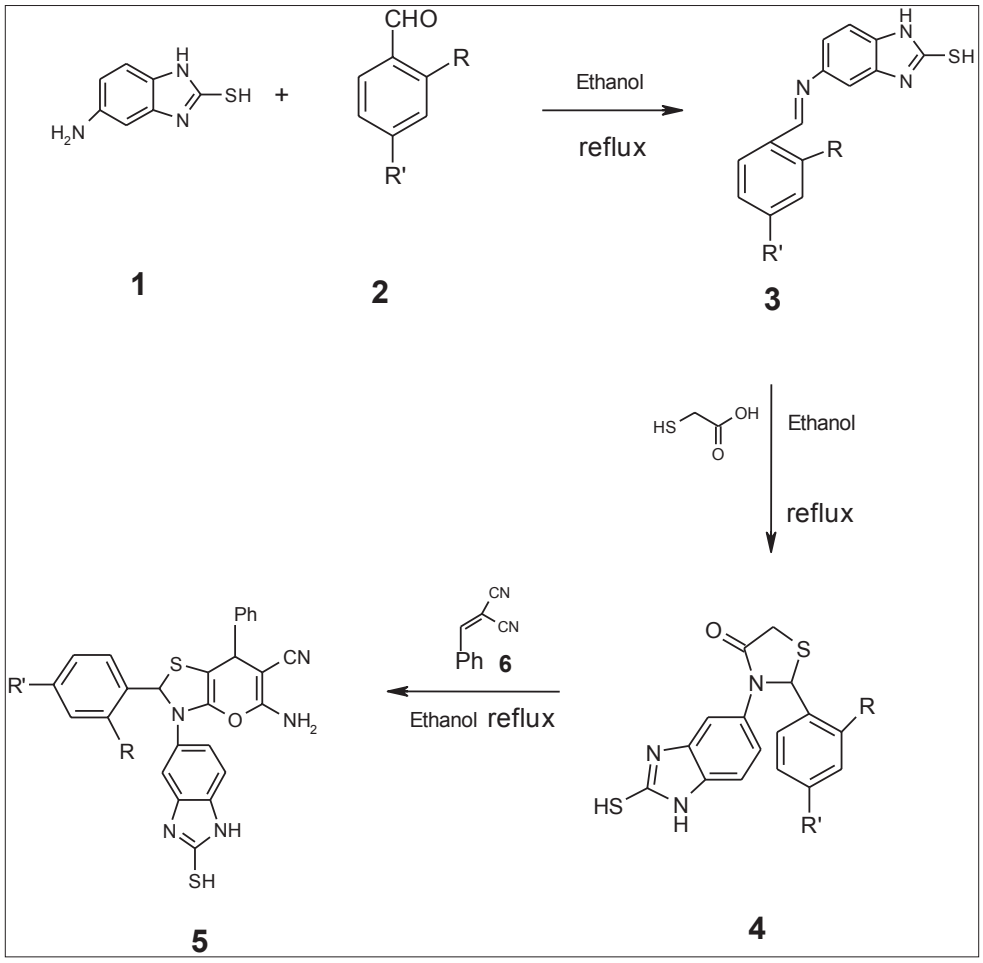



**Fig. 1: Glycosidase inhibitor.**
**R= OAc, OH. $R^1$= OAc, OH.$R^2$= $CH_2F$, $CF_3$, $CH_2$-O-$CH_3$, Ph, Ph-$CH_2$, $NH_2$, NH-$CH_3$, $CH_3$.**

**Synthesis of (Z)-5-(arylideneamino)-1*H*-benzo[*d*] imidazole-2-thiols (3a-j)-general Procedure:**

A mixture of 5-amino-2-mercaptobenzimidazole 1 (0.01 mol) and aromatic aldehyde 2 (0.01 mol) in ethanol (15 ml) were refluxed for 4 h. The reaction mixture was cooled to room temperature, and poured on to crushed ice. The solid separated was filtered off and purified by recrystallization from ethylacetate to give (*Z*)-5-(arylidene amino)-1*H*-benzo[*d*]imidazole-2-thiols.

5-[(*E*)-1-Phenylmethylidene]amino-1*H*-benzo[*d*] imidazole-2-thiole(3a); Yield: 68%, mp: 116-118°, IR ($cm^{-1}$): 3121 (NH). $^1$H NMR (300 MHz, $CDCl_3$): 3.24 (s, 1H, =CH), 4.03 (s, 1H, SH), 7.1-7.34(m, 8H, ArH), 7.93 (s, 1H, NH, $D_2O$ exchangeable). $^{13}$C NMR (75 MHz, $CDCl_3$): 107.4, 114.8, 119.0, 126.8, 130.2, 130.8, 131.2, 133.0, 138.4, 139.2, 142.4, 145.3, 158.0, 166.0. Anal. calcd for $C_{14}H_{11}N_3S$ (MW=254 $[M+H]^+$): C, 66.34; H, 4.34; N, 16.54. Found: C, 66.38; H,. 38; N, 16.59.




**Scheme 1. Synthesis of benzimidazolylpyrano[2,3-*d*][1,3]thiazolo carbonitriles (5a-j).**
**3, 4, 5: a: R=H, R′=H. b: R=H, R′=$NO_2$. c: R=H, R′=Cl. d: R=H, R′=$OCH_3$.e: R=H,R′=$N(CH_3)_2$. f: R=H, R′=Br. g: R=OH, R′=H. h: R=OH, R′=Br: i: R=OH,R′=$OCH_3$.j: R=OH,R′=Cl.**

5-[(*E*)-1-(4-Nitrophenyl)methylidene]amino-1*H*-benzo[*d*]imidazole-2-thiole(3b); Yield: 71%, mp: 132-134°, IR($cm^{-1}$): 3210(NH), 1535,1326 ($NO_2$). $^1$H NMR (300 MHz, $CDCl_3$): 3.33 (s, 1H, =CH), 4.01 (s, 1H, SH), 7.10-7.32 (m, 7H, ArH), 7.98 (s, 1H, NH, $D_2O$e changeable).$^{13}$C NMR (75 MHz, $CDCl_3$): 106.4, 114.2, 115.8, 125.4, 125.5, 126.0, 126.1, 135.4, 142.6, 144.7, 145.1, 153.2, 162.2, 166.2. Anal. Calcd for $C_{14}H_{10}N_4O_2S$ (MW=298$[M+H]^+$): C, 56.37; H, 3.38; N, 18.78. Found: C, 56.33; H, 3.34; N, 18.7.

5-[(*E*)-1-(4-Chlorophenyl)methylidene]amino-1*H*-benzo[*d*]imidazole-2-thiole (3c); Yield: 69%, mp: 121-123°, IR ($cm^{-1}$): 3121 (NH). $^1$H NMR (300 MHz, $CDCl_3$): 4.00 (s, 1H, SH), 4.31 (s, 1H, =CH), 7.00-7.98 (m, 7H, ArH), 8.13 (s, 1H, NH, $D_2O$ exchangeable).$^{13}$C NMR (75 MHz, $CDCl_3$): 107.8, 114.4, 115.2, 130.9, 131.9, 132.2 ,132.3, 132.4, 133.2, 135.6, 144.3, 145.6, 165.2, 166.1. Anal. Calcd for $C_{14}H_{10}ClN_3S$ (MW=287$[M+H]^+$): C, 58.43; H, 3.50; N, 14.60. Found: C, 58.39; H, 3.47; N, 14.57.

5-[(*E*)-1-(4-Methoxyphenyl)methylidene]amino-1*H*-benzo[*d*]imidazole-2-thiole (3d); Yield: 74%, mp:126-128°, IR ($cm^{-1}$): 3245 (NH).$^1$H NMR (300 MHz, $CDCl_3$): 3.62(s, 3H, $OCH_3$) 4.08 (s, 1H, SH), 4.19m (s, 1H, =CH), 6.99-7.89 (m, 7H, ArH), 9.00(s, 1H, NH, $D_2O$ exchangeable). $^{13}$CNMR (75 MHz, CDCl): 53.8, 107.5, 112.4, 116.4, 118.3, 119.2, 128.2, 133.0, 132.4, 135.3, 142.4, 145.3, 160.5, 163.0, 166.4. Anal. Calcd for $C_{15}H_{13}N_3OS$ (MW=283 $[M+H]^+$): C, 63.58; H, 4.62; N, 14.83. Found: C, 63.55; H, 4.59; N, 14.80.

5-((*E*)-1-[4-(Dimethylamino)phenyl]methylideneamino)-1*H*-benzo[*d*]imidazole-2-thiole (3e); Yield: 71%, mp: 129-131°, IR ($cm^{-1}$): 3115 (NH). $^1$H NMR (300 MHz, $CDCl_3$): 3.00 (s, 6H, $N(CH_3)_2$), 3.33 (s, 1H, =CH), 4.00 (s, 1H, SH), 6.93-7.26 (m, 7H, ArH), 8.48 (s, 1H, NH, $D_2O$ exchangeable). $^{13}$CNMR (75 MHz, $CDCl_3$): 41.4, 43.1**,** 109.7, 111.0, 113.9, 114.3, 115.2, 126.0, 127.6, 130.3, 139.2, 142.4, 145.3, 155.4, 162.1, 166.2. Anal.Calcd for $C_{16}H_{16}N_4S$ (MW=296$[M+H]^+$): C, 64.84; H, 5.44; N, 18.90. Found: C, 64.81; H, 5.42; N, 18.88.

5-[(*E*)-1-(4-Bromophenyl)methylidene]amino-1*H*-benzo[*d*]imidazole-2-thiole(3f); Yield: 70%, mp: 118-120°, IR ($cm^{-1}$): 3115 (NH). $^1$H NMR (300 MHz, $CDCl_3$): 4.11 (s, 1H, SH), 4.26 (s, 1H, =CH), 7.13-98 (m, 7H, ArH), 9.31 (s, 1H, NH, $D_2O$ exchangeable).$^{13}$CNMR(75 MHz, $CDCl_3$):111.2,114.5,115.0,127.4,130.2,130.5, 132.7, 132.7, 133.2, 135.2, 138.2, 145.6, 158.0, 166.4. Anal. Calcd for $C_{14}H_{10}BrN_3S$ (MW=332$[M+H]^+$): C, 50.62; H, 3.03; N, 12.65. Found: C, 50.66; H, 3.06; N, 12.69.

4-[(2-Sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)imino]methylphenol(3g); Yield: 73%, mp: 123-125°, IR ($cm^{-1}$): 3210 (NH). $^1$H NMR (300 MHz, $CDCl_3$): 4.00 (s, 1H, SH), 4.21 (s, 1H, =CH),7.04-.89 (m, 7H, ArH), 8.96 (s, 1H, NH, $D_2O$ exchangeable), 9.13 (s, 1H, OH, $D_2O$ exchangeable). 13C NMR (75 MHz, $CDCl_3$): 111.5, 114.3, 115.4, 119.0, 122.5, 123.4, 133.1, 134.4, 135.2, 142.2, 145.3, 162.0, 163.1, 166.2. Anal. Calcd for $C_{14}H_{11}N_3OS$ (MW =269$[M+H]^+$): C, 62.44; H, 4.12; N, 15.60. Found: C, 62.40; H, 4.17; N, 15.58.

5-Bromo-2-[(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)imino]methylphenol(3h); Yield: 69%, mp: 136-138°, IR ($cm^{-1}$): 3225 (NH). $^1$H NMR (300 MHz, $CDCl_3$): 4.18 (s, 1H, SH), 4.29 (s, 1H, =CH), 7.00-7.79 (m, 6H, ArH), 8.86 (s, 1H, NH, $D_2O$ exchangeable), 9.23 (s, 1H, OH, $D_2O$ exchangeable). $^{13}$CNMR (75 MHz, $CDCl_3$): 107.8, 115.0, 117.2, 117.5, 121.5, 122.1, 123.2, 134.2, 135.2, 142.2, 145.6, 162.0, 161.0, 166.2. Anal. Calcd for $C_{14}H_{10}BrN_3OS$ (MW=348$[M+H]^+$): C, 48.29; H, 2.89; N, 12.07. Found: C, 48.24; H, 2.93; N, 12.02.

5-Methoxy-2-[(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)imino]methylphenol(3i); Yield: 74%, mp:139-141°, IR($cm^{-1}$): 3205(NH).$^1$H NMR (300 MHz, $CDCl_3$): 3.58 (s, 3H, $OCH_3$),4.10 (s, 1H, SH), 4.26 (s, 1H,=CH), 6.99-7.94 (m, 6H, ArH), 8.46 (s, 1H, NH, $D_2O$ exchangeable), 8.73 (s, 1H, OH, $D_2O$ exchangeable).$^{13}$C NMR (75 MHz, $CDCl_3$): 56.3, 102.1, 109.0, 111.2, 114.3, 119.0, 119.3, 135.3,135.4, 142.1, 145.3, 152.3, 162.1, 165.1, 166.2. Anal. Calcd for $C_{15}H_{13}N_3O_2S$ (MW=299$[M+H]^+$): C,60.19; H, 4.38; N, 14.04. Found: C, 60.21; H, 4.41; N, 14.00.

5-Chloro-2-[(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)imino]methylphenol(3j); Yield: 75%, mp: 143-145°, IR ($cm^{-1}$): 3300 (NH). $^1$H NMR(300 MHz, $CDCl_3$): 4.00(s, 1H, SH), 4.2(s, 1H, =CH), 6.89-7.76(m, 6H, ArH), 8.04 (s, 1H, NH, $D_2O$ exchangeable), 8.61 (s,1H, OH, $D_2O$ exchangeable). $^{13}$C NMR (75 MHz, $CDCl_3$): 111.2, 114.5, 115.0, 116.3, 119.8, 123.2, 134.0, 137.2, 139.8, 143.0, 145.3, 162.0, 164.2,

166.2. Anal. Calcd for $C_{14}H_{10}ClN_3OS$ (MW=303 $[M+H]^+$):C,55.36; H, 3.32; N, 13.83.Found: C,55.32; H, 3.36; N, 13.87.

**Synthesis of 2-aryl-3-(2-sulfanyl-1*H*-benzo[*d*] imidazol-5-yl)-1,3-thiazolan-4-ones (4a-j) general procedure:**

A solution of (*Z*)-5-(arylidene amino)-1*H*-benzo[*d*] imidazole-2-thiol 3 (0.01 mol), and thioglycollic acid (0.01 mol) in ethanol (15 ml) were heated under reflux for 6 h. The reaction mixture was cool to room temperature and poured into ice-cold water. The precipitate that formed was filtered off, and purified by recrystallization from ethyl acetate to afford the product.

2-Phenyl-3-(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)-1,3-thiazolan-4-one(4a); Yield: 70%, mp: 151-153°, IR($cm^{-1}$): 3310 (NH), 1695 (C=O).$^1$HNMR (300 MHz, $CDCl_3$): 4.12 (s, 2H, thiazole-$CH_2$), 4.25 (s, 1H, SH), 5.62 (s, 1H, thiazole–CH), 6.89-7.46 (m, 8H, ArH), 9.12 (s, 1H, NH, $D_2O$ exchangeable). $^{13}$CNMR (75 MHz, $CDCl_3$): 32.5**,** 41.2, 66.6, 111.3, 113.2, 116.1, 124.9, 125.5, 128.5, 129.1, 130.2, 130.3, 133.2, 136.3, 137.4, 173.8. Anal. calcd for $C_{16}H_{13}N_3OS_2$ (MW=327 $[M+H]^+$): C, 58.69; H, 4.00; N, 12.83. Found: C, 58.73; H,4.03; N,12.88.

2-(4-Nitrophenyl)-3-(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)-1,3-thiazolan-4-one(4b); Yield: 73%, mp: 171-173°, IR ($cm^{-1}$): 3300 (NH), 1542, 1340 ($NO_2$), 1715 (C=O).$^1$H NMR (300 MHz, $CDCl_3$): 4.10 (s, 2H, thiazole-$CH_2$),4.24 (s, 1H, SH), 5.42 (s, 1H, thiazole–CH), 7.00-7.3 (m, 7H, ArH), 8.63 (s, 1H, NH, $D_2O$ exchangeable). $^{13}$C NMR (75 MHz, $CDCl_3$): 33.5, 65.6, 107.3, 117.3, 125.3, 125.5, 125.6, 126.9, 127.6, 133.4, 136.5, 137.1, 147.3, 148.3, 165.9, 173.3. Anal. calcd for $C_{16}H_{12}N_4O_3S_2$ (MW=372$[M+H]^+$): C, 51.60; H, 3.25; N, 15.04. Found: C, 51.57; H, 3.23; N, 15.01.

2-(4-Chlorophenyl)-3-(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)-1,3-thiazolan-4-one(4c); Yield: 70%, mp: 181-183°, IR ($cm^{-1}$): 3305 (NH), 1710 (C=O). $^1$H NMR (300 MHz, $CDCl_3$): 4.10 (s, 2H, thiazole-$CH_2$), 4.19 (s, 1H, SH), 5.31 (s, 1H, thiazole –CH), 6.94-7.77 (m, 7H, ArH), 8.62 (s, 1H, NH, $D_2O$ exchangeable).$^{13}$ C NMR (75 MHz, $CDCl_3$): 34.8, 64.4**,** 111.5, 113.2,116.2, 125.5, 128.1, 130.5, 130.5, 132.3, 133.2, 135.2, 137.3, 135.5, 137.7, 166.2 Anal.calcd for $C_{16}H_{12}ClN_3OS_2$ (MW=361$[M+H]^+$): C, 53.11; H, 3.34; N, 11.61. Found: C, 53.14; H, 3.32; N, 11.58.

2-(4-Methoxyphenyl)-3-(2-sulfanyl-1*H*-benzo[*d*] imidazol-5-yl)-1,3-thiazolan-4-one(4d); Yield: 71%, mp: 178-181°. IR($cm^{-1}$): 3117(NH), 1705 (C=O). $^1$H NMR(300 MHz, $CDCl_3$): 3.60 (s, 3H, $OCH_3$).4.00 (s, 2H, thiazole-$CH_2$), 4.26(s, 1H, SH), 5.52 (s, 1H, thiazole–CH), 6.92-7.84 (m, 7H, ArH),8.46 (s, 1H, NH, $D_2O$ exchangeable).$^{13}$C NMR (75 MHz, $CDCl_3$): 34.5, 56.8, 67.6,111.2,112.5,113.2,116.4,125.5, 127.3, 131.5, 132.3,133.1,133.3,141.1,163.7,170.0,173.2. Anal. calcd for $C_{17}H_{15}N_3O_2S_2$(MW=357 $[M+H]^+$): C, 57.12;H, 4.23 N, 11.76. Found: C, 57.16; H, 4.26; N, 11.73.

2-[4-(Dimethylamino)phenyl]-3-(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)-1,3-thiazolan-4-one(4e); Yield: 69%, mp:160-162°. IR ($cm^{-1}$): 3325 (NH), 1725 (C=O). $^1$H NMR (300 MHz, $CDCl_3$): 4.18 (s, 2H, thiazole-$CH_2$), 4.23 (s, 1H, SH), 5.49 (s, 1H, thiazole–CH), 7.10-7.93 (m, 7H, ArH), 8.24 (s, 1H, NH, $D_2O$ exchangeable). $^{13}$C NMR (75 MHz, $CDCl_3$): 34.5, 41.2, 43.1, 66.8, 111.5, 114.3, 114.4, 117.3, 125.1, 125.5, 129.2, 130.7, 132.3, 133.1, 137.9, 151.5, 166.2, 172.2. Anal. Calcd for $C_{18}H_{18}N_4OS_2$(MW=370$[M+H]^+$): C, 58.36; H, 4.90; N, 15.12. Found: C, 58.34; H, 4.94; N, 15.17.

2-(4-Bromophenyl)-3-(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)-1,3-thiazolan-4-one(4f);Yield:71%,mp: 186-188°. IR ($cm^{-1}$): 3310 (NH), 1720(C=O).$^1$H NMR (300 MHz, $CDCl_3$): 4.11 (s, 2H, thiazole-$CH_2$), 4.26 (s, 1H, SH), 5.44 (s, 1H, thiazole–CH), 7.00-7.86 (m, 7H, ArH), 8.10 (s, 1H, NH, $D_2O$ exchangeable). $^{13}$C NMR (75 MHz, $CDCl_3$):33.5, 65.6, 111.1, 113.2, 123.3, 125.5, 132.1, 132.4, 132.7, 133.2, 133.3, 133.4, 136.2, 141.1, 170.0, 173.2. Anal. calcd for $C_{16}H_{12}BrN_3OS_2$ (MW=406$[M+H]^+$): C, 47.30; H, 2.98; N, 10.34. Found: C, 47.33; H, 2.92; N, 10.30.

2-(2-Hydroxyphenyl)-3-(2-sulfanyl-1*H*-benzo[*d*] imidazol-5-yl)-1,3-thiazolan-4-one(4g); Yield: 70%, mp: 189-191°. IR ($cm^{-1}$): 3208 (NH), 1709 (C=O). $^1$H NMR (300 MHz, $CDCl_3$): 4.12 (s, 2H, thiazole-$CH_2$), 4.4 1(s, 1H, SH), 5.13 (s, 1H, thiazole–CH), 6.93-7.84 (m, 7H, ArH), 9.21 (s, 1H, NH,$D_2O$ exchangeable), 9.46 (s, 1H, NH, $D_2O$ exchangeable). $^{13}$C NMR (75 MHz, $CDCl_3$): 34.8, 60.5, 111.5, 117.2, 117.5, 120.1, 121.2, 125.6, 130.0, 130.3, 133.1, 135.7, 137.2, 155.5, 166.1, 173.3. Anal. Calcd for $C_{16}H_{13}N_3O_2S_2$ (MW=343$[M+H]^+$): C, 55.96; H, 3.82; N, 12.24. Found: C, 55.99; H, 3.86; N, 12.26.

2-(4-Bromo-2-hydroxyphenyl)-3-(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)-1,3-thiazolan-4-one(4h); Yield: 73%, mp: 175-177 °. IR ($cm^{-1}$): 3300 (NH), 1725 (C=O). $^1$H NMR(300 MHz, $CDCl_3$): 4.14(s, 2H, thiazole-$CH_2$), 4.26(s, 1H, SH), 5.26(s, 1H, thiazole –CH), 7.10-7.86 (m, 6H, ArH), 9.00(s, 1H, NH, $D_2O$ exchangeable). $^{13}$CNMR (75 MHz, $CDCl_3$): 33.5, 59.4, 111.3, 113.2, 115.1, 121.3, 123.3, 125.3, 126.3, 132.2, 133.2, 135.2, 141.1, 160.0, 166.1, 173.5. Anal. calcd for $C_{16}H_{12}BrN_3O_2S_2$ (MW=422 $[M+H]^+$): C, 45.51; H, 2.86; N, 9.95. Found: C, 45.55; H, 2.89; N,9.99.

2-(2-Hydroxy-4-methoxyphenyl)-3-(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)-1,3-thiazolan-4-one (4i);Yield:71%, mp: 155-157°. IR (KBr $cm^{-1}$): 3315(NH), 1745(C=O). $^1$HNMR(300 MHz, $CDCl_3$): 3.63(s, 3H, $OCH_3$), 4.00 (s, 2H, thiazole-$CH_2$), 4.18 (s, 1H, SH), 5.20 (s, 1H, thiazole–CH), 7.05-7.93 (m, 6H, ArH), 9.21 (s, 1H, NH, $D_2O$ exchangeable), 10.02(s, 1H, OH, $D_2O$ exchangeable). $^{13}$C NMR (75 MHz, $CDCl_3$): 34.8, 56.9, 58.9, 103.3, 104.4, 111.5, 112.4, 113.2, 125.4, 132.3, 133.1, 133.3, 141.1, 159.2, 158.4, 166.1, 173.0. Anal. calcd for $C_{17}H_{15}N_3O_3S_2$ (MW=373 $[M+H]^+$): C, 54.68; H, 4.05; N, 11.25. Found: C, 54.63; H, 4.01; N, 11.22.

2-(4-Chloro-2-hydroxyphenyl)-3-(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)-1,3-thiazolan-4-one (4j); Yield: 72%, mp: 156-158°. IR($cm^{-1}$): 3345(NH), 1735(C=O). $^1$H NMR (300 MHz, $CDCl_3$): 4.10 (s, 2H, thiazole-$CH_2$), 4.20(s,1H,SH), 5.31 (s, 1H, thiazole–CH), 7.00-7.36 (m, 6H, ArH), 9.00 (s, 1H, NH, $D_2O$ exchangeable),10.01 (s, 1H, OH, $D_2O$ exchangeable). $^{13}$C NMR (75 MHz, $CDCl_3$): 34.8, 60.4, 111.5, 117.2, 118.2, 118.4, 123.2, 125.6, 133.2, 133.3, 136.3, 137.1, 140.2, 155.2, 166.2, 173.2. Anal. calcd for $C_{16}H_{12}ClN_3O_2S_2$ (MW=377$[M+H]^+$): C, 50.86; H, 3.20; N, 11.12. Found: C, 50.89; H, 3.24; N, 11.10.

**Synthesis of 5-amino-2,7-diaryl-3-(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)-3,7-dihydro-2*H*-pyrano [2,3-*d*][1,3]thiazole-6-carbonitriles (5a-j), general procedure:**

To a solution of 2-aryl-3-(2-sulfanyl-1*H*-benzo[*d*] imidazol-5-yl)-1,3-thiazolan-4-one 4(0.01 mol) in ethanol (15 ml) 2-(phenyl methylene) malononitrile (0.01 mol) was added. The reaction mixture was heated at 80° for 4 h and then poured into ice-cold water. The separated solid was collected by filtration, dried and purified by recrystallization from ethyl acetate.

(5-Amino-2,7-diphenyl-3-(2-sulfanyl-1*H*-benzo[*d*] imidazol-5-yl)-3,7-dihydro-2H-pyrano[2,3-*d*] [1,3] thiazole-6-carbonitrile (5a); Yield: 73%, mp: 218-220°. IR($cm^{-1}$): 3410($NH_2$), 3118 (NH), 2204 (C≡N).$^1$H NMR (300 MHz, $CDCl_3$): 4.01 (s, 1H, SH), 4.26 (s, 1H, CH), 5.56 (s, 1H, CH), 6.86-7.86 (m, 13H, ArH), 8.00 (s, 1H, NH, $D_2O$ exchangeable), 9.10 (s, 2H, $NH_2$, $D_2O$ exchangeable).$^{13}$C NMR (75 MHz, $CDCl_3$): 18.7**,** 23.8, 52.9**,** 53.4, 85.6**,** 103.2, 117.3, 118.2, 122.4, 123.3, 125.1, 126.4, 127.2, 129.1, 130.7, 139.4, 141.3, 141.4, 142.1, 143.2, 156.2, 166.1.Anal. Calcd for $C_{26}H_{19}N_5OS_2$ (MW=481$[M+H]^+$): C, 64.84; H, 3.98; N, 14.54. Found: C, 64.80; H, 3.95; N, 14.59.

5-Amino-2-(4-nitrophenyl)-7-phenyl-3-(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)-3,7-dihydro-2*H*-pyrano[2,3-*d*] [1,3]thiazole-6-carbonitrile(5b); Yield: 71%, mp: 231-233°. IR ($cm^{-1}$): 3425 ($NH_2$), 3300 (NH), 2200 (C≡N),1538, 1320 ($NO_2$). $^1$H NMR (300 MHz, $CDCl_3$): 4.16 (s, 1H, SH), 5.15 (s, 1H, CH), 5.36 (s, 1H, CH), 6.93-7.80 (m, 12H, ArH), 8.42 (s, 1H, NH, $D_2O$ exchangeable), 8.82 (s, 2H, $NH_2$, $D_2O$ exchangeable). $^{13}$C NMR (75 MHz, $CDCl_3$): 42.5**,** 53.4, 57.3, 81.2, 103.3, 117.3, 119.0, 120.1, 125.2, 125.6, 126.6, 127.4, 129.4, 129.7, 129.7, 130.2, 130.3, 130.4, 139.4, 141.3, 143.4, 144.2, 148.5, 150.0, 160.1, 170.5. Anal. calcd for $C_{26}H_{18}N_6O_3S_2$ (MW=526$[M+H]^+$): C, 59.30; H, 3.45; N, 15.96.F ound: C, 59.34; H, 3.42; N, 15.94.

5-Amino-2-(4-chlorophenyl)-7-phenyl-3-(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)-3,7-dihydro-2*H*-pyrano[2,3-*d*][1,3]thiazole-6-carbonitrile(5c); Yield: 70%,mp: 197-199°.IR ($cm^{-1}$): 3400 ($NH_2$), 3200 (NH), 2205 (C≡N). $^1$H NMR (300 MHz, $CDCl_3$): 4.26(s, 1H, SH), 5.14(s, 1H, CH), 5.44 (s, 1H, CH), 7.00-7.84 (m, 12H, ArH), 8.26 (s, 1H, NH, $D_2O$ exchangeable), 8.80 (s, 2H, $NH_2$, $D_2O$ exchangeable). $^{13}$C NMR (75 MHz, $CDCl_3$): 41.3, 52.4, 58.2, 80.1, 103.4, 117.4, 119.0, 121.1, 127.1, 126.8, 129.3, 127.4, 129.4, 129.4, 130.1, 130.1, 130.2, 130.4, 130.6, 139.4, 141.3, 142.1, 143.4, 144.4, 161.2, 166.6. Anal. calcd for $C_{26}H_{18}ClN_5OS_2$ (MW=516$[M+H]^+$): C, 60.52; H, 3.52; N, 13.57. Found: C, 60.49; H, 3.49; N, 13.54.

5-Amino-2-(4-methoxyphenyl)-7-phenyl-3-(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)-3,7-dihydro-2*H*-pyrano[2,3-*d*][1,3]thiazole-6-carbonitrile (5d); Yield: 74%, mp: 206-208°. IR ($cm^{-1}$): 3410 ($NH_2$), 3245 (NH), 2200 (C≡N). $^1$H NMR (300 MHz, $CDCl_3$): 3.57 (s, 3H, $OCH_3$), 4.08 (s, 1H, SH), 5.21 (s, 1H, CH), 5.34 (s, 1H, CH), 7.05-7.96 (m, 12H, Ar H),

8.00 (s, 1H, NH, $D_2O$ exchangeable), 8.96 (s, 2H, $NH_2$, $D_2O$ exchangeable).$^{13}$C NMR (75 MHz,CD $Cl_3$): 42.5, 52.2, 54.4, 56.9, 81.8, 103.4, 112.3, 116.3, 117.6, 118.0, 121.1, 126.7, 127.3, 129.0, 129.3, 129.4, 130.3, 130.3 ,130.5, 132.2, 139.5, 141.4, 143.3, 144.1, 160.0, 160.2, 166.2. Anal. calcd for $C_{27}H_{21}N_5O_2S_2$ (MW=511[M+H]$^+$): C, 63.39; H, 4.14; N, 13.69. Found: C, 63.36; H, 4.11; N, 13.64.

5-Amino-2-[4-(dimethylamino)phenyl]-7-phenyl-3-(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)-3,7-dihydro -2*H*-pyrano[2,3-*d*][1,3]thiazole-6-carbonitrile (5e); Yield: 69%,mp: 193-195°. IR (cm$^{-1}$): 3400 ($NH_2$), 3210 (NH), 2205 (C≡N). $^1$H NMR (300 MHz, $CDCl_3$): 3.12 (s, 6H, N $(CH_3)_2$), 4.00 (s, 1H, SH), 5.26 (s, 1H, CH), 5.40 (s, 1H, CH), 7.00-7.85 (m, 12H, ArH), 8.66 (s, 1H, NH,$D_2O$ exchangeable), 9.3 (s, 2H, $NH_2$, $D_2O$ exchangeable).$^{13}$C NMR (75 MHz, $CDCl_3$): 39.9, 41.2, 41.5, 55.4, 58.9, 83.0, 103.6, 114.2, 114.9, 117.6, 119.0, 121.4, 128.4, 128.4, 127.4, 129.4, 129.4, 129.3, 130.5, 130.6, 133.5, 139.9, 140.7, 143.6, 142.6, 144.5, 151.4, 161.2, 170.2. Anal. Calcd for $C_{28}H_{24}N_6OS_2$(MW=524[M+H]$^+$): C, 64.10; H, 4.61; N, 16.02. Found: C,64. 15; H, 4.69; N, 16.07.

5-Amino-2-(4-bromophenyl)-7-phenyl-3-(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)-3,7-dihydro-2*H*-pyrano[2,3-*d*][1,3]thiazole-6-carbonitrile (5f); Yield: 70%, mp: 201-203°. IR(cm$^{-1}$): 3405 ($NH_2$), 3200 (NH), 2220 (C≡N). $^1$H NMR(300 MHz, $CDCl_3$): 4.14 (s, 1H, SH), 5.18 (s, 1H, CH), 5.36 (s, 1H, CH), 6.86-7.68 (m, 12H, ArH), 8.41(s, 1H, NH, $D_2O$ exchangeable), 9.00 (s, 2H, $NH_2$, $D_2O$ exchangeable). $^{13}$C NMR (75 MHz, $CDCl_3$): 42.5, 54.4, 57.9, 83.0, 103.4, 113.6, 119.0, 121.1, 123.4, 125.4, 126.6, 126.6, 127.7, 129.3, 129.7, 133.6, 130.4, 131.9, 132.6, 137.7, 139.9, 144.2, 142.4, 142.9, 161.2, 166.2. Anal. calcd for $C_{26}H_{18}BrN_5OS_2$ (MW=560[M+H]$^+$): C, 55.72; H, 3.24; N, 12.50. Found: C, 55.70; H, 3.28; N, 12.56.

5-Amino-2-(2-hydroxyphenyl)-7-phenyl-3-(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)-3,7-dihydro-2*H*-pyrano[2,3-*d*][1,3]thiazole-6-carbonitrile(5g);Yield: 73%, mp: 211-213°. IR (cm$^{-1}$): 3410 ($NH_2$),3225 (NH), 2210 (C≡N).$^1$H NMR (300 MHz, $CDCl_3$): 4.06 (s, 1H, SH), 5.14 (s, 1H, CH), 5.42 (s, 1H, CH), 7.05-7.86 (m, 12H, ArH), 8.66 (s, 1H, NH, $D_2O$ exchangeable), 9.26 (s, 2H, $NH_2$, $D_2O$ exchangeable), 9.40 (s, 1H, OH, $D_2O$ exchangeable). $^{13}$C NMR (75 MHz, $CDCl_3$): 42.5, 52.2, 54.9, 81.0, 103.4, 113.6, 113.9, 114.0, 121.1, 122.8, 123.3, 123.7, 125.3, 125.7, 125.7, 126.2, 126.5, 129.0, 130.6, 135.9, 137.7, 143.3, 144.2, 154.7, 157.2, 166.2. Anal. calcd for $C_{26}H_{19}N_5O_2S_2$ (MW=497[M+H]$^+$): C, 62.76; H,3.85; N, 14.07. Found: C, 62.73; H, 3.84; N, 14.09.

5-Amino-2-(4-bromo-2-hydroxyphenyl)-7-phenyl-3-(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)-3,7-dihydro-2*H*-pyrano[2,3-*d*][1,3]thiazole-6-carbonitrile(5h); Yield: 69%, mp: 225-227°. IR (cm$^{-1}$): 3405 ($NH_2$), 3310 (NH), 2200 (C≡N).$^1$H NMR (300 MHz, $CDCl_3$): 4.10 (s, 1H, SH), 4.26 (s, 1H, CH), 5.26 (s, 1H, CH), 6.93-7.71 (m, 11H, ArH), 8.42 (s, 1H, OH, $D_2O$ exchangeable), 9.01 (s,1H, NH, $D_2O$ exchangeable), 9.25 (s, 2H, $NH_2$, $D_2O$ exchangeable). $^{13}$C NMR (75 MHz, $CDCl_3$): 41.5, 53.2, 54.9, 83.0, 103.4, 113.3, 117.4, 119.0, 121.1, 121.2, 123.7, 123.7, 125.7, 126.2, 126.6, 126.6, 129.3, 129.7, 133.3, 139.4, 141.3, 142.2, 144.2, 159.0, 157.2, 166.2. Anal. calcd for $C_{26}H_{18}BrN_5O_2S_2$ (MW=576[M+H]$^+$): C, 54.17; H, 3.15; N, 12.15. Found: C, 54.18; H, 3.18; N, 12.10.

5-Amino-2-(2-hydroxy-4-methoxyphenyl)-7-phenyl-3-(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)-3,7-dihydro-2*H*-pyrano[2,3-*d*][1,3]thiazole-6-carbonitrile(5i); Yield: 74%, mp: 215-217°. IR(cm$^{-1}$): 3424 ($NH_2$), 3249 (NH), 2203 (C≡N). $^1$HNMR (300 MHz, $CDCl_3$): 3.64 (s, 3H, $OCH_3$), 4.10 (s, 1H, SH), 5.25 (s, 1H, CH), 5.26 (s, 1H, CH), 7.05-7.82 (m, 13H, ArH), 8.20 (s, 1H, NH, $D_2O$ exchangeable), 8.64 (s, 2H, $NH_2$, $D_2O$ exchangeable), 8.92 (s, 1H, OH, $D_2O$ exchangeable).$^{13}$C NMR (75 MHz, $CDCl_3$):41.5, 52.2, 52.2, 53.9, 54.8, 83.0, 103.0, 103.4, 108.9, 112.4, 114.0, 115.1, 117.6, 123.7, 129.3, 129.4, 129.6, 129.7, 130.6, 132.1, 135.9, 141.2, 143.4, 144.2, 153.8, 155.9, 161.2, 170.2. Anal. calcd for $C_{27}H_{21}N_5O_3S_2$ (MW=527[M+H]$^+$): C, 61.46; H, 4.01; N, 13.27. Found: C, 61.42; H, 4.06; N, 13.22.

5-Amino-2-(4-chloro-2-hydroxyphenyl)-7-phenyl-3-(2-sulfanyl-1*H*-benzo[*d*]imidazol-5-yl)-3,7-dihydro-2*H*-pyrano[2,3-*d*][1,3]thiazole-6-carbonitrile(5j); Yield: 75%, mp: 220-222°. IR (cm$^{-1}$): 3410 ($NH_2$), 3305 (NH), 2205 (C≡N). $^1$HNMR (300 MHz, $CDCl_3$): 4.25 (s, 1H, SH), 5.05(s, 1H, CH), 5.32 (s, 1H, CH), 7.00-7.63 (m, 11H, ArH), 8.10 (s, 1H, NH, $D_2O$ exchangeable), 8.42 (s, 2H, $NH_2$, $D_2O$ exchangeable), 8.61 (s, 1H, OH, $D_2O$ exchangeable).$^{13}$C NMR (75 MHz, $CDCl_3$): 40.5, 50.2, 59.9, 82.0, 103.4, 113.6, 114.7, 115.0, 117.1, 120.9, 123.4, 123.7, 125.7, 125.7,

127.6, 129.3, 130.6, 132.5, 133.3, 137.7, 139.9, 143.4, 144.2, 157.2, 158.2, 166.2. Anal. calcd for $C_{26}H_{18}ClN_5O_2S_2$ (MW=532[M+H]$^+$): C, 58.70; H, 3.41; N, 13.16. Found: C, 58.63; H, 3.44; N, 13.19.

***In vitro* antiinflammatory activity by human red blood cell membrane stabilization method:**

Human red blood cell membrane stabilization method (HRBC method) was used for the estimation of antiinflammatory activity *in vitro*[17]. Blood was collected from healthy volunteers and was mixed with equal volume of sterilized Alsevers solution. This blood solution was centrifuged at 3000 rpm and the packed cells were separated. The packed cells were washed with isosaline solution and a 10% v/v suspension was made with isosaline. This HRBC suspension was used for the estimation of antiinflammatory property. The concentrations of synthetic compounds 100 µg/ml, reference sample and control were separately mixed with 1 ml of phosphate buffer, 2 ml of hyposaline and 0.5 ml of HRBC suspension. All the assay mixtures were incubated at 37° for 30 min and centrifuged at 3000 rpm. The supernatant liquid was decanted and the hemoglobin content was estimated by a spectrophotometer at 560 nm. Content was estimated by a spectrophotometer at 560 nm. The percent hemolysis was estimated by assuming the hemolysis produced in the control as 100%, percent protection =100−(OD sample/OD control)×100. Antiinflammatory activity data of newly synthesized compounds resulted are shown in Table 1.

**Antioxidant assay:**

For the evaluation of antioxidant activity, we have used a stable-free radical α,α-diphenyl-β-picrylhydrazyl (DPPH), at the concentration of 0.2 mM in methanol[18]. To 0.1 ml of the test compound (at different concentrations), 1.5 ml of methanol and 0.5 ml of DPPH solution were added, mixed thoroughly and absorbance (OD) was read at 517 nm against the blank. The % reduction of the free radical concentration (OD) with different concentration of test compounds was calculated and was compared with standard ascorbic acid. The results were expressed as $IC_{50}$values (the concentration of the test required to scavenge 50% free radicals). The antioxidant DPPH free radical scavenging activity of all the synthesized compounds performed using DPPH method results shown in Table 2.

**TABLE 1: *IN VITRO* ANTIINFLAMMATORY OF BENZIMIDAZOLYLPYRANO[2,3-*d*][1,3] THIAZOLOCARBONITRILES (5a-j)**

| Compound | Concentration of synthetic compounds Dose (100 µg/ml) | | |
|---|---|---|---|
| | R | R' | Percent protection |
| 5a | H | H | 54.12 |
| 5b | H | $NO_2$ | 18.56 |
| 5c | H | Cl | 62.46 |
| 5d | H | $OCH_3$ | 14.78 |
| 5e | H | N $(CH_3)_2$ | 60.88 |
| 5f | H | Br | 40.99 |
| 5g | OH | H | 15.98 |
| 5h | OH | Br | 68.12 |
| 5i | OH | $OCH_3$ | 32.39 |
| 5j | OH | Cl | 69.01 |
| Control | - | - | - |
| Standard | Diclofenac sodium | | 64.72 |

**TABLE 2: ANTIOXIDANT ACTIVITY OF BENZIMIDAZOLYLPYRANO[2,3-*d*][1,3] THIAZOLOCARBONITRILES (5a-j)**

| Compound | R | R' | $IC_{50}$ (µM) |
|---|---|---|---|
| 5a | H | H | 18.10 |
| 5b | H | $NO_2$ | 14.16 |
| 5c | H | Cl | 26.02 |
| 5d | H | $OCH_3$ | 20.05 |
| 5e | H | N $(CH_3)_2$ | 24.10 |
| 5f | H | Br | 17.03 |
| 5g | OH | H | 15.06 |
| 5h | OH | Br | 13.02 |
| 5i | OH | $OCH_3$ | 16.20 |
| 5j | OH | Cl | 17.18 |
| | Ascorbic acid | | 8.64 |

## RESULTS AND DISCUSSION

The synthesis of the compounds (3-5) was accomplished by the synthetic route shown in scheme 1. The reaction of 5-amino-2-mercaptobenzimidazole (1), with substituted aldehydes (2) in refluxing ethanol furnished (*Z*)-5-(arylideneamino)-1*H*-benzo[*d*]imidazole-2-thiols (3) in quantitative yields (68-74%). Cyclocondensation of 3 with mercaptoacetic acid in boiling ethanol afforded benzimidazolyl-1,3-thiazolan-4-ones (4). Compound 4 reacted with 2-(phenylmethylene) malononitrile in boiling ethanol delivered the corresponding benzimidazolylpyrano[2,3-*d*][1,3] thiazolecarbonitrile (5). The formation benzimidazolyl pyrano[2,3-*d*][1,3]thiazolecarbonitriles is explained with the plausible mechanism (Scheme 2). The reaction occurs *via* an initial Michael addition of the endocyclic methylene group in 4 to the activated double bond in 6 to give the intermediate A,

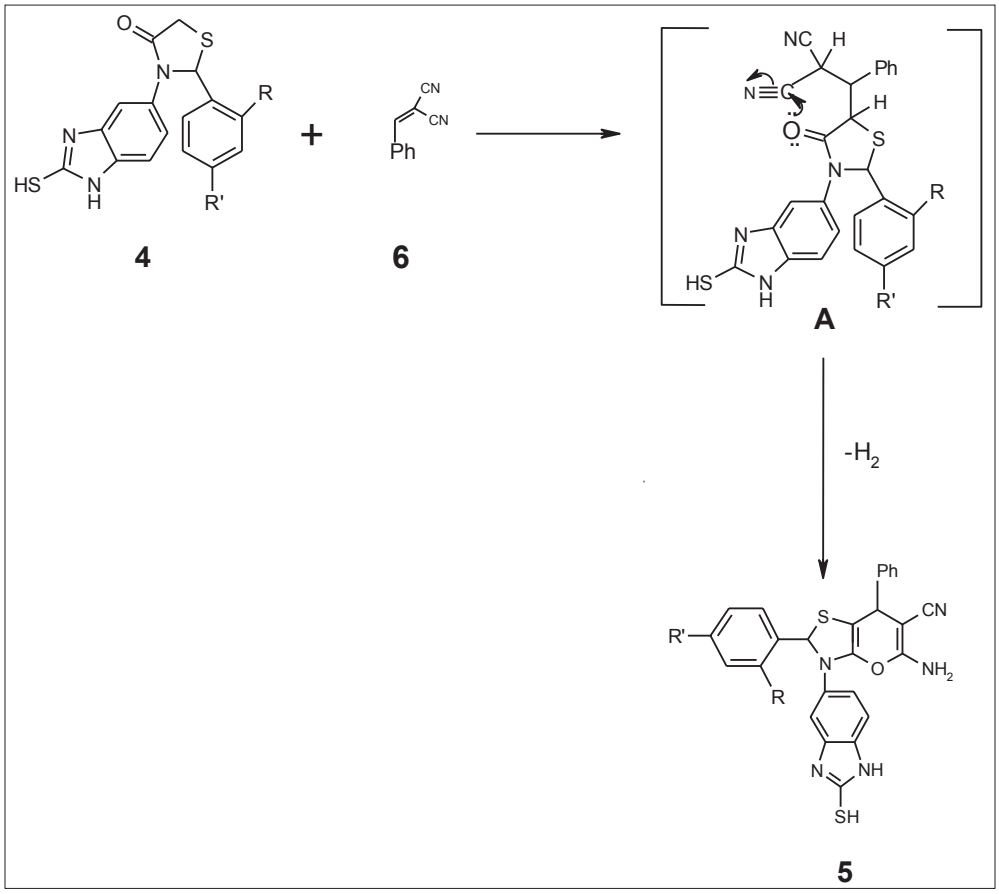
which underwent cyclization through addition of oxygen to the nitrile functional group followed by autooxidation[19] to afford the final product 5. The structures of the products (3-5) have been elucidated on the basis of IR, $^1$HNMR, $^{13}$CNMR and MS spectral data.

Compound 3 displayed a characteristic absorption band in the IR spectra around 3121 cm$^{-1}$ due to the NH functional group. In the $^1$HNMR spectra of 3, the absence of $NH_2$ proton signals, which are present in its precursor 1, establish the formation of Schiff base. The mass spectrum of 3 agrees well with the condensed product formed. Compound 4 displayed a characteristic absorption band in IR spectra around 1695 cm$^{-1}$ due to the C=O functional group. In the $^1$H NMR spectrum of 4, displayed distinct singlets at δ 4.12 and 5.62 due to thiazole-$CH_2$ and thiazole-CH protons of the thiazolone ring, confirming the formation of the thiazole ring.

IR spectra of compounds 5 displayed a characterization absorption band around 3380 and 2204 cm$^{-1}$ due to $NH_2$ and CN functional groups. The absence of C=O functional group absorption band which is present in its precursor 4, clearly confirms the formation of pyran ring. The $^1$HNMR spectral of 5 exhibited singlet at δ 5.56 due to pyran-CH protons, confirming the formation of the pyran ring.

The newly synthesized compounds (5a-j) were tested for *in vitro* antiinflammatory activity. Compared to the standard, diclofenac sodium, they have shown adequate antiinflammatory activity. *In vitro* antiinflammatory activity of synthesized compounds is summarized in Table 1. Among all the tested compounds 5c, 5e, 5h and 5j possessing chloro, *N,N*-dimethylamine, hydroxylbromo and hydroxylchloro groups as substituents on the benzene ring showed potent activity in the compound 5 series. The compound 5a have showed moderate activity because it has no substituent on the benzene ring. While other compounds having weak activity.

The antioxidant or DPPH free radical scavenging activity of all the synthesized compounds (5a-j)




**Scheme 2. The mechanistic equations for formation of pyrano[2,3-*d*] thiazolocarbonitriles.**

performed using DPPH method and the results were found in Table 2. All the synthesized compounds produced a concentration dependant scavenging of free radical, DPPH. The $IC_{50}$ values of all the compounds (5a-j) were found between 13 and 26 µM, with antioxidant activity. In the series, compounds 5b, 5g and 5h possessing nitro, hydroxyl and hydroxylbromo groups as substitutions on benzene ring showed better activity against DPPH free radicals. This may be due to the increased lipophilicity of molecules because of substitution with electronegative atom such as chloro/bromo at the $C_2$ and $C_4$ positions of the aromatic ring. These results suggest that $C_2$ and $C_5$ substitution increases the antioxidant activity of benzimidazolyl pyrano[2,3-*d*][1,3]thiazolocarbonitriles.

In conclusion, a elegant synthesis of benzimidazolyl pyrano[2,3-*d*][1,3]thiazolo carbonitriles were achieved by using in expensive and commercial available staring material, moreover, fused pyrano ring derivatives are potent pharmacological agent, this study may motivates the researchers concerned in this field to explore the pharmacological activity of the compounds.

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