Synthesis and Evaluation of Antimicrobial Activity of Some Novel Heterocyclic Compounds from 5-Bromosalicylaldehyde

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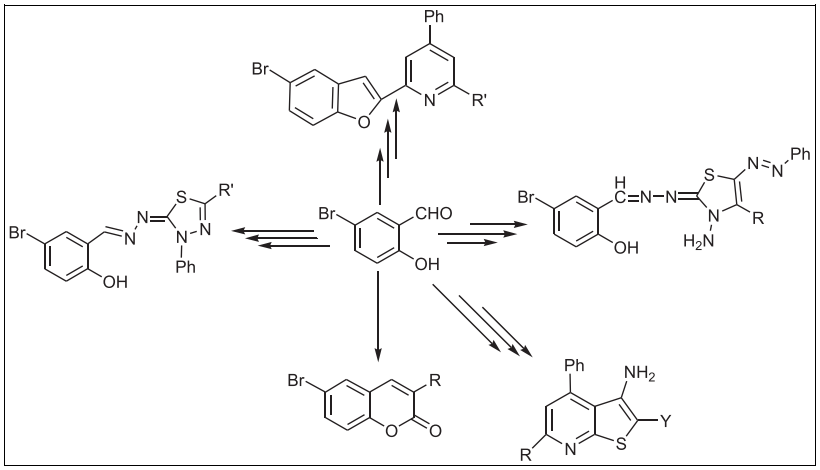


A novel series of coumarins, thiadiazoles, thiazoles, and pyridines were synthesized *via* reaction of 5-bromosalicylaldehyde with different reagents. Thus, 5-bromosalicylaldehyde **1** was reacted with compounds **2a–d** affording iminocoumarins **3a–d**, which on hydrolysis with 10% hydrochloric acid, afforded coumarins **4a–d**, respectively. On the other hand, reaction of **1** with benzylhydrazinecarbodithioate **5** afforded derivative **6**, which reacted with hydrazonoyl halides **7a–f**, afforded 1,3,4-thiadiazoles **11a–f**, respectively. Moreover, thiazoles **15** and **16** were obtained *via* reaction of **1** with thiocarbohydrazide **13** and hydrazonoyl halides. However, condensation of 2-acetyl-5-bromobenzofuran **17** with benzaldehyde afforded chalcone **18**, which reacted with pyridiniumbromides **19a–c**, afforded pyridines **20a–c**, respectively. Furthermore, pyridines **21–24** were synthesized from the reaction of chalcone **18** with different active methylene compounds. Reaction of **24** with ethylchloroacetate, chloroacetone, and chloroacetonitrile afforded thienopyridines **26a–c**, respectively. The structures of the newly synthesized compounds were established based on their spectral data and elemental analyses. Also, selected newly synthesized compounds were screened for their antimicrobial activity against various microorganisms by disk diffusion method.

INTRODUCTION

Due to the interesting activity of coumarins as biological agents, considerable attention has been focused on this class of heterocycles. The pharmaceutical importance of these compounds lies in the fact that they can be utilized as anti-inflammatory [1], anticancer [2], anticoagulant [3], antimicrobial, and antioxidant activities [4,5]. A literature survey revealed that a special attention was given to 1,3,4-thiadiazole derivatives that proved to have promising biological activities such as antimicrobial [6–8], anticancer [9–11], antioxidant [12], antiamoebic [13], anticonvulsant [14], anti-inflammatory, and analgesic activities [15]. Also, 1,3-thiazoles have promising biological activities such as antimicrobial [16,17], anticancer [18], anti-inflammatory, analgesic, and anti-ulcerogenic activities [19].

On the other hand, pyridine derivatives are very interesting heterocycles, having a wide range of biological activities. They are known to exhibit anticancer and antimicrobial [20,21], anti-inflammatory, anti-ulcer, analgesic, anticonvulsant, and antiparkinsonian activities [22,23]. In view of all these facts, we report herein a convenient general method for synthesis of coumarins, thiadiazoles, thiazoles, and pyridines and evaluating their antimicrobial activity.

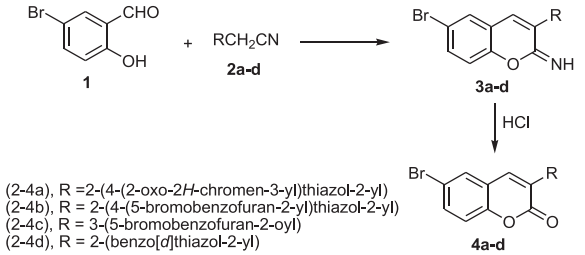
RESULTS AND DISCUSSION

In the interest of the aforementioned suggestion, Knoevenagel condensation of 5-bromosalicylaldehyde (**1**) with 2-(4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl)acetonitrile (**2a**) [24], 2-(4-(5-bromobenzofuran-2-yl)thiazol-2-yl)

acetonitrile (**2b**) [25], 3-(5-bromobenzofuran-2-yl)-3-oxopropanenitrile (**2c**), and 2-(benzo[*d*]thiazol-2-yl) acetonitrile (**2d**) [26] under solvent-free condition led to formation of the corresponding iminocoumarins **3a–d**, respectively (Scheme 1). The structure of the reaction products was ascertained on the basis of their elemental analysis and spectral data, where the IR spectra showed the absence of cyano function and displayed an absorption bands at 3280–3210 cm^{-1} characteristic to NH group. Also, their ^1H NMR spectra showed the absence of CH_2 proton and revealed a new signal at δ = 8.50–10.80 ppm corresponding to NH group of imino in addition to other signals due to the rest of the molecule.

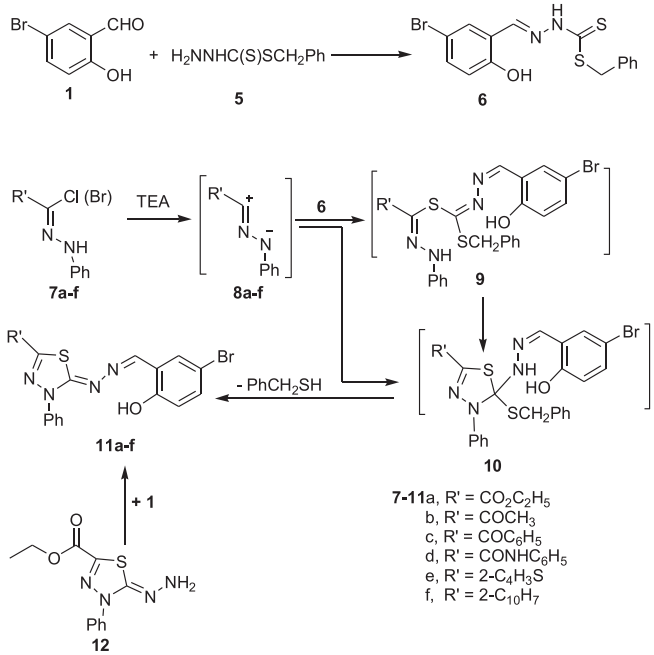
Furthermore, iminocoumarins **3a–d** undergo hydrolysis upon grinding with few drops of concentrated hydrochloric acid affording the corresponding coumarin derivatives **4a–d** (Scheme 1). The structure of compounds **4a–d** was established through elemental analyses and spectroscopic data. (See Experimental section.)

Scheme 1. Synthesis of coumarins **3a–d** and **4a–d**.



On the other hand, grinding of 5-bromosalicylaldehyde (**1**) with benzylhydrazinecarbodithioate (**5**) [27] in the presence of two drops of acetic acid afforded benzyl 2-(5-bromo-2-hydroxybenzylidene)hydrazine-1-carbodithioate (**6**) (Scheme 2). The structure of **6** was confirmed *via* spectral data, elemental analysis, and chemical transformation. The IR spectrum of compound **6** revealed the disappearance of carbonyl group and the presence of characteristic band at 3209 cm^{-1} for NH group. Thus, benzylhydrazinecarbodithioate derivative **6** and the appropriate hydrazonoyl halides **7a–f** [28–33] were mixed and grinded with three drops of triethylamine underwent cyclization affording 1,3,4-thiadiazole derivatives **11a–f**, respectively (Scheme 2). The structure of **11a–f** was established based on elemental analyses, spectroscopic data, and alternative synthetic routes. Thus, ethyl 5-hydrazono-4-phenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (**12**) [34] was reacted with **1** giving product identical in all aspects (mp, mixed mp, and spectra) with **11a**. The IR spectra of **11a–f** revealed absorption bands in the range of 1652–1716 cm^{-1} due to the carbonyl group. The ^1H NMR spectrum of **11a** as an example showed new signals at δ = 1.42 and 4.44 ppm correspond to triplet and quartet signals of the ester group, respectively. The formation of compounds **11a–f** could be interpreted through the elimination of benzyl mercaptan from the corresponding cycloadduct **10**, which are assumed to be formed from thiohydrazonate **9**, which undergo intermolecular cyclization as soon as it is formed to yield the intermediate **10** or *via* 1,3-dipolar cycloaddition of

Scheme 2. Synthesis of 1,3,4-thiadiazoles **11a–f**.



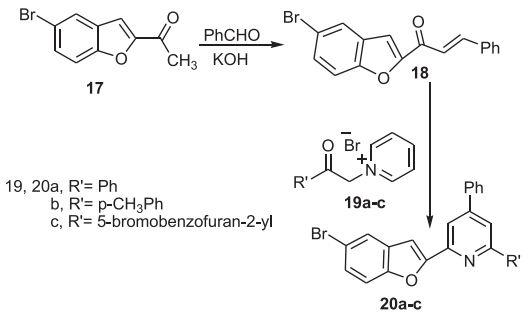
nitrileimine **8** [prepared *in situ* from **7a–f** with triethylamine] to the C═S double bond of **6**. The formation of **9** and **10** is similar to the reaction of hydrazonoyl chloride with 1-phenyl-1,4-dihydrotetrazole-5-thione [35] and 5-phenyl-1,3,4-thiadiazole-2(3*H*)-thione [36] as shown in Scheme 2.

Moreover, 5-bromosalicylaldehyde (**1**) condenses easily with hydrazine carbothiohydrazide (**13**) [37] in acetic acid, afforded 1-(5-bromo-2-hydroxybenzylidene) thiocarbonohydrazide (**14**) in excellent yield (Scheme 3). The IR spectrum of **14** showed absorption bands in the region 3417, 3387, 3290, and 3132 cm^{-1} due to OH, NH_2 and N–H stretching and 1280 cm^{-1} was attributed to C═S bond vibration. Compound **14** was used as the key intermediate in the synthesis of the desired thiazoles *via* its reaction with the appropriate hydrazonoyl halides **7a–c**. Thus, compound **14** was reacted with *C*-ethoxycarbonyl-*N*-phenylhydrazonoyl chloride **7a** in ethanol containing few drops of trietylamine under reflux, afforded one isolable product that may be formulated as **15** or **15A**. To get evidence for the correct product, molecular orbital calculation is carried out. The calculation using Gaussian 9 package for the two possible structures uses basis set b3lyp/6-31G*; the total energy values for **15** are more stable than **15A** according to the two values respectively (−2529077.4 and −2529026.1 kcal/mol). The UV spectrum for the product shows main band at 350.5 nm; the calculation transitions for the two structures (**15** and **15A**) give 348.0 and 339.8 nm, respectively. This gives evidence that the agreement is between the calculation of **15** and the experimental data.

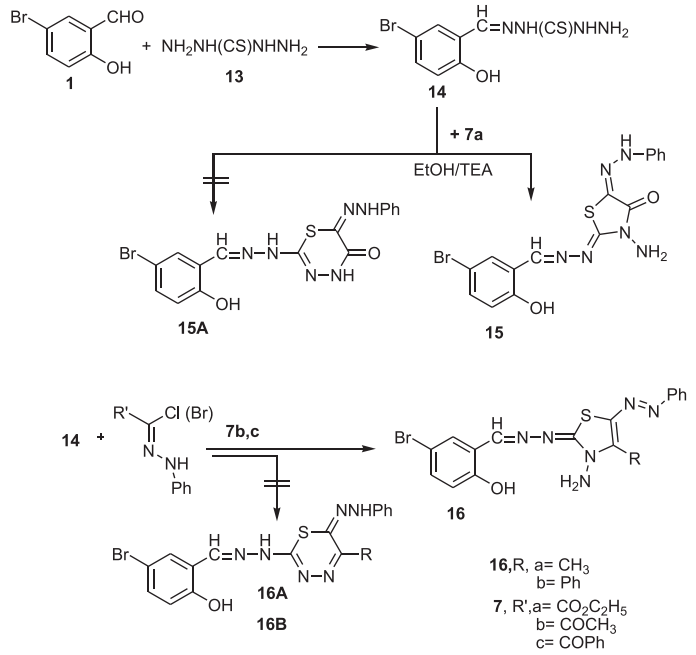
Similarly, compounds **7b** and **7c** were reacted with **14** to afford 1,3-thiazoles **16a** and **16b**, respectively, as shown in Scheme 3. Structure **16A** was ruled out based on molecular orbital calculation. The value of the total energy for the structure **16** is more stable than **16A** (−2551646.4 and −2551615.667 kcal/mol), respectively. The UV spectrum for the product shows main bands at 408 and 468 nm; the calculated transitions for two possible structures showed that **16** is 444.1 and 364.8 nm while **16A** 384.8 and 347 nm. Comparison between the calculated values and the experimental confirmed that structure **16** is the possible structure.

Furthermore, treatment of 2-acetyl-5-bromobenzofuran **17** [38] with benzaldehyde in ethanol in the presence of potassium hydroxide gave 1-(5-bromobenzofuran-2-yl)-3-

Scheme 4. Synthesis of pyridines **20a–c**.



Scheme 3. Synthesis of 1,3-thiazoles **15** and **16a,b**.



phenyl-prop-2-en-1-one (**18**) (Scheme 4). Structure of the product **18** was confirmed on the basis of its correct elemental analysis, spectral data, and chemical transportation. Thus, ^{1}H NMR spectrum of **18** showed signals at δ = 7.26–7.94 (m, 11H, Ar-H's + –CH═CH–). In addition, mass spectrum of **18** showed a molecular ion peak at 328 with a base peak at 327. Thus, compound **18** was reacted with the appropriate of 1-(2-oxo-2-substituted ethyl)pyridinium bromides **19a–c** in acetic acid containing ammonium acetate, afforded 2-(5-bromobenzofuran-2-yl)-4-phenyl-6-substituted pyridines **20a–c** (Scheme 4). Structures **20a–c** were elucidated on the basis of elemental analyses and spectral data. (See Experimental section)

Finally, one-pot reaction of 2-acetyl-5-bromobenzofuran **17**, benzaldehyde and each of malononitrile, ethyl cyanoacetate, benzoyl acetonitrile or cyanothioacetamide in acetic acid containing ammonium acetate afforded pyridine derivatives **21–24**, respectively (Scheme 5). The structures of **21–24** were confirmed on the basis of their elemental analyses and spectral data. For example, the IR spectrum of **21** revealed new bands at 3467 and 3367 cm^{-1} for NH_2 function and 2214 cm^{-1} assigned to CN function. The structure of **21** was also supported by its ^{1}H NMR spectrum, which showed signals at δ = 6.82 ppm for NH_2 beside aromatic protons. Structure **24** was also confirmed by chemical transformation. Thus, compound **24** was reacted with each of iodomethane, ethylchloroacetate, chloroacetone, and chloroacetonitrile in ethanolic potassium hydroxide solution at room temperature, afforded the corresponding products **25** and **26a–c**, respectively (Scheme 5).

ANTIMICROBIAL ACTIVITY

All the tested microorganisms were chosen on the bases of their pathogenicity. The investigation of antibacterial and antifungal screening data revealed that most of the newly synthesized compounds displayed intermediate to low activity in comparison with standards against tested organisms. The organisms were tested against the activity of solutions with two concentrations, 100 and 50 mg/mL, and then 10 μL of each preparation was dropped on disk of 6 mm in diameter and the concentrations became 1 and 0.5 mg/disk, respectively. In the case of insoluble compounds, the compounds were suspended in dimethylformamide (DMF) and vortexed then processed. Chloramphencol was used as standard reference in the case of Gram-negative bacteria, cephalothin was used as standard reference in the case of Gram-positive bacteria, and cycloheximide was used as standard reference in the case of yeasts and fungi evaluating the potency of the tested compounds under the same conditions. The results were depicted in Table 1.

From antibacterial activity data (Table 1), the results demonstrated that for high and low concentrations, compounds **3a**, **11e**, and **14** showed low inhibition activity against Gram-positive bacteria *Staphylococcus aureus*, compound **11b** showed intermediate activity, and the other tested compounds showed no effect. Compounds **6**, **11b**, and **11e** showed low inhibition activity against Gram-positive bacteria *Bacillus subtilis* while compounds **3a**, **14**, and **16b** were capable of intermediate inhibition activity. All the tested compounds exhibited no activity against Gram-positive bacteria *Salmonella typhimurium* except compound **14** that shows low activity. In the case of *Escherichia coli*, only compounds **11b**, **11e**, and **14** were capable intermediate inhibition activity.

From *in vitro* antifungal activity (Table 1), it was shown that compounds **3a**, **14**, **15**, and **16b** were capable of intermediate inhibition activity towards *Candida albicans*, and compounds **4c**, **11b**, and **11e** showed low activity. On the other hand, compound **14** was highly active towards *Aspergillus fumigatus*. Compounds **3c** and **4a** show no effect with all tested microorganisms.

Scheme 5. Synthesis of pyrindines **21–26**.

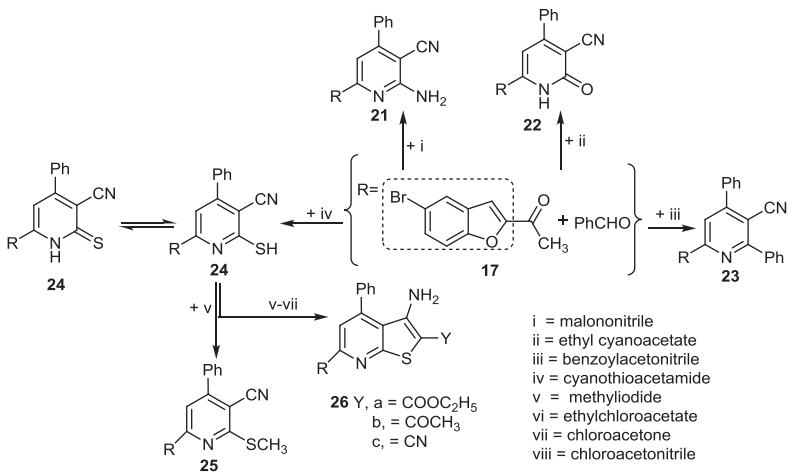


Table 1

Response of various microorganisms to some synthesized compounds *in vitro* culture.

	Mean[a] of zone diameter, nearest whole mm											
	Gram-positive bacteria				Gram-negative bacteria				Yeast and fungi[b]			
Organism	*Staphylococcus aureus*		*Bacillus subtilis*		*Salmonella typhimurium*		*Escherichia coli*		*Candida albicans*		*Aspergillus fumigatus*	
Conc. sample	1 mg/mL	0.5 mg/mL	1 mg/mL	0.5 mg/mL	1 mg/mL	0.5 mg/mL	1 mg/mL	0.5 mg/mL	1 mg/mL	0.5 mg/mL	1 mg/mL	0.5 mg/mL
3a	11 L	8 L	13 I	9 I	—	—	—	—	14 I	12 I	22 I	17 I
3c	—	—	—	—	—	—	—	—	—	—	—	—
4a	—	—	—	—	—	—	—	—	—	—	—	—
4c	—	—	—	—	—	—	—	—	10 L	8 L	13 I	9 I
6	—	—	10 L	7 L	—	—	—	—	—	—	12 L	8 L
11b	12 I	7 L	9 L	7 L	—	—	14 I	11 I	11 L	8 L	8 L	7 L
11e	9 L	7 L	9 L	7 L	—	—	15 I	13 I	10 L	8 L	8 L	7 L
14	10 L	8 L	14 I	12 I	11 L	9 L	13 I	10 I	15 I	13 I	24 I	20 H
15	—	—	8 L	7 L	—	—	—	—	15 I	12 I	—	—
16b	—	—	12 I	9 I	—	—	—	—	14 I	12 I	19 I	16 I
Control #	35	26	35	25	36	28	38	27	35	28	37	26

—, no effect; L, low activity = mean of zone diameter ≤ 1/3 of mean zone diameter of control; I, intermediate activity = mean of zone diameter ≤ 2/3 of mean zone diameter of control; H, high activity = mean of zone diameter > 2/3 of mean zone diameter of control; #, chloramphenicol in the case of Gram-positive bacteria and cephalothin in the case of Gram-negative bacteria.

[a]Calculated from three values.

[b]Identified on the basis of routine culture, morphological, and microscopical characteristics.

CONCLUSIONS

In this work, we carried out a highly effective and simple synthetic procedure to obtain coumarins, thiadiazoles, thiazoles, and pyridines *via* reaction of 5-bromosalicylaldehyde with different reagents. Also, selected newly synthesized compounds were screened for their antimicrobial activity against four bacterial species including Gram-positive bacteria and Gram-negative bacteria as well as two fungal species. The results revealed that compounds **3a**, **14**, and **16b** were capable of intermediate inhibition activity against Gram-positive bacteria *B*. *subtilis*. Compounds **11b**, **11e**, and **14** were capable of intermediate inhibition activity against *E*. *coli*. For antifungal activity, it is evident that compounds **3a**, **14**, **15**, and **16b** shows intermediate inhibition activity towards *C*. *albicans*, while only compound **14** was highly active towards *A*. *fumigatus*.

EXPERIMENTAL

Measurements. All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr disks) on a Shimadzu FTIR 8201 PC spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ and $(CD_3)_2SO$ solutions on a Varian Gemini 300 MHz and JNM-LA 400 FT-NMR system spectrometer, and chemical shifts are expressed in ppm units using TMS as an internal reference. Mass spectra were recorded on a GC–MS QP1000 EX Shimadzu. Elemental analyses were carried out at Microanalytical Center of Cairo University, Cairo, Egypt. Screening of antimicrobial activity was performed at a Microbiology Lab in Faculty of Agriculture, Al-Azhar University, Cairo, Egypt.

Synthesis. ***Synthesis of 3-(5-bromobenzofuran-2-yl)-3-oxopropanenitrile (2c).*** A mixture 2-bromo-1-(5-bromobenzofuran-2-yl)ethanone (3.17 g, 10 mmol) and potassium cyanide (3.17 g, 10 mmol) in ethanol (20 mL) and water (5 mL) was heated at 80°C while stirring for 30 min. The reaction mixture was cooled and diluted with water then, acidified with hydrochloric acid (6 *M*). The solid so formed was collected and recrystallized from ethanol giving **2c**.

Paige powder; yield: 75%; mp: 144–46°C; FTIR (KBr, *v*, cm^{-1}): 3087, 2918 (CH), 2212 (CN), 1676 (C═O); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 4.54 (s, 2H, CH_2), 7.42–7.91 (m, 4H, ArH's). *Anal*. Calcd for $C_{11}H_6BrNO_2$ (264.07): C, 50.03; H, 2.29; Br, 30.26; N, 5.30. Found: C, 50.12; H, 2.37; Br, 30.17; N, 5.19.

Synthesis of iminocoumarin derivatives 3a–d. To 5-bromosalicyaldehyde (**1**) (1 g, 5 mmol) and appropriate of 2-(4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl) acetonitrile (**2a**), 2-(4-(5-bromobenzofuran-2-yl)thiazol-2-yl)acetonitrile (**2b**), 3-(5-bromobenzofuran-2-yl)-3-oxopropanenitrile (**2c**), and 2-(benzo[*d*]thiazol-2-yl) acetonitrile (**2d**) (5 mmol each), three drops of piperidine

were added and grinded using a pestle in an open mortar for 5 min until the mixture turned into a melt. The grinding was continued for 3 min until the mixture solidify. The solid was washed with ethanol, and recrystallized from *N*,*N*-dimethylformamide to afford the corresponding **3a–d**, respectively.

3-(2-(6-Bromo-2-imino-2H-chromen-3-yl)thiazol-4-yl)-2H-chromen-2-one (3a). Yellow powder; yield: 85%; mp: 260–62°C; FTIR (KBr, *v*, cm^{-1}): 3262 (NH), 3062 (CH-aroma), 1716 (C═O), 1604 (C═N), 1558 (C═C); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.13 (d, 1H, *J* = 8 Hz), 7.38–7.66 (m, 4H, ArH's), 7.81 (d, 1H, *J* = 8 Hz), 7.94 (s, 1H), 8.48 (s, 1H), 8.61 (s, 1H), 8.90 (s, 1H), 9.10 (s, 1H, NH); MS (EI, *m*/*z* (%): 451.9 (5.51), 450.9 (3.52), 449.9 (5.12). *Anal*. Calcd for $C_{21}H_{11}BrN_2O_3S$ (451.29): C, 55.89; H, 2.46; Br, 17.71; N, 6.21; S, 7.11. Found: C, 55.74; H, 2.57; Br, 17.59; N, 6.32; S, 7.20.

6-Bromo-3-(4-(5-bromobenzofuran-2-yl)thiazol-2-yl)-2H-chromen-2-imine (3b). Yellow powder; yield: 83%; mp: 250–51°C; FTIR (KBr, *v*, cm^{-1}): 3280 (NH), 3062 (CH-aroma), 1604 (C═N), 1589 (C═C); ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.08 (d, 1H, *J* = 8 Hz), 7.23–7.42 (m, 3H, ArH's), 7.54 (d, 1H, *J* = 8 Hz), 7.70 (s, 1H), 7.77 (s, 1H), 7.88 (s, 1H), 8.96 (s, 1H), 10.80 (s, 1H, NH); MS (EI, *m*/*z* (%): 503.9 (8.01), 501.9 (62), 499.9 (7.23). *Anal*. Calcd for $C_{20}H_{10}Br_2N_2O_2S$ (502.18): C, 47.83; H, 2.01; Br, 31.82; N, 5.58; S, 6.39. Found: C, 47.72; H, 2.10; Br, 31.71; N, 5.49; S, 6.28.

(6-Bromo-2-imino-2H-chromen-3-yl)(5-bromobenzofuran-2-yl)methanone (3c). Yellow powder; yield: 86%; mp: 170–72°C; FTIR (KBr, *v*, cm^{-1}): 3232 (NH), 3093 (CH-aroma), 1702 (C═O), 1627 (C═N), 1594 (C═C); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.91 (d, 1H, *J* = 8 Hz), 7.25–7.31 (m, 4H, ArH's), 7.38 (d, 1H, *J* = 8 Hz), 7.59 (s, 1H), 8.60 (s, 1H), 8.56 (s, 1H, NH); MS (EI, *m*/*z* (%): 448.9 (6), 446.90 (24), 444.90 (8). *Anal*. Calcd for $C_{18}H_9Br_2NO_3$ (447.08): C, 48.36; H, 2.03; Br, 35.75; N, 3.13. Found: C, 48.28; H, 2.10; Br, 35.67; N, 3.20.

3-(Benzo[d]thiazol-2-yl)-6-bromo-2H-chromen-2-imine (3d). Yellow powder; yield: 88%; mp: 240–41°C; FTIR (KBr, *v*, cm^{-1}): 3210 (NH), 3062 (CH-aroma), 1593 (C═N), 1554 (C═C); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.59 (d, 1H, *J* = 8 Hz), 7.17 (d, 1H, *J* = 8 Hz), 7.41 (s, 1H), 7.43 (s, 1H), 7.56–8.20 (m, 4H, ArH's), 8.50 (s, 1H, NH). MS (EI, *m*/*z* (%): 359 (3.13), 358 (4.85), 457 (4.98). *Anal*. Calcd for $C_{16}H_9BrN_2OS$ (357.22): C, 53.80; H, 2.54; Br, 22.37; N, 7.84; S, 8.98. Found: C, 53.71; H, 2.43; Br, 22.26; N, 7.72; S, 8.89.

Synthesis of coumarin derivatives 4a–d. A mixture of the appropriate iminocoumarins **3a–d** (5 mmoles) and few drops of hydrochloric acid were grinded with a pestle in an open mortar at room temperature for 7–10 min. The solid was collected, washed with ethanol, and recrystallized from *N*,*N*-dimethylformamide, afforded **4a–d**, respectively.

6-Bromo-3-(4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)-2H-chromen-2-one (4a). Yellow powder; yield: 87%; mp: >300°C; FTIR (KBr, *v*, cm^{-1}): 3074 (CH-aroma), 1732, 1647 (2C═O), 1604 (C═N), 1558 (C═C); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.12 (d, 1H, *J* = 8 Hz), 7.31–7.65 (m, 4H, ArH's), 7.79 (d, 1H, *J* = 8 Hz), 7.91 (s, 1H), 8.44 (s, 1H), 8.60 (s, 1H), 8.89 (s, 1H); MS (EI, *m*/*z* (%): 452.9 (4.24), 451.9 (3.52), 450.9 (2.8), 449.9 (3.11). *Anal*. Calcd for $C_{21}H_{10}BrNO_4S$ (452.28): C, 55.77; H, 2.23; Br, 17.67; N, 3.10; S, 7.09. Found: C, 55.67; H, 2.12; Br, 17.78; N, 3.01; S, 7.19.

6-Bromo-3-(4-(5-bromobenzofuran-2-yl)thiazol-2-yl)-2H-chromen-2-one (4b). Yellow powder; yield: 86%; mp: 270–71°C; FTIR (KBr, *v*, cm^{-1}): 3062 (CH-aroma), 1660 (C═O), 1604 (C═N), 1589 (C═C); ^{1}H NMR (300 MHz, $CDCL_3$, δ, ppm): 7.07 (d, 1H, *J* = 8 Hz), 7.20–7.40 (m, 3H, ArH's), 7.51 (d, 1H, *J* = 8 Hz), 7.71 (s, 1H), 7.75 (s, 1H), 7.86 (s, 1H), 8.90 (s, 1H); MS (EI, *m*/*z* (%): 504.9 (8.35), 502.9 (63), 500.9 (7.85). *Anal*. Calcd for $C_{20}H_9Br_2NO_3S$ (503.16): C, 47.74; H, 1.80; Br, 31.76; N, 2.78; S, 6.37. Found: C, 47.82; H, 1.69; Br, 31.64; N, 2.88; S, 6.28.

(6-Bromo-2-oxo-2H-chromen-3-yl)(5-bromobenzofuran-2-yl)methanone (4c). Yellow powder; yield: 85%; mp: 275–76°C; FTIR (KBr, *v*, cm^{-1}): 3089 (CH-aroma), 1728, 1643 (2C═O), 1608 (C═N), 1554 (C═C); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.99 (d, 1H, *J* = 8 Hz), 7.22–7.30 (m, 4H, ArH's), 7.36 (d, 1H, *J* = 8 Hz), 7.60 (s, 1H), 8.63 (s, 1H); MS (EI, *m*/*z* (%): 449.91 (3), 447.90 (25), 445.90 (9). *Anal*. Calcd for $C_{18}H_8Br_2O_4$ (448.06): C, 48.25; H, 1.80; Br, 35.67. Found: C, 48.36; H, 1.68; Br, 35.80.

3-(Benzo[d]thiazol-2-yl)-6-bromo-2H-chromen-2-one (4d). Yellow powder; yield: 86%; mp: 260–61°C; FTIR (KBr, *v*, cm^{-1}): 3086 (CH-aroma), 1728 (C═O), 1600 (C═N), 1554 (C═C); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.54 (d, 1H, *J* = 8 Hz), 7.15 (d, 1H, *J* = 8 Hz), 7.40 (s, 1H), 7.39 (s, 1H), 7.53–8.23 (m, 4H, ArH's); MS (EI, *m*/*z* (%): 359 (5.81), 358 (4.41), 457 (5.70). *Anal*. Calcd for $C_{16}H_8BrNO_2S$ (358.21): C, 53.65; H, 2.25; Br, 22.31; N, 3.91; S, 8.95. Found: C, 53.77; H, 2.14; Br, 22.40; N, 3.80; S, 8.84.

Benzyl 2-(5-bromo-2-hydroxybenzylidene)hydrazine-1-carbodithioate (6) [39]. A mixture of 5-bromosalicylaldehyde (**1**) (2.01 g, 10 mmol) and benzylhydrazine carbodithioate (**5**) (1.97 g, 10 mmol) was grinded with a pestle in an open mortar at room temperature for 3–5 min. The initial syrupy continued for 5–7 min. The solid was collected, washed with ethanol, and recrystallized from *N*,*N*-dimethylformamide to afford **6** as white powder; yield: 89%; mp: 220–21°C; FTIR (KBr, *v*, cm^{-1}): 3375 (OH), 3209 (NH), 3097, 2973 (CH), 1615 (C═N), 1324 (C═S); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 4.60 (s, 2H, SCH_2), 6.88–7.89 (m, 8H, ArH's), 7.91 (s, 1H, CH═N), 10.25 (s, 1H, NH),

11.28 (s, 1H, OH); MS (EI, *m*/*z* (%): 381 (6.5), 379 (5.5). *Anal*. Calcd for $C_{15}H_{13}BrN_2OS_2$ (381.31): C, 47.25; H, 3.44; Br, 20.96; N, 7.35; S, 16.82. Found: C, 47.13; H, 3.57; Br, 20.84; N, 7.43; S, 16.70.

Synthesis of 2-(5-substituted 3-phenyl-1,3,4-thiadiazol-2(3*H*)-ylidene)-1-(5-bromo-2-hydroxybenzylidene)hydrazines (11a–f). Benzylhydrazine carbodithioate derivative **6** (1.90 g, 5 mmol), the appropriate hydrazonoyl halides **7a–f** (5 mmoles), and two drops of triethylamine were mixed and grinded with a pestle in an open mortar at room temperature. The grinding was continued for 3 min. The solid was washed with ethanol and recrystallized from *N*,*N*-dimethylformamide giving 2,3-dihydro-1,3,4-thiadiazoles **11a–f**, respectively.

Ethyl-5-[(5-bromo-2-hydroxybenzylidene)-hydrazono]-4-phenyl-4,5-dihydro-[1,3,4]thiadiazole-2-carboxylate (11a). Yellow crystals; yield: 82%; mp: 189°C; FTIR (KBr, *v*, cm^{-1}): 3414 (OH), 3066, 2978, 2866 (CH), 1716 (C═O), 1612 (C═N), 1550 (C═C); ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.42 (t, 3H, *J* = 7 Hz, CH_3), 4.44 (q, 2H, *J* = 7 Hz, CH_2), 6.91 (d, 2H, *J* = 8 Hz), 7.27 (s, 1H), 7.35–7.48 (m, 2H), 7.49 (t, 2H, *J* = 7.8 Hz), 7.93 (d, 1H, *J* = 8 Hz), 8.42 (s, 1H), 10.91 (s, 1H, OH); MS (EI, *m*/*z* (%): 447 (20), 445 (18). *Anal*. Calcd for $C_{18}H_{15}BrN_4O_3S$ (447.31): C, 48.33; H, 3.38; Br, 17.86; N, 12.53; S, 7.17. Found: C, 48.42; H, 3.25; Br, 17.75; N, 12.64; S, 7.29.

1-{5-[(5-Bromo-2-hydroxybenzylidene)-hydrazono]-4-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl}-ethanone (11b). Yellow powder; yield: 83%; mp: 190°C; FTIR (KBr, *v*, cm^{-1}): 3370 (OH), 3074, 2916, 2877 (CH), 1678 (C═O), 1608 (C═N), 1562 (C═C); ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.63 (s, 3H, CH_3), 6.89 (d, 2H, *J* = 8 Hz), 7.26 (s, 1H), 7.27–7.40 (m, 2H), 7.50 (t, 2H, *J* = 7.8 Hz), 7.95 (d, 1H), 8.39 (s, 1H, CH═N), 10.90 (s, 1H, OH); MS (EI, *m*/*z* (%): 417 (5), 416 (3), 415 (4). *Anal*. Calcd for $C_{17}H_{13}BrN_4O_2S$ (417.28): C, 48.93; H, 3.14; Br, 19.15; N, 13.43; S, 7.68. Found: C, 48.82; H, 3.03; Br, 19.02; N, 13.34; S, 7.56.

5-[(5-Bromo-2-hydroxybenzylidene)-hydrazono]-4-phenyl-4,5-dihydro-[1,3,4]thiadiazol 2-yl)phenyl-methanone (11c). Yellow powder; yield: 82%; mp: 190°C; FTIR (KBr, *v*, cm^{-1}): 3387 (OH), 3097, 2974, 2897 (CH), 1652 (C═O), 1604 (C═N), 1562 (C═C); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.80 (d, 2H, *J* = 8 Hz), 7.24 (s, 1H), 7.24–7.52 (m, 9H, ArH's), 7.90 (d, 1H, *J* = 8 Hz), 8.41 (s, 1H, CH═N), 11.12 (s, 1H, OH). MS (EI, *m*/*z* (%): 479 (10), 478 (5), 477 (6). *Anal*. Calcd for $C_{22}H_{15}BrN_4O_2S$ (479.35): C, 55.12; H, 3.15; Br, 16.67; N, 11.69; S, 6.69. Found: C, 55.23; H, 3.03; Br, 16.56; N, 11.57; S, 6.81.

5-[(5-Bromo-2-hydroxybenzylidene)-hydrazono]-4-phenyl-2-phenyl-carbamoyl-4,5-dihydro-[1,3,4]thiadiazole (11d). Yellow powder; yield: 84%; mp: 200°C; FTIR (KBr, *v*, cm^{-1}): 3375 (OH), 3271 (NH), 3105, 2974, 2854 (CH), 1685 (C═O), 1604 (C═N), 1523 (C═C); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.86 (d, 2H, *J* = 8 Hz), 7.26 (s, 1H), 7.27–7.55 (m, 9H, ArH's), 7.93 (d, 1H, *J* = 8 Hz), 8.41 (s, 1H, CH═N), 8.90 (s, 1H, NH), 11.10 (s, 1H, OH); MS (EI, *m*/*z* (%): 494 (5), 492 (4). *Anal*. Calcd for $C_{22}H_{16}BrN_5O_2S$ (494.36): C, 53.45; H, 3.26; Br, 16.16; N, 14.17; S, 6.49. Found: C, 53.34; H, 3.34; Br, 16.05; N, 14.08; S, 6.37.

5-(5-Bromo-2-hydroxybenzylidene)hydrazono)-4-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)(thiophen-2-yl)methanone (11e). Orange powder; yield: 81%; mp: 185°C; FTIR (KBr, *v*, cm^{-1}): 3402 (OH), 3068, 2981 (CH), 1712 (C═O), 1612 (C═N), 1539 (C═C); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.84 (d, 2H, *J* = 8 Hz), 7.25 (s, 1H), 7.26–7.55 (m, 7H, ArH's), 7.91 (d, 1H, *J* = 8 Hz), 8.43 (s, 1H, CH═N), 10.95 (s, 1H, OH); MS (EI, *m*/*z* (%): 485 (10), 483 (8). *Anal*. Calcd for $C_{20}H_{13}BrN_4O_2S_2$(485.38): C, 49.49; H, 2.70; Br, 16.46; N, 11.54; S, 13.21. Found: C, 49.39; H, 2.81; Br, 16.34; N, 11.46; S, 13.32.

5-[(5-Bromo-2-hydroxybenzylidene)-hydrazono]-4-phenyl-4,5-dihydro-[1,3,4] thiadiazole-2-yl-naphthalen-2-yl-methanone (11f). Orange powder; yield: 82%; mp: 190–91°C; FTIR (KBr, *v*, cm^{-1}): 3417 (OH), 3059, 2981, 2866 (CH), 1650 (C═O), 1604 (C═N), 1582 (C═C); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.87 (d, 2H, *J* = 8 Hz), 7.26 (s, 1H), 7.28–7.54 (m, 11H, ArH's), 7.94 (d, 1H, *J* = 8 Hz), 8.38 (s, 1H, CH═N), 11.03 (s, 1H, OH); MS (EI, *m*/*z* (%): 529 (6.5), 528 (4), 527 (5). *Anal*. Calcd for $C_{26}H_{17}BrN_4O_2S$ (529.41): C, 58.99; H, 3.24; Br, 15.09; N, 10.58; S, 6.06. Found: C, 58.87; H, 3.36; Br, 15.22; N, 10.70; S, 6.18.

Synthesis of 1-(5-bromo-2-hydroxybenzylidene) thiocarbonohydrazide (14). A mixture of compound **1** (2.01 g, 10 mmol) and hydrazine carbothiohydrazide (1.06 g, 10 mmol) (**13**) in acetic acid was refluxed for 1 h. The solid that separated on hot was filtered, washed with ethanol, and recrystallized from acetone, afforded **14** as white crystals; yield: 85%; mp: 302–04°C; FTIR (KBr, *v*, cm^{-1}): 3417 (OH), 3387, 3290, 3132 (NH_2, NH), 3074, 2989, 2866 (CH), 1593 (C═N), 1280 (C═S); ^{1}H NMR: (300 MHz, $CDCl_3$, δ, ppm): 3.98 (br, 2H, NH_2), 6.86 (d, 1H, *J* = 8 Hz), 7.38 (d, 1H, *J* = 8 Hz), 7.92 (s, 1H), 8.70 (s, 1H, CH═N), 10.40 (s, 1H, NH), 11.67 (s, 1H, NH), 12.11 (s, 1H, OH); MS (EI, *m*/*z* (%): 289 (13), 287 (10). *Anal*. Calcd for $C_8H_9BrN_4OS$ (289.15): C, 33.23; H, 3.14; Br, 27.63; N, 19.38; S, 11.09. Found: C, 33.32; H, 3.23; Br, 27.52; N, 19.49; S, 11.20.

General method for synthesis of 15, 16a, and 16b. A mixture of thiocarbohydrazone **14** (1.44 g, 5 mmol) and the appropriate hydrazonoyl halides **7a–c** (5 mmoles) in ethanol (15 mL) containing triethylamine (0.75 mL, 5 mmol) was heated under reflux for 8 h. The solid that separated after cooling was filtered and recrystallized from DMF/EtOH, which afforded the corresponding **15**, **16a**, and **16b**, respectively.

3-amino-2-((5-bromo-2-hydroxybenzylidene)hydrazono)-5-(2-phenylhydrazono)thiazolidin-4-one (15). Yellow powder; yield: 80%; mp: 259–60°C; FTIR (KBr, *v*, cm^{-1}): 3421

(OH), 3387, 3178, 3113 (NH, NH_2), 3055 (CH-aroma), 1735 (C═O), 1608 (C═N), 1597 (C═C); ^{1}H NMR: (300 MHz, DMSO-d_6, δ, ppm): 6.91–6.99 (m, 2H), 7.28–7.34 (t, 2H, *J* = 8 Hz), 7.47 (d, 1H, *J* = 8 Hz), 7.58 (d, 1H, *J* = 8 Hz), 7.88–7.97 (m, 2H), 8.77 (s, 1H, CH═N), 9.44 (s, 1H, NH), 10.83 (s, 2H, NH_2), 11.00 (s, 1H, OH); MS (EI, *m*/*z* (%): 433 (2), 431 (1.5). *Anal*. Calcd for $C_{16}H_{13}BrN_6O_2S$ (433.28): C, 44.35; H, 3.02; Br, 18.44; N, 19.40; S, 7.40. Found: C, 44.23; H, 3.12; Br, 18.33; N, 19.31; S, 7.29.

2-(((3-amino-4-methyl-5-(phenyldiazenyl)thiazol-2(3H)-ylidene)hydrazono)methyl)-4-bromophenol (16a). Brown powder; yield: 79%; mp: 190–91°C; FTIR (KBr, *v*, cm^{-1}): 3452 (OH), 3278, 3190, 3120 (NH, NH_2), 3109, 2958, 2854 (CH), 1600 (C═N),1531 (C═C); ^{1}H NMR: (300 MHz, $CDCl_3$, δ, ppm): 2.55 (s, 3H, CH_3), 6.93 (d, 1H, *J* = 8 Hz), 7.11 (t, 2H, *J* = 7.5 Hz), 7.26 (s, 1H), 7.27–7.53 (m, 5H, ArH's + NH_2), 7.95 (d, 1H, *J* = 8 Hz), 8.63 (s, 1H, CH═N), 11.56 (s, 1H, OH); MS (EI, *m*/*z* (%): 433 (0.9), 432 (1.2), 431 (9.7), 430 (2.5). *Anal*. Calcd for $C_{17}H_{15}BrN_6OS$ (431.31): C, 47.34; H, 3.51; Br, 18.53; N, 19.48; S, 7.43. Found: C, 47.23; H, 3.63; Br, 18.42; N, 19.69; S, 7.32.

2-(((3-amino-4-phenyl-5-((E)-phenyldiazenyl)thiazol-2(3H)-ylidene)hydrazono)methyl)-4-bromophenol (16b). Brown powder; yield: 78%; mp: 189–90°C; FTIR (KBr, *v*, cm^{-1}): 3452 (OH), 3270, 3220, 3155, (NH, NH_2), 3059, 2931 (CH), 1612 (C═N), 1570 (C═C); ^{1}H NMR: (300 MHz, $CDCl_3$, δ, ppm): 6.93 (d, 1H, *J* = 8 Hz), 7.12–7.30 (m, 5H, ArH's + NH_2), 7.42 (s, 1H), 7.45–7.51 (m, 8H, ArH's), 8.63 (s, 1H, CH═N), 11.60 (s, 1H, OH); MS (EI, *m*/*z* (%): 495 (2), 494 (3), 493 (4). *Anal*. Calcd for $C_{22}H_{17}BrN_6OS$ (493.38): C, 53.56; H, 3.47; Br, 16.20; N, 17.03; S, 6.50. Found: C, 53.65; H, 3.33; Br, 16.32; N, 17.12; S, 6.62.

Synthesis of 1-(5-bromobenzofuran-2-yl)-3-phenyl-prop-2-en-1-one (18). Potassium hydroxide (10 mL, 10%) was added dropwise to a mixture of 2-acetyl-5-bromobenzofuran (**17**) (1.2 g, 5 mmol) and benzaldehyde (0.5 mL, 5 mmol) in ethanol (20 mL) with stirring at 0–5°C for 2 h. The resulting solid was collected and recrystallized from ethanol to give **18** as paige powder; yield: 80%; mp: 128–30°C; FTIR (KBr, *v*, cm^{-1}): 3074 (CH-aroma), 1662 (C═O), 1600 (C═N), 1546 (C═C); ^{1}H NMR: (300 MHz, $CDCL_3$, δ, ppm): 7.26–7.94 (m, 11 ArH's and –CH═CH–); MS (EI, *m*/*z* (%): 328 (75), 327 (100), 326 (78). *Anal*. Calcd for $C_{17}H_{11}BrO_2$ (327.17): C, 62.41; H, 3.39; Br, 24.42. Found: C, 62.34; H, 3.47; Br, 24.53.

Synthesis of trisubstituted pyridines 20a–c. A mixture of **18** (1.63 g, 5 mmol), the appropriate l-(2-oxo-2-substituted ethyl)pyridinium bromides **19a–c** (5 mmoles), and ammonium acetate (0.65 g, 5 mmol), in acetic acid (10 mL), was heated under reflux for 4 h. The mixture was allowed to cool, and the resulting solid was collected, washed with water, and recrystallized from dioxane affording **20a–c**, respectively.

2-(5-Bromobenzofuran-2-yl)-4,6-diphenylpyridine (20a). White crystals; yield: 82%; mp: 190–92°C; FTIR (KBr, *v*, cm^{-1}): 3031 (CH-aroma), 1608 (C═N), 1546 (C═C); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.50–7.87 (m, 16H, ArH's); MS (EI, *m*/*z* (%): 426 (1.40), 425 (0.9), 424 (1.2). *Anal*. Calcd for $C_{25}H_{16}BrNO$ (426.3): C, 70.43; H, 3.78; Br, 18.74; N, 3.29. Found: C, 70.34; H, 3.66; Br, 18.63; N, 3.18.

2-(5-Bromobenzofuran-2-yl)-4-phenyl-6-(p-tolyl)pyridine (20b). Paige crystals; yield: 80%; mp: 150–52°C; FTIR (KBr, *v*, cm^{-1}): 3031, 2916, 2858 (CH), 1612 (C═N), 1546 (C═C); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.34 (s, 3H, CH_3), 7.13–8.11 (m, 15H, ArH's); MS (EI, *m*/*z* (%): 440 (1.6), 438 (2). *Anal*. Calcd for $C_{26}H_{18}BrNO$ (440.33): C, 70.92; H, 4.12; Br, 18.15; N, 3.18. Found: C, 70.80; H, 4.25; Br, 18.01; N, 3.30.

2,6-Bis (5-bromobenzofuran-2-yl)-4-phenylpyridine (20c). Paige crystals; yield: 82%; mp: 224–26°C; FTIR (KBr, *v*, cm^{-1}): 3031 (CH-aroma), 1616 (C═N), 1546 (C═C); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.18–8.20 (m, 15H, ArH's); MS (EI, *m*/*z* (%): 545 (4), 544 (2), 543 (3). *Anal*. Calcd for $C_{27}H_{15}Br_2NO_2$ (545.22): C, 59.48; H, 2.77; Br, 29.31; N, 2.57. Found: C, 59.57; H, 2.65; Br, 29.23; N, 2.65.

Synthesis of pyridine derivatives 21–25. A mixture of 2-acetyl-5-bromobenzofuran (**17**) (1.2 g, 5 mmol), benzaldehyde (0.5 g, 5 mmol), the appropriate malononitrile, ethyl cyanoacetate, benzoylacetonitrile, or cyanothioacetamide (5 mmol each) and ammonium acetate (4.3 g, 6 mmol) in acetic acid was heated (10 mL) under reflux for 3 h. The reaction mixture was cooled; the separated solid was collected, filtered, and recrystallized from *N*,*N*-dimethylformamide, which afforded **21–24**, respectively.

2-Amino-4-phenyl-6-(5-bromobenzofuran-2-yl)pyridine-3-carbonitrile (21). Orange powder; yield: 75%; mp: >300°C; FTIR (KBr, *v*, cm^{-1}): 3467, 3367 (NH_2), 3066 (CH-aroma), 2214 (CN), 1627 (C═N), 1581 (C═C); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.82 (br, 2H, NH_2), 7.30 (s, 1H, Ar-H), 7.54–7.65 (m, 7H, ArH's), 7.83 (s, 1H, Ar-H), 8.02 (s, 1H, Ar-H); MS (EI, *m*/*z* (%): 390 (5), 388 (4). *Anal*. Calcd for $C_{20}H_{12}BrN_3O$ (390.23): C, 61.56; H, 3.10; Br, 20.48; N, 10.77. Found: C, 61.42; H, 3.22; Br, 20.60; N, 10.65.

6-(5-Bromobenzofuran-2-yl)-1,2-dihydro-2-oxo-4-phenylpyridine-3-carbonitrile (22). Yellow powder; yield: 80%; mp: >300°C; FTIR (KBr, *v*, cm^{-1}): 3213 (NH), 3089 (CH-aroma), 2218 (CN), 1643 (C═O), 1616 (C═N), 1539 (C═C); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.56–8.04 (m, 11H, ArH's + NH); MS (EI, *m*/*z* (%): 391 (6), 389 (5). *Anal*. Calcd for $C_{20}H_{11}BrN_2O$ (391.22): C, 61.40; H, 2.83; Br, 20.42; N, 7.16. Found: C, 61.32; H, 2.78; Br, 20.34; N, 7.07.

6-(5-Bromobenzofuran-2-yl)-2,4-diphenylpyridine-3-carbonitrile (23). White powder; yield: 72%; mp: 256–58°C; FTIR (KBr, *v*, cm^{-1}): 3055 (CH-aroma), 2221 (CN), 1596 (C═N), 1558 (C═C); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.54–8.06 (m, 15H, ArH's); MS (EI, *m*/*z* (%): 451 (3), 450 (1.9), 449 (2). *Anal*. Calcd for $C_{26}H_{15}BrN_2O$ (451.31): C, 69.19; H, 3.35; Br, 17.70; N, 6.21. Found: C, 69.30; H, 3.23; Br, 17.82; N, 6.32.

6-(5-bromobenzofuran-2-yl)-2-mercapto-4-phenylnicotinonitrile (24). Orange powder; yield: 75%; mp: 226–28°C; FTIR (KBr, *v*, cm^{-1}): 3060 (CH-aroma), 2210 (CN), 1590 (C═N), 1553 (C═C); ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 3.71 (s, 1H, SH), 7.25–7.84 (m, 10H, ArH's); MS (EI, *m*/*z* (%): 407 (7), 406 (6), 405 (3). *Anal*. Calcd for $C_{20}H_{11}BrN_2OS$ (407.28): C, 58.98; H, 2.72; Br, 19.62; N, 6.88; S, 7.87. Found: C, 58.86; H, 2.61; Br, 19.50; N, 6.84; S, 7.75.

2-(Substituted 6-(5-bromobenzofuran-2-yl)-4-phenylpyridine-3-carbonitrile 25 and **26a–c**. A mixture of **24** (2.03 g, 5 mmol) and potassium hydroxide (0.28 g, 5 mmol) in ethanol (10 mL) was stirred for 2 h at room temperature. The appropriate of iodomethane, ethyl chloroacetate, chloroacetone or chloroacetonitrile (5 mmol each) was added. Stirring was continued for 2 h. The resulting solid was collected and recrystallized from a proper solvent, which afforded **25** and **26a–c**, respectively.

6-(5-Bromobenzofuran-2-yl)-2-(methylthio)-4-phenylpyridine-3-carbonitrile (25). Paige powder recrystallized from acetic acid; yield: 73%; mp: 264–66°C; FTIR (KBr, *v*, cm^{-1}): 3061, 2925 (CH), 2210 (CN), 1593 (C═N), 1549 (C═C); ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.76 (s, 3H, SCH_3), 7.21–7.80 (m, 10H, ArH's); MS (EI, *m*/*z* (%): 423 (20) 421 (100), 420 (62), 419 (20). *Anal*. Calcd for $C_{21}H_{13}BrN_2OS$ (421.31): C, 59.87; H, 3.11; Br, 18.97; N, 6.65; S, 7.61. Found: C, 59.76; H, 3.23; Br, 18.85; N, 6.76; S, 7.54.

Ethyl 3-amino-6-(5-bromobenzofuran-2-yl)-4-phenylthieno[2,3-b]pyridine-2-carboxylate (26a). Paige powder recrystallized from acetic acid; yield: 73%; mp: 197–99°C; FTIR (KBr, *v*, cm^{-1}): 3400 broad (NH_2), 3061, 2969 (CH), 1732 (C═O), 1593 (C═N), 1549 (C═C); ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.42 (t, 3H, *J* = 7 Hz, CH_3), 4.04 (br, 2H, NH_2), 4.25 (q, 2H, *J* = 7.5 Hz, CH_2), 7.26–7.81 (m, 10H, ArH's). *Anal*. Calcd for $C_{24}H_{17}BrN_2O_3S$ (493.37): C, 58.43; H, 3.47; Br, 16.20; N, 5.68; S, 6.50. Found: C, 58.55; H, 3.34; Br, 16.34; N, 5.57; S, 6.61.

1-(3-Amino-6-(5-bromobenzofuran-2-yl)-4-phenylthieno[2,3-b]pyridin-2-yl)ethanone (26b). Yellow powder from dioxane; yield: 79%; mp: 226–28°C; FTIR (KBr, *v*, cm^{-1}): 3370, 3286 (NH_2), 3073 (CH-aroma); ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.40 (s, 3H, $COCH_3$), 4.03 (br, 2H, NH_2), 7.27–7.86 (m, 10H, ArH's); MS (EI, *m*/*z* (%): 463 (10), 462 (5), 461 (11), 460 (12). *Anal*. Calcd for $C_{23}H_{15}BrN_2O_2S$ (463.35): C, 59.62; H, 3.26; Br, 17.24; N, 6.05; S, 6.92. Found: C, 59.71; H, 3.15; Br, 17.33; N, 6.15; S, 6.83.

3-Amino-6-(5-bromobenzofuran-2-yl)-4-phenylthieno[2,3-b]pyridine-2-carbonitrile (26c). Brown powder from dioxane; yield: 79%; mp: 296–98°C; FTIR (KBr, *v*, cm^{-1}): 3433 broad (NH_2), 3063 (CH-aroma), 2209 (CN), 1589 (C═N), 1549 (C═C); ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 4.15 (br, 2H, NH_2), 7.27–7.89 (m, 10H, ArH's); MS (EI, *m*/*z* (%): 446.9 (16), 445.9 (20), 444.9 (10). *Anal*. Calcd for $C_{22}H_{12}BrN_3OS$ (446.32): C, 59.20; H, 2.71; Br, 17.90; N, 9.41; S, 7.18. Found: C, 59.09; H, 2.82; Br, 17.82; N, 9.53; S, 7.26.

Biological screening. Antimicrobial activity of the newly synthesized compounds was determined *in vitro* by standardized disk – agar diffusion method [40]. Cultures of one fungi, namely, *A. fumagitus* and, one yeast fungus, *C. albicans,* as well as four bacterial species, namely, Gram-positive bacteria: *S. aureus* (*ATCC 25923*) and *B. subtilis* (*ATCC 6635*); Gram-negative bacteria: *E. coli* (*ATCC 25922*) and *S. typhimurium* (*ATCC 14028*), were used to investigate the antimicrobial activity of the newly synthesized compounds. The tested compounds were dissolved in DMF solvent and prepared in two concentrations, 100 and 50 mg/mL, and then 10 μL of each preparation was dropped on disk of 6 mm in diameter and the concentrations became 1 and 0.5 mg/disk, respectively. In the case of insoluble compounds, the compounds were suspended in DMF and vortexed then processed.

Testing for antibacterial and yeasts activity. Bacterial cultures were grown in nutrient broth medium at 30°C. After 16 h of growth, each microorganism, at a concentration of 10^8 cells/mL, was inoculated on the surface of Mueller–Hinton agar plates using sterile cotton swab. Subsequently, uniform size filter paper disks (6 mm in diameter) were impregnated by equal volume (10 μL) from the specific concentration of dissolved compounds and carefully placed on surface of each inoculated plate. The plates were incubated in the upright position at 36°C for 24 hours. Three replicates were carried out for each extract against each of the test organism. Simultaneously, addition of the respective solvent instead of dissolved compound was carried out as negative controls. After incubation, the diameters of the growth inhibition zones formed around the disk were measured with transparent ruler in millimeter, averaged, and the mean values were tabulated. The antibiotic chloramphencol was used as standard reference in the case of Gram-negative bacteria; cephalothin was used as standard reference in the case of Gram-positive bacteria. The results are summarized in Table 1.

Testing for antifungal activity. Active inoculum for experiments was prepared by transferring many loopfuls of spores from the stock cultures to test tubes of sterile distilled water that were agitated and diluted with sterile distilled water to achieve optical density corresponding to 2.0 × 105 spore/mL. Inoculum of 0.1% suspension was swabbed uniformly, and the inoculum was allowed to dry

for 5 min then the same procedure was followed as described previously. Cycloheximide was used as standard reference in the case of yeasts and fungi. Measurements were considered after 72 h for fungi and 24 h for bacteria. The results are summarized in Table 1.

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