Received: 10 February 2020 | Revised: 2 April 2020 | Accepted: 20 April 2020

DOI: 10.1002/jhet.4012

WILEY

ARTICLE

Synthesis and biological evaluation of some heterocyclic scaffolds based on the multifunctional *N*-(4-acetylphenyl)-2-chloroacetamide

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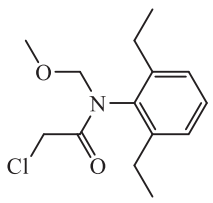
Abstract

The chloroacetamide derivative, **1**, was used as a versatile precursor for the synthesis of various types of *N*-aryl-2-(benzothiazol-2-ylthio)acetamide derivatives. The reaction of **1** with 2-mercaptobenzothiazole followed by condensation reaction of the produced sulfide with phenylhydrazine, 2-cyanoacetohydrazide, and/or thiosemicarbazide furnished the conforming condensation products, **4**, **7**, and **10**, respectively. Treatment of the phenylhydrazone product, **4**, with Vilsmeier formylation reagent ($POCl_3$/DMF) yielded the corresponding 4-formylpyrazole derivative, **5**. The thiosemicarbazone product, **10**, was reacted with ethyl bromoacetate to furnish the thiazolin-4-one derivative, **11**. The substitution reactions of chloroacetamide derivative, **1**, with 2-mercapto-4,6-dimethylnicotinonitrile and 6-amino-2-mercaptopyrimidin-4-ol, were explored to identify the sulfide products, **14** and **17**. Cyclization of **14** into its corresponding thieno[2,3-*b*]pyridine compound, **15**, was performed using sodium ethoxide. The thiosemicarbazone, **10**, and sulfide derivative, **14**, were found to be the most potent antibacterial compounds against *Escherichia coli* and *Staphylococcus aureus*, exhibiting growth inhibitory activities of 80.8% and 91.7%, respectively. Moreover, the thiosemicarbazone, **10**, displayed the most significant antioxidant activity with inhibitory activity of 82.6%, which comes close to the antioxidant activity of L-ascorbic acid.

1 | INTRODUCTION

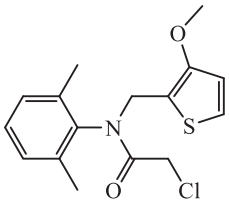
Halogenated acid derivatives gained much attention for their promising acidity that prohibits the growth of bacteria, fungi, parasites, and viruses.[1,2] Several *N*-Aryl 2-chloroacetamides displayed myriad biological potentialities as herbicides, antifungals, and disinfectants. This might be exemplified by the two herbicidal 2-chloroacetamides derivatives, 2-chloro-*N*-(2,6-diethylphenyl)-*N*-(methoxymethyl) acetamide **(a)** and 2-chloro-*N*-(2,6-dimethyl-phenyl)-*N*-[(3-methoxy-2-thienyl)methyl]acetamide **(b)** (Figure 1).[3,4] The 2-chloroacetamides possess key structural features, including an easy replacement of chlorine atom, a reactive N—H group, amide, ketonic carbonyls, and methylene group, which make them highly attractive synthetic platforms for synthesizing diverse heterocyclic systems, including aziridine,[5] *N*-lactam,[6] piperazine,[7] imidazolidine-containing compounds,[8] and macrocyclic ligands.[9] In addition, various 2-chloroacetamide reagents have been exploited in the field of solid-state chemistry[10] and pharmacologically promising compounds.[11–14]

Moreover, compounds containing pyrazole moiety have attracted significant attention as they showed diverse bioactivities that include antimicrobial,[15,16] antimalarial,[17]



2-Chloro-*N*-(2,6-diethylphenyl)-*N*-(methoxymethyl)acetamide

(a)



2-Chloro-*N*-(2,6-dimethylphenyl)-*N*-((3-methoxythiophen-2-yl)methyl)acetamide

(b)

FIGURE 1 Examples of 2-chloroacetamide herbicides

antioxidant,[18] anticancer,[19] and antidepressant activities.[20] In addition, several thiazole derivatives have been recognized to have a wide spectrum of biological activity such as antimicrobial,[21,22] antioxidant,[23] anticancer,[24,25] and anti-inflammatory properties,[26] and potential cholinesterase inhibitors.[27] Besides, thienopyridine derivatives were indicated to possess marked anticancer activities, especially against both hepatocellular carcinoma (HepG-2) and breast cancer (MCF-7) cell lines.[28] As a part of our continued program dedicated to the chemistry of bioactive *N*-aryl(heteroaryl)-2-chloroacetamides derivatives,[29–31] herein we report on the reactivity of *N*-(4-acetylphenyl)-2-chloroacetamide toward various types of nitrogen and sulfur nucleophiles (phenylhydrazine, 2-cyanoacetohydrazide, thiosemicarbazide, 4,6-dimethyl-2-mercapto-nicotinonitrile, and 6-amino-2-mercaptopyrimidin-4-ol), and the biological evaluations of the newly synthesized compounds.

2 | RESULTS AND DISCUSSION

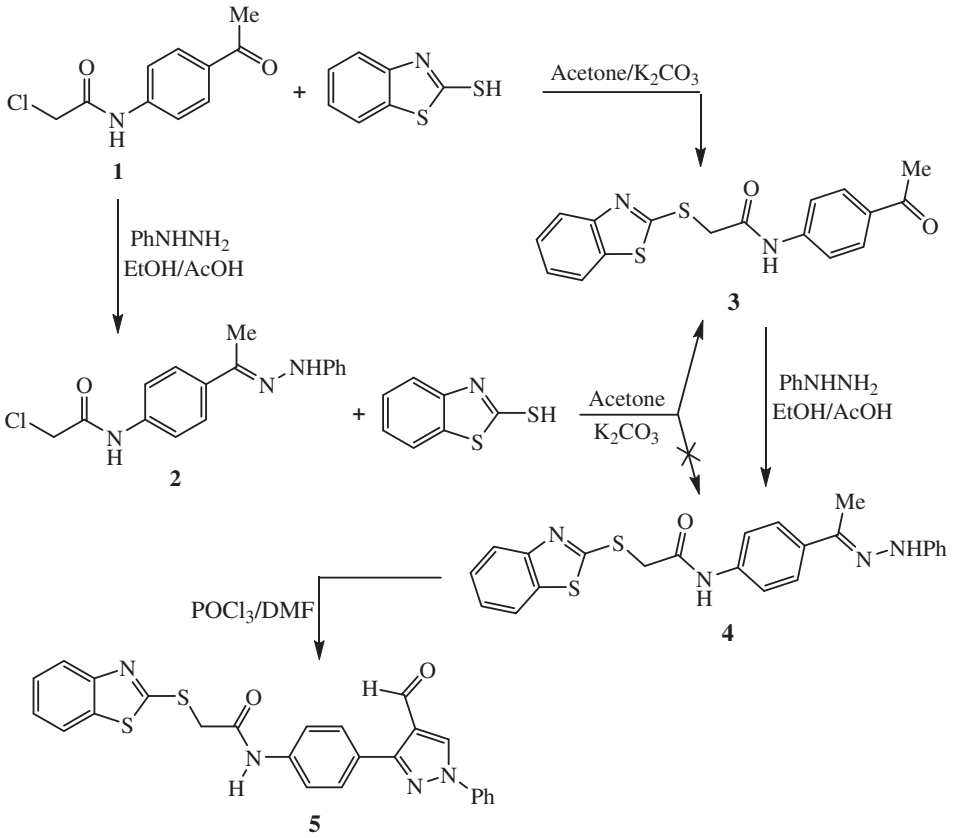
2.1 | CHEMISTRY

The highly versatile *N*-(4-acetylphenyl)-2-chloroacetamide (**1**) was prepared according to the previously reported literature through the chloroacetylation of 4-aminoacetophenone, with chloroacetyl chloride, in the presence of potassium carbonate in acetone.[32] The multifunctional features, including a chloroacetamide moiety, ketonic carbonyl group, and active methyl group, featured by the key **1** encouraged us to exploit its chemical reactivity toward a panel of nucleophilic and electrophilic reagents. Firstly, refluxing equimolar amounts of compound, **1**, and phenylhydrazine in ethanol with catalytic drops of acetic acid affected condensation at the ketonic carbonyl group to produce the anticipated phenylhydrazone, 2-chloro-*N*-(4-(1-(2-phenylhydrazono)ethyl) phenyl)-acetamide (**2**) (Scheme 1). A nucleophilic substitution of the chorine atom in chloroacetamide derivative, **2**, by 2-mercaptobenzothiazole was proceeded successfully by stirring in acetone and potassium carbonate. However, in a surprise action accompanying the substitution, the imine linkage affected hydrolysis and the product was identified as *N*-(4-acetylphenyl)-2-(benzothiazol-2-ylthio)acetamide (**3**),[33] which has been previously prepared by the direct reaction of compound, **1**, with 2-mercaptobenzothiazole in acetone and potassium carbonate. The reaction failed to produce our target compound, 2-(benzothiazol-2-ylthio)-*N*-(4-(1-(2-phenyhydrazono)-ethyl)phenyl)-acetamide (**4**). The source of water that is responsible for hydrolysis may be attributed to the neutralization between HCl (generated in situ during reaction progress) and K_2CO_3 (Figure 2). However, compound **4** was realized by alternative route via the condensation of phenylhydrazine at the ketonic carbonyl group of the acetamide derivative, **3**, under refluxing in ethanol with drops of acetic acid. This acid-catalyzed condensation of phenylhydrazine was successfully achieved at the ketonic carbonyl rather than nucleophilic substitution at the second carbon of benzothiazole, which requires base catalyst to occur.

Phenylhydrazone of the type **4** was treated with DMF and phosphorous oxychloride under the condition of Vilsmeier formylation reaction and successfully transformed into the conforming 2-(benzothiazolylthio)-*N*-(4-(4-formyl-1-phenylpyrazolyl)-phenyl)acetamide derivative, **5**. The suggested structure of 4-formylpyrazole derivative, **5**, finds support from its compatible spectral data. The methylene function, flanked by amidic carbonyl and sulfur atom, did not formylate under the reaction condition. This may be attributed to the low reactivity of such methylene as indicated from the poor literature reviews.

The condensation of compound, **1**, with 2-cyanoacetohydrazide[34] was achieved under refluxing in ethanol and drops of acetic acid to furnish the condensation product at the ketonic functionality, which was identified as 2-chloro-*N*-(4-(1-(2-(2-cyanoacetyl)-hydrazono)ethyl)phenyl) acetamide (**6**). Similarly, the nucleophilic substitution of the chorine atom, **6**, by 2-mecrcaptobenzothiazole affected the hydrolysis of the imine linkage to afford **3**[33] instead of having the target product, 2-(benzothiazol-2-ylthio)-*N*-(4-(1-(2-(2-cyanoacetyl)hydrazono)ethyl)phenyl)-acetamide (**7**). The target compound, **7**, was obtained by an alternative route via the condensation reaction of 2-cyanoacetohydrazide at the ketonic carbonyl group rather

SCHEME 1 Synthesis of 2-(benzothiazolylthio)-*N*-(4-(4-formylpyrazolyl)phenyl)-acetamide derivative, **5**



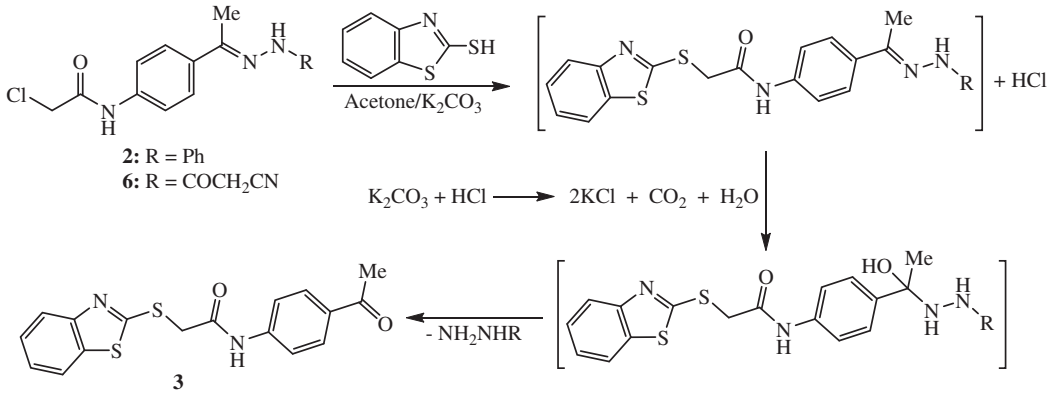
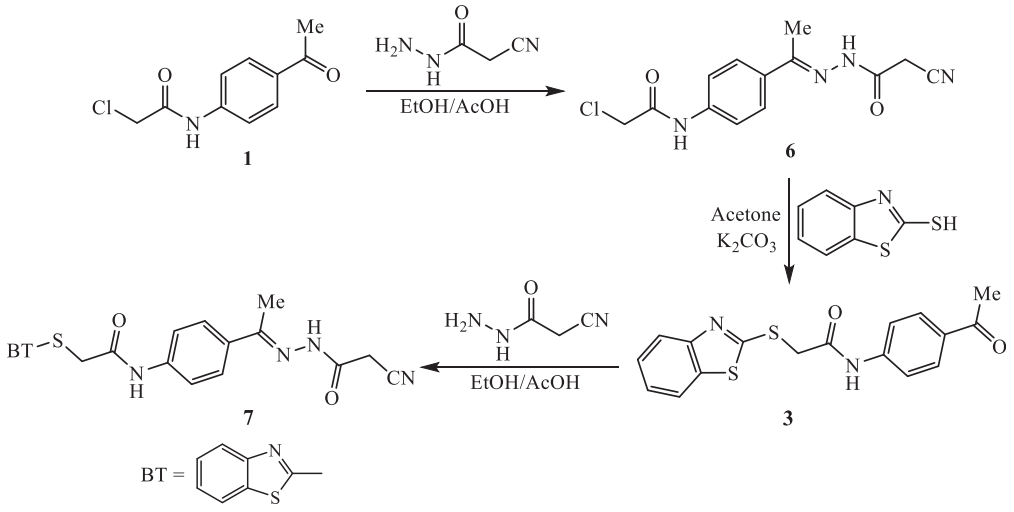


FIGURE 2 The proposed mechanism for the cleavage of imine bond

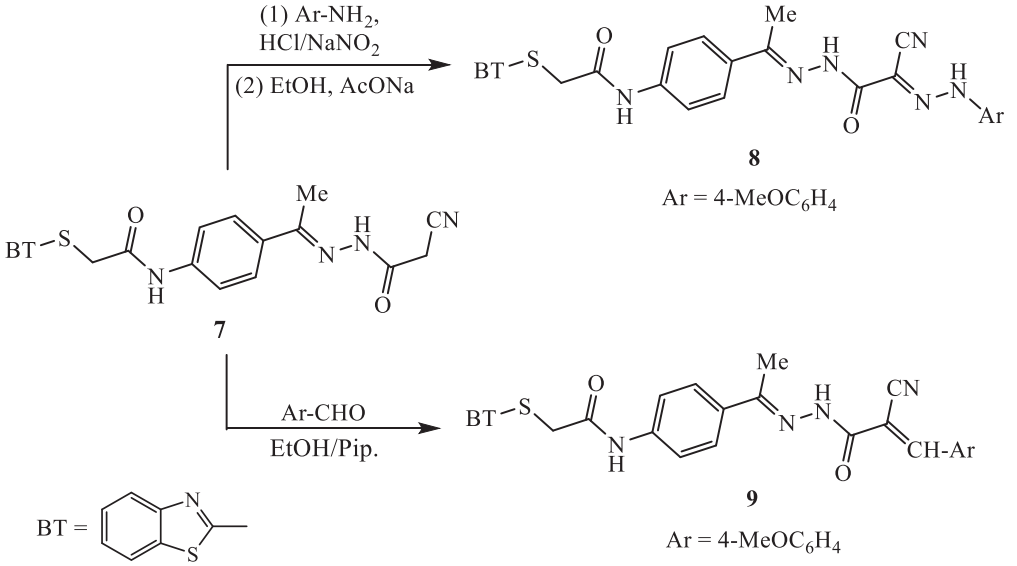
than the amidic carbonyl of acetamide derivative, **3**. The condensation reaction was achieved in boiling ethanol and drops of acetic acid (Scheme 2).

The cleavage of imine bond in either compounds, **2** or **6**, by the action of 2-mecraptobenzothiazole, under the reaction conditions, appears to follow the suggested mechanism outlined in Figure (2).

Moreover, the activated nitrile functionality of cyanoacetyl-hydrazone derivative, **7**, was investigated toward electrophilic diazo-coupling and Knoevenagel condensation reactions. Thus, coupling reaction of compound, **7**, with diazotized *p*-anisidine (obtained by diazotization of *p*-anisidine with conc. HCl and sodium nitrile at 0°C-5°C) proceeded in ethanol and sodium acetate to furnish the corresponding 2-oxoacetohydrazonoyl cyanide product, **8** (Scheme 3). The benzothiazole-S linkage was strong enough and did not cleavage under the reaction condition, as indicated from the correct and compatible spectral analyses for the structure of compound, **8**. The active methylene group flanked between two withdrawing groups (cyano and carbonyl groups) in compound **7** is acidic enough to condense with aldehyde (Knoevenagel condensation). The condensation of compound, **7**, with *p*-anisaldehyde was achieved by stirring in ethanol, containing a catalytic amount of piperidine, to afford the corresponding 2-cyano-acrylohydrazone derivative, **9** (Scheme 3).



SCHEME 2 Synthesis of 2-(benzothiazolylthio)-*N*-(4-(1-(2-(2-cyanoacetyl) hydrazono)-ethyl)phenyl) acetamide derivative, **7**



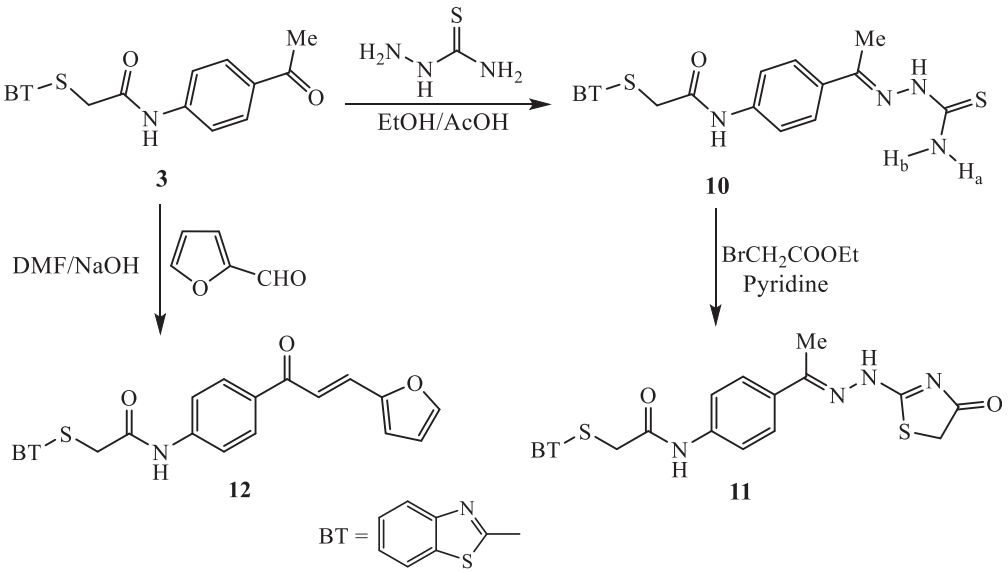
SCHEME 3 Synthesis of 2-(benzothiazolylthio)-*N*-(4-(1-(2-(2-cyanoacetyl) hydrazono)-ethyl)phenyl)-acetamide derivatives, 8 and 9

Although for the previously synthesized hydrazones, **2**, **4**, **6**, **7**, **8**, and **9**, it is possible to have *E*/*Z* isomerization around the C═N double bond. The ^{1}H NMR spectra of these hydrazones in DMSO-d_6 showed just one set of signals, that can be related to the geometric (*E*)-configuration about the C═N bond due to steric hindrance on the imine bond as revealed from literature survey.[35–37]

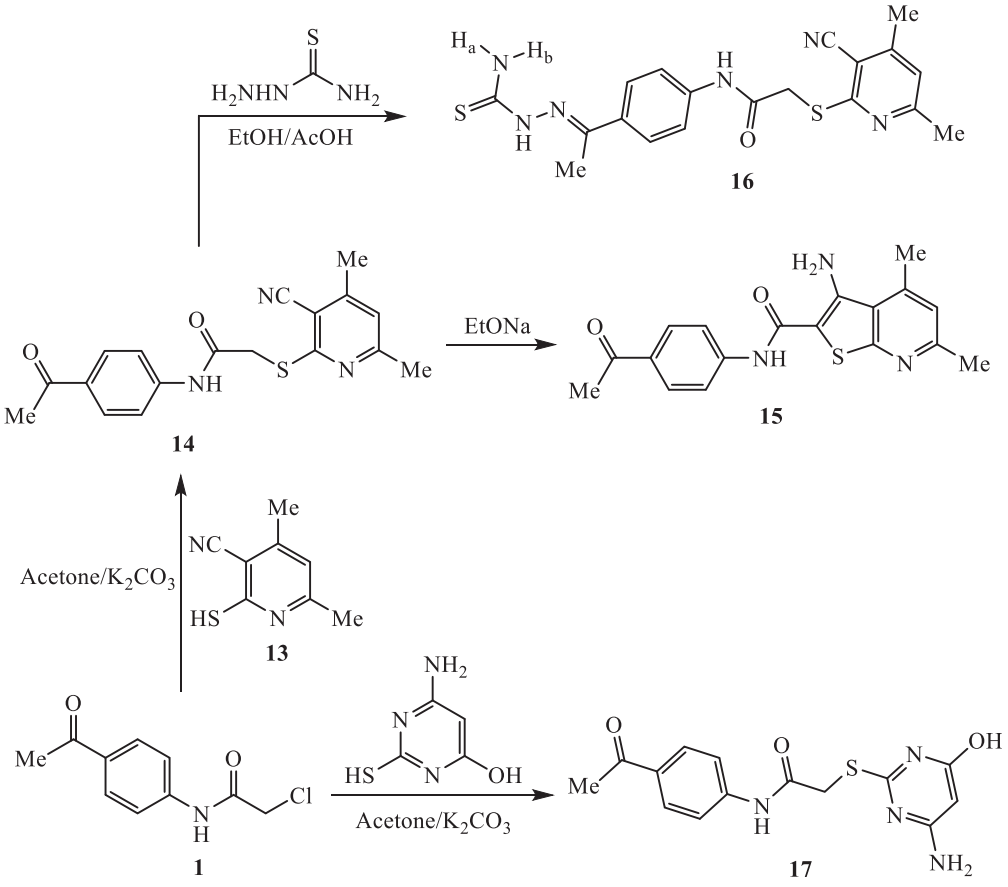
Furthermore, the condensation of *N*-(4-acetylphenyl)-2-(benzothiazol-2-ylthio)-acetamide (**3**) with thiosemicarbazide required heating in ethanol containing drops of acetic acid, furnishing the anticipated condensation product 2-(benzothiazol-2-ylthio)-*N*-(4-(1-(2-carbamothioylhydrazineylidene)ethyl)phenyl)acetamide (**10**). Heterocyclization of thiosemicarbazone derivative, **10**, upon treatment with ethyl bromoacetate to generate the 2-(benzothiazol-2-ylthio)-*N*-(4-(1-(2-(4-oxo-4,5-dihydrothiazol-2-yl)hydrazineylidene)-ethyl)phenyl)acetamide (**11**) was achieved by heating in pyridine, under reflux, for 4 hours. The formation of benzothiazole-based chalcone compound, 2-(benzothiazol-2-ylthio)-*N*-(4-(3-(furan-2-yl)acryloyl) phenyl)acetamide (**12**) was undertaken using sodium hydroxide as a basic-catalyzed aldol condensation reaction, for the condensation between *N*-(4-acetylphenyl)-2-(benzothiazol-2-ylthio)-acetamide (**3**) and furan-2-carbaldehyde in dimethylformamide (Scheme 4).

The replacement of the chlorine atom from *N*-(4-acetylphenyl)-2-chloroacetamide (**1**) by 2-mercaptonicotinonitrile derivative, **13**,[38] was performed by boiling in acetone in the presence of potassium carbonate as a base to produce, *N*-(4-acetylphenyl)-2-((3-cyanopyridin-2-yl)thio) acetamide sulfide derivative, **14**. Heating of sulfide derivative, **14**, in ethanolic solution of sodium hydroxide induced intramolecular hetero-cyclization between the methylene and nitrile functionalities, yielding the *N*-(4-acetylphenyl)-3-amino-4,6-dimethylthieno [2,3-*b*]-pyridine-2-carboxamide (**15**). In addition, the

SCHEME 4 Synthesis of 2-(benzothiazolylthio)-*N*-(4-substitutedphenyl)acetamide derivatives, **11** and **12**

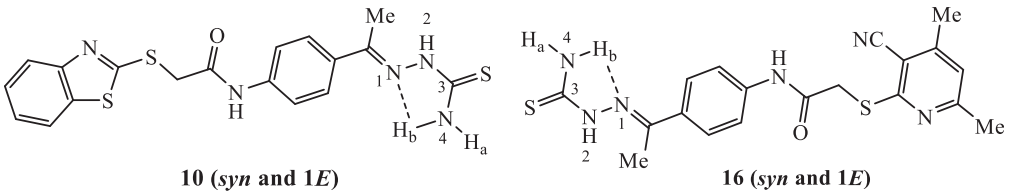


SCHEME 5 Synthesis of 2-(pyridylthio)-*N*-(4-acetylphenyl)-acetamide and 2-(pyrimidylthio)-*N*-(4-acetylphenyl)-acetamide derivatives, **14**, **16**, and **17**



condensation of sulfide derivative, **14**, with thiosemicarbazide was realized in boiling ethanol and 1 mL of acetic acid as a catalyst to afford the thiosemicarbazone, *N*-(4-(1-(2-carbamothioylhydrazono)-ethyl)phenyl)-2-((3-cyano-4,6-dimethylpyridin-2-yl)thio)acetamide (**16**). Finally, *N*-(4-acetylphenyl)-2-chloroacetamide (**1**) and 6-amino-2-mercaptopyrimidin-4-ol were allowed to react by stirring in acetone in the presence of potassium carbonate to yield the sulfide derivative, *N*-(4-acetylphenyl)-2-((4-amino-6-hydroxypyrimidin-2-yl)thio)acetamide (**17**) (Scheme 5).

As previously described in the literature,[39] the N4 unsubstituted thiosemicarbazones, of the types **10** and **16**, can adopt *syn* conformation and 1*E* configuration (Figure 3). The proposed molecular configuration with the N4-H cis to



10 (*syn* and 1*E*) 16 (*syn* and 1*E*)

FIGURE 3 Configurations of thiosemicarbazones, **10** and **16**

TABLE 1 Antimicrobial activity (inhibition zone, mm) of the newly synthesized *N*-aryl chloroacetamide-based compounds, (NA → No Activity)

	Escherichia coli (mg/mL)		*Staphylococcus aureus* (mg/mL)	
Compound #	**Diameter (mm) inhibition zone**	**Activity index (%)**	**Diameter (mm) inhibition zone**	**Activity index (%)**
2	17	65.4	19	79.2
4	13	50.0	17	70.8
5	NA	–	2	8.3
6	NA	–	8	28.0
7	10	38.5	15	62.5
8	18	69.2	19	79.2
9	11	42.3	14	58.3
10	21	80.8	22	91.7
11	9	34.6	14	58.3
12	17	65.4	21	87.5
14	21	80.8	22	91.7
15	14	53.8	18	75.0
16	12	46.1	17	70.8
17	9	34.6	15	62.5
Ampicillin	26	100	24	100

the thiocarbonyl group, leaving the second N4-H disposed for intramolecular hydrogen-bond formation. The proposed configurations of these thiosemicarbazones can explain the appearance of the NH_2 in the ^1H NMR spectra as two separated singlet signals. They resonated in the spectrum of compound **10** (as an example) as two singlet signals at δ 8.25 ppm, for the non-hydrogen bonded proton (H_a), and at δ 8.64 ppm, for the hydrogen-bonded proton (H_b).

2.2 | Biological activities of the synthesized *N*-aryl chloroacetamide-based compounds

2.2.1 | Antibacterial activity

The antibacterial properties of synthesized heterocycles, derived from *N*-aryl chloroacetamides, were explored against Gram-negative bacteria (*Escherichia coli*) and Gram-positive bacteria (*Staphylococcus aureus*).[40] Each compound of the investigated compounds was dissolved in DMSO and solutions of the concentration, 1 mg/mL, were prepared separately. Paper discs of Whatman filter paper were prepared with standard size (5 cm) and sterilized in an autoclave. The paper discs were soaked in the desired concentration of the tested solution and placed aseptically in the Petri dishes containing nutrient agar media (agar 20**g** + beef extract 3**g** + peptone 5**g**) seeded with *E coli* or *S aureus*. The Petri dishes were incubated at 36°C and the inhibition zones were recorded after 24 hours of incubation. Each treatment was replicated three times. The antibacterial activity of a common standard antibiotic, ampicillin, was also recorded as a positive control using the same procedures used for the investigated compounds. The % activity index for the test compound was calculated by the formula:

A preliminary exploration of the antibacterial activity of the newly synthesized *N*-aryl chloroacetamide-based compounds (Table 1) indicated that the thiosemicarbazone derivative, **10**, and the sulfide derivative *N*-(*p*-acetylphenyl)-2-((3-cyano-4,6-dimethylpyridin-2-yl)thio)-acetamide (**14**) are the most active compounds against *E coli*, with

TABLE 2 Antioxidant activity of the newly synthesized *N*-aryl chloroacetamide-based compounds

Method	ABTS [Abs(control) − Abs(test)/Abs (control)] × 100	
Compounds	Absorbance of samples	% Inhibition
Control of ABTS	0.500	0
Ascorbic-acid	**0.059**	**88.2%**
2	0.171	65.8%
4	0.233	53.4%
5	0.462	7.6%
6	0.359	39.8%
7	0.295	41.0%
8	0.145	71.0%
9	0.341	31.8%
10	0.087	82.6%
11	0.347	30.6%
12	0.123	75.4%
14	0.099	80.2%
15	0.158	68.4%
16	0.194	61.2%
17	0.294	41.2%

inhibitory relative activity index 80.8%. Meantime, the synthesized compounds, 2-(benzothiazol-2-ylthio)-*N*-(4-(1-(2-carbamothioyl-hydrazineylidene)-ethyl)-phenyl)-acetamide (**10**) and *N*-(*p*-acetylphenyl)-2-((3-cyano-4,6-dimethyl-pyridin-2-yl)thio)-acetamide (**14**) displayed significant antibacterial potentiality against *S aureus* (inhibition zone = 22 mm, activity index = 91.7%). Compounds, **10** and **14**, displayed very close inhibitory activities to that displayed by the reference antibiotic, ampicillin, which inhibits the growth of bacteria with 24 mm inhibition zone. In addition, the 2-(benzothiazol-2-ylthio)-*N*-(4-(3-(furan-2-yl)acryloyl)-phenyl)-acetamide (**12**) comes second against *S aureus* with activity index 87.5% (inhibition zone, 21 mm). Furthermore, the phenylhydrazone derivative, **2**, and 2-oxoacetohydrazonoyl carbonitrile derivative, **8**, inhibit the growth of *S aureus* with activity index, 79.2% (inhibition zone 19 mm).

2.2.2 | Antioxidant assay

The new compounds were further investigated for their antioxidant activities (Table 2) using the ABTS radical cation decolorization assay.[41] The results indicated that the conversion of *N*-(4-acetylphenyl)-2-(benzothiazol-2-ylthio)-acetamide (**3**) into its corresponding thiosemicarbazone, **10**, promoted the antioxidant activity to the highest percent of inhibition = 82.6%, which comes close to that observed by the reference antioxidant L-ascorbic acid (88.2%). The sulfide derivative, *N*-(*p*-acetylphenyl)-2-((3-cyano-4,6-dimethylpyridin-2-yl)thio)-acetamide (**14**) showed significant antioxidant activity with percent of inhibition = 80.2%. The combination between benzothiazole and furan moieties in the chalcone-containing compound, 2-(benzothiazol-2-ylthio)-*N*-(4-(3-(furan-2-yl)-acryloyl)phenyl)acetamide (**12**), also revealed good antioxidant activity with inhibitory percent = 75.4%.

3 | CONCLUSION

In summary, simple and direct synthetic strategies were employed to exploit the reactivity of *N*-(4-acetylphenyl)-2-chloroacetamide (**1**) toward various nucleophilic and electrophilic reagents. A group of 14 compounds was synthesized with structural diversity. All the newly synthesized compounds were tested for their antibacterial and antioxidant activities. Most of these compounds showed significant antibacterial and antioxidant potentialities. Particularly, compounds, **10** and **14**, were the most potent antibacterial and antioxidant agents, which highlight a demand to extend this chemical synthesis to generate a lead-library, which features a diversity of heterocyclic scaffolds to enable us to set structure-activity relationships.

4 | EXPERIMENTAL

All chemicals were obtained from Sigma-Aldrich and used without any further purification. Progress of the reactions was monitored by thin-layer chromatography on Merck's silica plates. Melting points were measured in degree centigrade on Gallenkamp apparatus and are uncorrected. The infrared spectra were recorded (KBr) on Thermo Scientific Nicolet iS10 FTIR spectrometer. Nuclear magnetic resonance spectra were recorded in $CDCl_3$ or DMSO-d_6 as a solvent at 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR) on JEOL's NMR spectrometer, using TMS as internal standard, and chemical shifts are expressed as δ/ppm. Perkin-Elmer 2400 analyzer has been utilized to measure the elemental analyses (C, H, and N).

4.1 | (*E*)-2-Chloro-*N*-(4-(1-(2-phenylhydrazono)ethyl)phenyl) acetamide (2)

Phenylhydrazine (0.005 mol, 0.55 mL) was added to a solution of chloroacetamide derivative, **1** (0.005 mol, 1.05 g) in

EtOH (20 mL) and 0.5 mL acetic acid. The reaction mixture was boiled under reflux for 2 hours. The precipitate obtained upon cooling was filtered off and recrystallized from EtOH-DMF mixture (10:3) to give the phenylhydrazone derivative, **2**.

Yellowish green crystals, yield = 80%, m.p. = 178°C to 180°C. IR: 3346, 3314 (NH), 1683 cm^{-1} (C═O). ^1H NMR (DMSO-d_6): 2.22 (s, 3H, CH_3), 4.26 (s, 2H, CH_2), 6.73 (t, J = 6.50 Hz, 1H, Ar—H), 7.21 (m, 4H, Ar—H), 7.61 (d, J = 9.00 Hz, 2H, Ar—H), 7.76 (d, J = 9.00 Hz, 2H, Ar—H), 9.21 (s, 1H, NH), 10.38 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 12.68, 43.63, 112.76 (2C), 118.72, 119.05 (2C), 125.67 (2C), 128.88 (2C), 134.76, 137.88, 140.15, 146.12, 164.55. Analysis of $C_{16}H_{16}ClN_3O$ (301): Calculated: C, 63.68; H, 5.34; N, 13.92%. Found: C, 63.55; H, 5.38; N, 13.98%.

4.2 | (*E*)-2-(Benzothiazol-2-ylthio)-*N*-(4-(1-(2-phenylhydrazineylidene)ethyl)-phenyl)acetamide (4)

To a suspension of compound **3** (0.005 mol, 1.71 g) and phenylhydrazine (0.005 mol, 0.55 mL) in 20 mL ethanol, 0.5 mL acetic acid was added. The reaction mixture was boiled under reflux for 4 hours. The solid that formed was collected by filtration to give the phenylhydrazone derivative, **4**.

Orange powder, yield = 75%, m.p. = 152°C to 154°C. IR (KBr): 3358, 3280 (NH), 1661 cm^{-1} (C═O). ^1H NMR (DMSO-d_6): 2.21 (s, 3H, CH_3), 4.41 (s, 2H, CH_2), 6.72 (m, 1H, Ar—H), 7.18 to 7.222 (m, 4H, Ar—H), 7.35 (t, J = 7.50 Hz, 1H, Ar—H), 7.45 (t, J = 7.20 Hz, 1H, Ar—H), 7.61 (d, J = 8.00 Hz, 2H, Ar—H), 7.75 (d, J = 8.00 Hz, 2H, Ar—H), 7.83 (d, J = 7.50 Hz, 1H, Ar—H), 8.02 (d, J = 7.50 Hz, 1H, Ar—H), 9.20 (s, 1H, NH), 10.53 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 12.69, 37.75, 112.75 (2C), 118.70, 118.85 (2C), 121.08, 121.91, 124.55, 125.68 (2C), 126.44, 128.88 (2C), 134.55, 134.77, 138.19, 140.22, 146.13, 152.53, 165.13, 166.12. Analysis of $C_{23}H_{20}N_4OS_2$ (432): Calculated: C, 63.86; H, 4.66; N, 12.95%. Found: C, 63.92; H, 4.61; N, 12.88%.

4.3 | 2-(Benzothiazol-2-ylthio)-*N*-(4-(4-formyl-1-phenyl-1*H*-pyrazol-3-yl) phenyl)acetamide (5)

Phosphorus oxychloride (0.004 mol, 0.6 mL) was gradually added to a well-cooled dimethylformamide (DMF, 10 mL) and then allowed to stir for about 30 minutes. After addition of compound **4** (1.08 g, 0.0025 mol), the reaction mixture was settled at room temperature for 5 minutes and then heated on water bath at 60°C to 65°C for 6 hours. The reaction mixture was cooled, poured onto crushed ice, and neutralized with Na_2CO_3 solution. The solid product was filtered off, dried, and recrystallized from ethanol to furnish compound **5**.

Brown powder, yield = 37%, m.p. = 140°C to 142°C. IR (KBr): 3255 (NH), broad centered at 1678 cm^{-1} (C═O). ^1H NMR ($CDCl_3$): 4.09 (s, 2H, CH_2), 7.36 to 7.82 (m, 12H, Ar—H), 7.99 (d, J = 9.00 Hz, 1H, Ar—H), 8.50 (s, 1H, pyrazole-H_4), 10.01 (s, 1H, CHO), 10.35 ppm (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 38.05, 113.28, 119.52 (2C), 120.40 (2C), 121.81, 122.17, 124.48, 125.61, 126.44, 127.25, 129.03 (2C), 129.49 (2C), 131.69, 134.48, 138.52, 140.54, 148.17, 152.54, 165.18, 166.27, 183.42. Analysis of $C_{25}H_{18}N_4O_2S_2$ (470): Calculated: C, 63.81; H, 3.86; N, 11.91%. Found: C, 63.96; H, 3.78; N, 11.84%.

4.4 | (*E*)-2-Chloro-*N*-(4-(1-(2-(2-cyanoacetyl)hydrazineylidene)ethyl)-phenyl)acetamide (6)

To a mixture of equimolar amounts of chloroacetamide derivative, **1**, (0.002 mol, 0.42 g) and 2-cyanoacetohydrazide (0.002 mol, 0.2 g) in 15 mL ethanol, five drops of acetic acid was added. The reaction components were boiled under reflux for 90 minutes. The solid that was obtained upon cooling was picked up by filtration to furnish the target 2-chloroacetamide derivative, **6**.

Pale yellow powder, yield = 72%, m.p. = 254°C to 256°C. IR: 3301, 3193 (N—H), 2265 (C≡N), 1692, 1660 cm^{-1} (C═O). ^1H NMR (DMSO-d_6): 2.21 (s, 3H, CH_3), 4.22 (s, 2H, CH_2), 4.26 (s, 2H, CH_2), 7.61, (d, J = 9.00 Hz, 2H, Ar—H), 7.78 (d, J = 9.00 Hz, 2H, Ar—H), 10.44 (s, 1H, NH), 10.99 ppm (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 14.05, 26.11, 43.30, 120.15 (2C), 124.35, 129.18 (2C), 134.10, 140.18, 146.15, 164.76, 170.40. Analysis of $C_{13}H_{13}ClN_4O_2$ (292): Calculated: C, 53.34; H, 4.48; N, 19.14%. Found: C, 53.21; H, 4.55; N, 19.25%.

4.5 | (*E*)-2-(Benzothiazol-2-ylthio)-*N*-(4-(1-(2-(2-cyanoacetyl)-hydrazineylidene) ethyl)phenyl)acetamide (7)

To a mixture of compound, **3** (0.002 mol, 0.68 g) and 2-cyanoacetohydrazide (0.002 mol, 0.2 g), in 20 mL ethanol, five drops of acetic acid were added. The reaction components were boiled under reflux for 90 minutes. The solid that formed upon cooling was collected by filtration to give the acetamide derivative, **7**.

Yellow powder, yield = 82%, m.p. = 150°C to 152°C. IR: 3342 (N—H), 2260 (C≡N), broad centered at 1691 cm^{-1} (C═O). ^1H NMR (DMSO-d_6):2.21 (s, 3H, CH_3), 4.22 (s, 2H, CH_2), 4.41 (s, 2H, CH_2), 7.35 (t, J = 7.50 Hz, 1H, Ar—H),

7.45 (t, J = 7.50 Hz, 1H, Ar—H), 7.62 (d, J = 9.00 Hz, 2H, Ar—H), 7.78 (d, J = 9.00 Hz, 2H, Ar—H), 7.81 (d, J = 8.00 Hz, 1H, Ar—H), 8.02 (d, J = 7.50 Hz, 1H, Ar—H), 10.60 (s, 1H, NH), 10.98 ppm (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 13.67, 24.90, 37.74, 116.31, 118.63, 121.07, 121.92, 124.56, 126.44 (2C), 127.01 (2C), 129.59, 132.79, 134.76, 139.78, 148.64, 152.50, 165.40, 166.04. Analysis of $C_{20}H_{17}N_5O_2S_2$ (423): Calculated: C, 56.72; H, 4.05; N, 16.54%. Found: C, 56.60; H, 4.13; N, 16.64%.

4.6 | (*E*)-2-(2-((*E*)-1-(4-(2-(Benzothiazol-2-ylthio)acetamido)phenyl)ethylidene)-hydrazinyl)-*N*-(*p*-anisyl)-2-oxoacetohydrazonoyl cyanide (8)

A solution of $NaNO_2$ (0.14 g in 10 mL cold water) was added to a well cold suspension (0°C-5°C) of *p*-anisidine (0.002 mol, 0.24 g) in conc. HCl (0.6 mL) with stirring. The diazonium chloride solution formed was added with stirring to cold solution (0°C-5°C) of cyanoacetyl-hydrazone derivative, **7**, (0.002 mol, 0.84 g) in 15 mL pyridine. After the addition was completed, the stirring was continued for an additional 90 minutes. The solid obtained was filtered off, washed with water, and recrystallized from ethyl alcohol.

Brown powder, yield = 42%, m.p. = 224°C to 226°C. IR (KBr): 3368, 3280 (NH), 2208 (C≡N), broad centered at 1677 cm^{-1} (C═O). ^{1}H NMR (DMSO-d_6): 2.21 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 4.41 (s, 2H, CH_2), 7.01 to 8.02 (m, 12H, Ar—H), 10.56 (s, 1H, NH), 11.01 (s, 1H, NH), 11.88 ppm (s, 1H, NH). Analysis of $C_{27}H_{23}N_7O_3S_2$ (557): Calculated: C, 58.15; H, 4.16; N, 17.58%. Found: C, 58.24; H, 4.15; N, 17.65%.

4.7 | 2-(Benzothiazol-2-ylthio)-*N*-(4-((*E*)-1-(2-((*E*)-2-cyano-3-(*p*-anisyl)acryloyl)-hydrazineylidene)ethyl)phenyl) acetamide (9)

To a suspension of cyanoacetyl-hydrazone derivative, **7**, (0.001 mol, 0.42 g) in 30 mL ethyl alcohol, *p*-anisaldehyde (0.001 mol, 0.12 mL) and three drops of piperidine were added. The reaction components were refluxed for 2 hours. The precipitate obtained was picked up by filtration to furnish the targeted acetamide derivative, **9**.

Yellow powder, yield = 40%, m.p. = 176°C to 178°C. IR: 3329, 3222 (NH), 2206 (C≡N), broad centered at 1690 cm^{-1} (C═O). ^{1}H NMR (DMSO-d_6): 2.23 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.41 (s, 2H, CH_2), 7.12 to 8.02 (m, 13H, Ar—H and olefinic C═CH), 10.60 (s, 1H, NH), 10.99 ppm (s, 1H, NH). Analysis of $C_{28}H_{23}N_5O_3S_2$ (541): Calculated: C, 62.09; H, 4.28; N, 12.93%. Found: C, 62.31; H, 4.26; N, 12.75%.

4.8 | (*E*)-2-(Benzothiazol-2-ylthio)-*N*-(4-(1-(2-carbamothioyl-hydrazineylidene] ethyl)phenyl)acetamide (10)

A solution of compound **3** (0.002 mol, 0.68 g) and thiosemicarbazide (0.002 mol, 0.2 g) in 30 mL ethyl alcohol and acetic acid (0.5 mL) was heated under reflux for 4 hours. The reaction mixture was cooled to room temperature. The crude solid product was filtered off, dried, and recrystallized from EtOH-DMF mixture (10:7) to afford compound **10**.

Yellow powder, yield = 69%, m.p. = 224°C to 226°C. IR (KBr): 3375, 3254, 3164 (NH_2 and NH), 1684 cm^{-1} (C═O). ^{1}H NMR (DMSO-d_6): 2.25 (s, 3H, CH_3), 4.40 (s, 2H, CH_2), 7.36 (t, J = 7.60 Hz, 1H, Ar—H), 7.45 (t, J = 7.60 Hz, 1H, Ar—H), 7.60 (d, J = 9.00 Hz, 2H, Ar—H), 7.81 (d, J = 8.00 Hz, 1H, Ar—H), 7.91 (d, J = 9.00 Hz, 2H, Ar—H), 8.01 (d, J = 7.50 Hz, 1H, Ar—H), 8.25 (s, 1H, NH_a), 8.64 (s, 1H, NH_b), 10.17 (s, 1H, NH), 10.57 ppm (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 13.69, 37.73, 118.51 (2C), 121.04, 121.89, 124.53, 126.41, 127.31 (2C), 132.68, 134.75, 139.66, 147.34, 152.48, 165.33, 166.01, 178.69. Analysis of $C_{18}H_{17}N_5OS_3$ (415): Calculated: C, 52.03; H, 4.12; N, 16.85%. Found: C, 52.10; H, 4.07; N, 16.91%.

4.9 | 2-(Benzothiazol-2-ylthio)-*N*-(4-(1-(2-(4-oxo-4,5-dihydrothiazol-2-yl) hydrazineylidene)ethyl)phenyl) acetamide (11)

To a solution of thiosemicarbazone compound, **10**, (0.001 mol, 0.41 g) in 10 mL pyridine, ethyl 2-bromoacetate (0.001 mol, 0.16 mL) was added and the reaction mixture was refluxed for 2 hours. After this, the reaction mixture was poured into 10 g crushed ice. The solid obtained after standing 1 day (at 0°C-5°C in a refrigerator) was filtered off. The product was recrystallized by heating in ethanol to furnish the conforming thiazolin-4-one derivative, **11**.

Yellow powder, yield = 35%, m.p. = 210°C to 212°C. IR (KBr): 3377 (NH), 1667 cm^{-1} (C═O). ^{1}H NMR (DMSO-d_6): 2.33 (s, 3H, CH_3), 3.84 (s, 2H, CH_2), 4.41 (s, 2H, CH_2), 7.35 (t, J = 7.50 Hz, 1H, Ar—H), 7.45 (t, J = 7.50 Hz, 1H, Ar—H), 7.65 (d, J = 9.00 Hz, 2H, Ar—H), 7.80 (d, J = 9.00 Hz, 2H, Ar—H), 7.82 (d, J = 9.00 Hz, 1H, Ar—H), 7.80 to 7.82 (d, J = 9.00 Hz, 3H, Ar—H), 8.01 (d, J = 8.00 Hz, 1H, Ar—H), 10.62 (s, 1H, NH), 11.92 ppm (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 14.44, 32.79, 37.77, 118.72 (2C), 121.10, 121.93, 124.57 (2C), 126.45, 127.17 (2C), 132.87 (2C), 134.78, 140.20, 152.52, 159.66, 165.45, 166.05. Analysis of $C_{20}H_{17}N_5O_2S_3$ (455): Calculated: C, 52.73; H, 3.76; N, 15.37%. Found: C, 52.61; H, 3.79; N, 15.45%.

4.10 | 2-(Benzothiazol-2-ylthio)-*N*-(4-(3-(furan-2-yl)-acryloyl)phenyl) acetamide (12)

To a well-stirred suspension of compound, **3**, (0.002 mol, 0.68 g) in 15 mL DMF, NaOH granules (0.16 g) was added followed by furan-2-carbaldehyde (0.002 mol, 0.19 mL). The reaction components were stirred at 25°C to 30°C for 4 hours and then poured into 15 g crushed ice. After neutralization with dilute HCl, the solid formed was filtered off and recrystallized from EtOH.

Brown powder, yield = 81%, m.p. = 230°C to 232°C. IR (KBr): 3429 (NH), 1671 cm^{-1} (C═O). ^1H NMR (DMSO-d_6): 4.42 (s, 2H, CH_2), 6.69 (t, J = 3.75 Hz, 1H, furan-H_4), 6.85 (d, J = 3.60 Hz, 1H, furan-H_3), 7.33 (t, J = 7.50 Hz, 1H, Ar—H), 7.46 (t, J = 7.50 Hz, 1H, Ar—H), 7.61 (d, J = 8.00 Hz, 2H, Ar—H), 7.75 (d, J = 8.00 Hz, 2H, Ar—H), 7.83 (d, J = 7.50 Hz, 1H, Ar—H), 7.94 (d, J = 15.50 Hz, 1H, olefinic C═CH), 8.02 (d, J = 8.00 Hz, 1H, Ar—H), 8.11 (d, J = 3.60 Hz, 1H, furan-H_5), 8.26 (d, J = 15.50 Hz, 1H, olefinic C═CH), 10.67 ppm (s, 1H, NH). Analysis of $C_{22}H_{16}N_2O_3S_2$ (420): Calculated: C, 62.84; H, 3.84; N, 6.66%. Found: C, 62.63; H, 3.75; N, 6.53%.

4.11 | *N*-(*p*-Acetylphenyl)-2-((3-cyano-4,6-dimethylpyridin-2-yl)thio)-acetamide (14)

To a stirred solution of chloroacetamide scaffold **1** (0.005 mol, 1.05 g) in 30 mL acetone, containing potassium carbonate (0.005 mol 0.69 g), 2-mercapto-4,6-dimethylnicotinonitrile (**13**) (0.005 mol, 0.82 g) was added and refluxed for 4 hours. The reaction solution was poured into 30 g crushed ice. The solid obtained was filtered and purified by recrystallization form ethanol to give the sulfide compound, **14**.

Yellow crystals, yield = 82%, m.p. = 196°C to 198°C. IR: 3373 (NH), 2214 (C≡N), 1713, 1666 cm^{-1} (C═O).^1H NMR (DMSO-d_6): 2.33 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.51 (s, 3H, $COCH_3$), 4.18 (s, 2H, CH_2), 7.08 (s, 1H, pyridine-H_5), 7.69 (d, J = 8.00 Hz, 2H, Ar—H), 7.92 (d, J = 8.00 Hz, 2H, Ar—H), 10.65 ppm (s, 1H, NH). Analysis of $C_{18}H_{17}N_3O_2S$ (339): Calculated: C, 63.70; H, 5.05; N, 12.38%. Found: C, 63.81; H, 5.09; N, 12.41%.

4.12 | *N*-(*p*-Acetylphenyl)-3-amino-4,6-dimethylthieno[2,3-*b*]pyridine-2-carboxamide (15)

A solution of compound **14** (0.002 mol, 0.68 g) was heated for 45 minutes in sodium ethoxide solution (0.05 g sodium granules in 20 mL absolute ethanol). The reaction mixture was cooled and diluted with 20 mL cold water. The solid material obtained by filtration was dried and purified by recrystallization form EtOH-DMF mixture (10:3) to give the conforming 3-aminothieno[2,3-*b*]pyridine compound, **15**.

Yellow powder, yield = 60%, m.p. = 226°C to 228°C. IR (KBr): 3494, 3322, 3187 (NH_2 and NH), 1657, 1632 cm^{-1} (C═O). ^1H NMR (DMSO-d_6): 2.51 (s, 3H, $COCH_3$), 2.53 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 7.06 (s, 1H, pyridine-H_5), 7.86 (d, J = 9.00 Hz, 2H, Ar—H), 7.92 (d, J = 8.00 Hz, 2H, Ar—H), 10.71 ppm (s, 1H, NH). Analysis of $C_{18}H_{17}N_3O_2S$ (339): Calculated: C, 63.70; H, 5.05; N, 12.38%. Found: C, 63.62; H, 5.12; N, 12.48%.

4.13 | (*E*)-*N*-(4-(1-(2-Carbamothioylhydrazono)-ethyl)phenyl)-2-((3-cyano-4,6-dimethylpyridin-2-yl)thio) acetamide (16)

To a suspension of compound **14** (0.002 mol, 0.68 g) in 20 mL ethanol, thiosemicarbazide (0.002 mol, 0.18 g) and 0.5 mL acetic acid were added. The reaction proceeded by boiling under reflux for 4 hours. A precipitate was picked up upon cooling, recrystallized from a mixture of EtOH-DMF (10:3) to furnish thiosemicarbazone compound, **16**.

Yellow crystals, yield = 75%, m.p. = 238°C to 240°C. IR: 3399, 3322, 3288 (NH_2 and NH), 2216 (C≡N), 1668 cm^{-1} (C═O). ^1H NMR (DMSO-d_6): 2.25 (s, 3H, CH_3), 2.37 (s, 6H, 2 CH_3), 4.16 (s, 2H, CH_2), 7.07 (s, 1H, pyridine-H_5), 7.58 (d, J = 9.00 Hz, 2H, Ar—H), 7.88 (d, J = 9.00 Hz, 3H, Ar—H and NH_a), 8.25 (s, 1H, NH_b), 10.16 (s, 1H, NH), 10.43 ppm (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 13.72, 19.65, 24.23, 34.97, 103.59, 115.04, 118.45 (2C), 120.49, 127.30 (2C), 132.44, 139.94, 147.43, 152.52, 160.27, 161.33, 166.20, 178.68. Analysis of $C_{19}H_{20}N_6OS_2$ (412): Calculated: C, 55.32; H, 4.89; N, 20.37%. Found: C, 55.47; H, 4.85; N, 20.29%.

4.14 | *N*-(*p*-Acetylphenyl)-2-((4-amino-6-hydroxypyrimidin-2-yl)thio) acetamide (17)

A mixture of chloroacetamide derivative, **1** (0.001 mol, 0.21 g) and 6-amino-2-mercaptopyrimidin-4-ol (0.001 mol, 0.14 g), in 25 mL acetone containing K_2CO_3 (0.002 mol 0.27 g) was stirred at room temperature for 4 hours. The reaction mixture was poured into 15 g crushed ice. The precipitate formed was filtered off and washed with cold ethanol to give the conforming sulfide, **17**.

White powder, yield = 81%, m.p. = 258°C to 260°C. IR (KBr): 3439, 3320, 3202 (NH_2 and NH), 1696, 1661 cm^{-1}

(C═O). ^{1}H NMR (DMSO-d_6): 2.51 (s, 3H, CH_3), 3.98 (s, 2H, CH_2), 5.01 (s, 1H, pyrimidine-H), 6.52 (s, 2H, NH_2), 7.70 (d, J = 9.00 Hz, 2H, Ar—H), 7.92 (d, J = 8.50 Hz, 2H, Ar—H), 10.48 ppm (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 26.49, 34.69, 81.44, 118.48 (2C), 129.54 (2C), 131.89, 143.14, 160.74, 162.01, 167.16, 170.07, 196.57. Analysis of $C_{14}H_{14}N_4O_3S$ (318): Calculated: C, 52.82; H, 4.43; N, 17.60%. Found: C, 52.66; H, 4.51; N, 17.69%.

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How to cite this article: Abdel-Latif E, Fahad MM, El-Demerdash A, Ismail MA. Synthesis and biological evaluation of some heterocyclic scaffolds based on the multifunctional *N*-(4-acetylphenyl)-2-chloroacetamide. *J Heterocyclic Chem*. 2020;1–11. https://doi.org/10.1002/jhet.4012