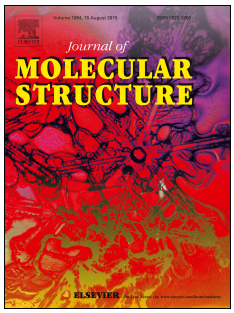

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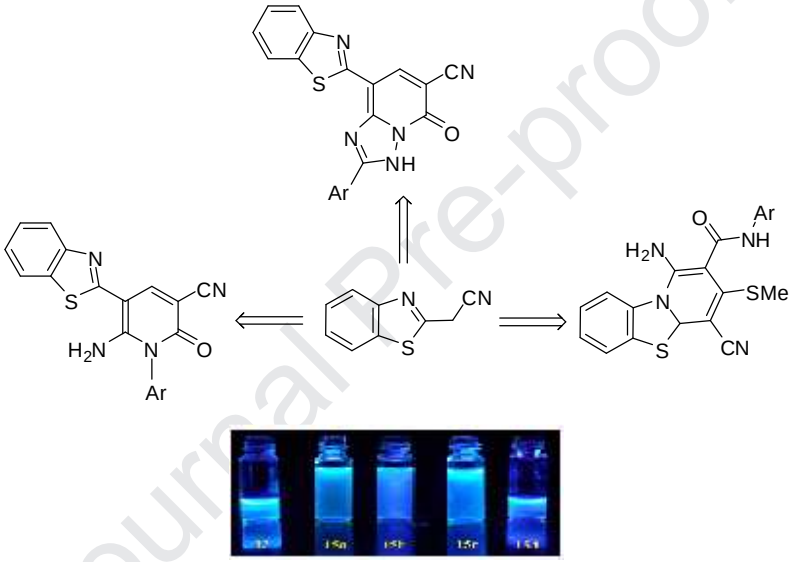

Synthesis of novel pyrido[2,1-*b*]benzothiazole and *N*-substituted 2-pyridylbenzothiazole derivatives showing remarkable fluorescence and biological activities

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Abstract

The synthesis of novel pyrido[2,1-*b*]benzothiazole and pyrido[2,1-*b*]benzoimidazole derivatives was achieved via the reaction of *N*-aryl-2-cyano-3,3-bis(methylthio)acrylamide with benzothiazoleylacetonitrile and benzoimidazoleylacetonitrile, respectively, while *N*-substituted 2-pyridylbenzothiazole derivatives were synthesized by reacting 2-(benzo[*d*]thiazol-2-yl)-3-(dimethylamino)acrylonitrile with either cyanoacetamide, aryl cyanoacetamides or 2-cyano-*N*′-(4-substituted benzylidene)acetohydrazide. Based on the steady state fluorescence measurements, the newly synthesized *N*-substituted 2-pyridylbenzothiazole derivatives exhibited remarkable fluorescence properties with considerably high quantum yields (0.25-0.29). In addition, the antimicrobial and antiviral activities were evaluated for all the newly synthesized derivatives. The antimicrobial examination revealed that triazolo-pyridone **21a** had the highest potency among all tested compounds against Escherichia coli, Klebsiella pneumonia and Staphylococcus aureus while pyrido[2,1-*b*]benzoimidazole derivatives **9a** and **9b** had the highest potency over other compounds against Candida albicans fungus.

1. Introduction

Organic compounds containing pyridine scaffold as a core unit exhibit potent pharmacological activities such as anti-hypertensive [1], anti-histamine [2], anticoagulant [3], anti-inflammatory [4], antibacterial [5], antifungal [6], antiviral [7], anti-tubercular [8] and anti-malarial [9]. It is interesting to note that the replacement of the substituents on the pyridine nucleus with others has widened both its biological activities and the spectrum of its biological targets from microbes to viruses and a variety of cancerous cells [10]. This class of compounds and their derivatives are valuable synthetic target compounds and their syntheses

have been extensively reviewed [11,12]. Inasmuch, compounds containing benzothiazole moieties were also found to exhibit a number of biological activities such as anticancer [13], antitumor [14], antimicrobial [15] and antiviral [16,17] that demonstrated special significance in the field of medicinal chemistry due to their remarkable pharmacological potentialities. It is interesting to note that different pyridine and benzothiazole heterocyclic compounds may show biological activities while others may possess some fluorescence properties in which case the latter may be utilized as a fluorescent probe [18-21]. In specific compounds bearing pyridine or benzothiazole rings, a significant increase in quantum yield, dual fluorescence and solid stat fluorescence [22,23] as well as high Stokes shift, [24-26] were observed. It is worth noting that combining two or more types of different heterocycle rings into one structure may lead to novel substances with enhanced bioactivity [27,28]. For example, pyridines bearing benzothiazole moieties exhibited enhanced antibacterial and antifungal activity [29]. Moreover, dihydropyridino benzothiazole derivatives have been developed as Pr-set7 inhibitors for therapeutic prevention of cancer [30].

To achieve this interesting target, a variety of new methods has been developed to synthesize pyridine bearing benzothiazole moiety as well as pyrido[2,1-*b*]benzothiazole derivatives by our research group [31-35]. The attractive biological profiles and fluorescence properties of pyridine and benzothiazole derivatives prompted us to develop efficient methods and direct routes for the synthesis of new derivatives that encompasses both the pyridine and benzothiazole moieties. We report here on the synthesis of novel pyrido[2,1-*b*]benzothiazole derivatives through the reaction of benzothiazoleylacetonitrile with *N*-aryl-2-cyano-3,3-bis(methylthio)acrylamide and the synthesis of novel 2-pyridylbenzothiazole through the reaction of 2-(benzo[*d*]thiazol-2-yl)-3-(dimethylamino)acrylonitrile with cyanoacetamide, aryl cyanoacetamides or 2-cyano-*N*′-(4-substituted benzylidene)acetohydrazide. The study is further extended to evaluate the fluorescence properties of these newly synthesized compounds as well as their antiviral and antimicrobial activities.

2. Material and Methods

2.1 Measurements

All melting points were measured using a SMP3 melting point apparatus. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance (III)-400 Spectrometer (400 and 100 MHz, respectively) in DMSO-d_6 using $Si(CH_3)_4$ as an internal standard at Ain Shams

university, Cairo, Egypt. The mass spectra were run in Al-Azhar university. Progress of the reactions was monitored by thin-layer chromatography (TLC) using aluminum sheets coated with silica gel F254 (Merck), and UV lamp. Optical absorption and fluorescence measurements were carried out using JASCO spectrophotometer (V-780) and JASCO spectrofluorometer (model FP-8300), respectively.

2.2. Synthesis procedures

*2.2.1. General procedures for the synthesis of **7a-f***

To a stirred solution of 2-cyanomethylbenzothiazole **4** (10 mmol) in dry 1,4-dioxane (30 ml) containing potassium hydroxide (10 mmol), aryl-2-cyano-3,3-bis(methylthio)-acrylamide derivatives **3a-f** (10 mmol) were added and the reaction mixture was stirred further at room temperature for an additional one hour. The solid precipitate in each case was filtered off and was then recrystallized from ethanol.

*2.2.1.1. 4-Cyano-1-imino-3-methylsulfanyl-benzo[4,5]thiazo[1,2-a]pyridine-2-carboxylic acid phenylamide **7a***

Yellow needles; (DMF); Yield 83%; m.p 290-292 ^{o}C; IR (KBr, cm^{-1}): υ 3443, 3252 (=NH, -NH), 2204 (CN), 1647 (C=O) and 1597 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.51 (s, 3H, SCH_3), 7.15 (t, 1H, *J*=8 Hz, benzothiazole-H), 7.38-7.62 (m, 4H, Ar-H & benzothiazole-H), 7.71 (d, 2H, *J*=8 Hz, Ar-H), 8.13 (d, 1H, *J*=8 Hz, benzothiazole-H), 8.25 (br, 1H, NH), 9.50 (d, 1H, *J*=8 Hz, benzothiazole-H), 10.66 (br, 1H, NH)); ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.5 (SCH_3), 81.2 (Ar-C), 117.1 (CN), 121.4, 122.0, 124.4, 124.0, 126.0, 128.0, 129.1, 129.9, 132.4, 135.1, 136.5, 138.5, 150.1, 155.3 (Ar-C), 159.5 (C=O). Anal.Calcd.For. $C_{20}H_{14}N_4OS_2$ (390.48): C% 61.52; H% 3.61; N% 14.35. Found: C% 61.82; H% 3.56; N% 14.10.

*2.2.1.2. 4-Cyano-1-imino-3-methylsulfanyl-benzo[4,5]thiazo[1,2-a]pyridine-2-carboxylic acid (4-chlorophenyl)amide **7b***

Yellow needles; (DMF); Yield 85%; m.p 248-250 ^{o}C; IR (KBr, cm^{-1}): υ 3439, 3260 (=NH, -NH), 3115 (Ar C), 2201 (CN), 1644 (C=O), and 1589 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.54 (s, 3H, SCH_3), 7.44 (d, 2H, *J*=8 Hz, Ar-H), 7.56–7.63 (m, 2H, benzothiazole-H), 7.73 (d, 2H, *J*=8 Hz, Ar-H), 8.13 (d, 1H, *J*=8 Hz, benzothiazole-H), 8.27 (br, 1H, NH), 9.52 (d, 1H, *J*=8 Hz, benzothiazole-H), 10.79 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ

12.7 (SCH_3), 83.0 (Ar-C), 113.0 (CN), 120.1, 121.2, 123.4, 124.8, 125.3, 127.2, 127.5, 129.7, 133.7, 136.5, 137.8, 139.6, 155.2, 157.8 (Ar-C), 158.1 (C=O). MS: m/z = 424. Anal.Calcd.For. $C_{20}H_{13}ClN_4OS_2$ (424.93): C% 56.53; H% 3.08; N% 13.19. Found: C% 56.76; H% 2.90; N% 13.45.

2.2.1.3. 4-Cyano-1-imino-3-methylsulfanyl-benzo[4,5]thiazo[1,2-a]pyridine-2-carboxylic acid (3-chlorophenyl)amide ***7c***

Buff crystals; (DMF); Yield 77 %; m.p 338-340 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ 2.91 (s, 3H, SCH_3), 7.29 (s, 1H, C_6H_4), 7.40 (t, 1H, *J*=8 Hz, benzothiazole-H), 7.48 (t, 1H, *J*=8 Hz, benzothiazole-H), 7.52-7.74 (m, 3H, Ar-H), 8.27 (d, 1H, *J*=8 Hz, benzothiazole-H), 9.01 (d, 1H, *J*=8 Hz, benzothiazole-H), 9.46 (br, 1H, NH)); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.5 (SCH_3), 82.6 (Ar-C), 111.5 (CN), 121.9, 122.6, 123.7, 124.9, 125.9, 126.7, 127.9, 128.4, 133.0, 136.0, 137.2, 139.0, 153.9, 156.5 (Ar-C), 160.0 (C=O). Anal.Calcd.For. $C_{20}H_{13}ClN_4OS_2$ (424.93): C% 56.53; H% 3.08; N% 13.19. Found: C% 56.21; H% 3.35; N% 13.06.

2.2.1.4. 4-Cyano-1-imino-3-methylsulfanyl-benzo[4,5]thiazo[1,2-a]pyridine-2-carboxylic acid p-tolylamide ***7d***

Yellow needles; (DMF); Yield 87%; m.p 271-273 ^oC; IR (KBr, cm^{-1}): υ 3436, 3261 (=NH, -NH), 3119 (Ar C), 2204 (CN), 1641 (C=O) and 1590 (C=N). ^1H NMR (400 MHz, DMSO-d_6): δ 2.29 (s, 3H, CH_3), 2.54 (s, 3H, SCH_3), 7.18 (d, 2H, *J*=8 Hz, Ar-H), 7.58–7.60 (m, 4H, 2Ar-H & 2benzothiazole-H), 8.13 (d, 1H, *J*=8 Hz, benzothiazole-H), 8.18 (br, 1H, NH), 9.50 (d, 1H , *J*=8 Hz, benzothiazole-H), 10.57 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.2 (CH_3), 21.0 (SCH_3), 83.0 (Ar-C), 116.8 (CN), 120.1, 121.2, 123.4, 124.8, 125.3, 127.2, 127.5, 129.7, 133.7, 136.5, 137.8, 139.6, 155.2, 157.8 (Ar-C), 162.6 (C=O). Anal.Calcd.For. $C_{21}H_{16}N_4OS_2$ (404.51): C% 62.35; H% 3.99; N% 13.85. Found: C% 62.45; H% 3.91; N% 14.05.

2.2.1.5. 4-Cyano-1-imino-3-methylsulfanyl-benzo[4,5]thiazo[1,2-a]pyridine-2-carboxylic acid m-tolylamide ***7e***

Orange crystals; (DMF); Yield 85%; m.p 235-237 ^oC; IR (KBr, cm^{-1}): υ 3442, 3258 (C=NH, C-NH), 3068 (Ar CH), 2202 (CN), 1644 (C=O) and 1588 (C=N). ^1H NMR (400 MHz, DMSO-d_6): δ 2.32 (s, 3H, CH_3), 2.55 (s, 3H, SCH_3), 6.97 (d, 1H, *J*=8 Hz, Ar-H), 7.25 (t, 1H,

J=8 Hz, benzothiazole-H), 7.46–7.69 (m, 4H, 3Ar-H & benzothiazole-H), 7.85 (d, 1H, *J*=8 Hz, benzothiazole-H), 8.27 (br, 1H, NH), 8.60 (d, 1H, *J*=8 Hz, benzothiazole-H), 10.9 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.2 (CH_3), 21.0 (SCH_3), 83.0 (Ar-C), 116.8 (CN), 118.0, 120.1, 121.2, 123.4, 124.8, 125.3, 127.5, 129.7, 137.7, 138.5, 138.8, 139.6, 155.2, 157.8 (Ar-C), 162.6 (C=O). Anal.Calcd.For. $C_{21}H_{16}N_4OS_2$ (404.51): C% 62.35; H% 3.99; N% 13.85. Found: C% 62.72; H% 3.86; N% 13.91.

*2.2.1.6. 4-Cyano-1-imino-3-methylsulfanyl-benzo[4,5]thiazo[1,2-a]pyridine-2-carboxylic acid o-tolylamide **7f***

Yellow crystals; (DMF); Yield 72%; m.p 263 ^{o}C; IR (KBr, cm^{-1}): υ 3435, 3234 (C=NH, C-NH), 3057 (Ar C), 2202 (CN), 1635 (C=O) and 1582 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.32 (s, 3H, CH_3), 2.61 (s, 3H, SCH_3), 7.17 (t, 1H, *J*=8 Hz, benzothiazole-H), 7.23–7.29 (m, 2H, Ar-H & benzothiazole-H), 7.56 -7.64 (m, 3H, Ar-H), 8.14 (d, 1H, *J*=8 Hz, benzothiazole-H), 8.21 (br, 1H, NH), 9.53 (d, 1H, *J*=8 Hz, benzothiazole-H), 10.07 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.0 (CH_3), 20.0 (SCH_3), 84.2 (Ar-C), 115.0 (CN), 121.4, 122.0, 123.6, 125.0, 126.1, 127.7, 128.0, 129.5, 131.5, 134.9, 136.0, 138.6, 154.0, 156.0 (Ar-C), 160.0 (C=O). Anal.Calcd.For. $C_{21}H_{16}N_4OS_2$ (404.51): C% 62.35; H% 3.99; N% 13.85. Found: C% 62.54; H% 4.14; N% 13.98.

*2.2.2. General procedures for the synthesis of **9a-c***

To a stirred solution of 2-cyanomethylbenzimidazole **8** (10 mmol) in dry 1,4-dioxane (30ml) containing potassium hydroxide (10mmol), aryl-2-cyano-3,3-bis(methylthio)-acrylamide derivatives **3*b,d,e*** (10 mmol) were added and the reaction mixture was stirred further at room temperature for an additional one hour. The solid precipitate was filtered off and then recrystallized from ethanol.

*2.2.2.1. 1-Amino-4-cyano-3-methylsulfanyl-benzo[4,5]imidazo[1,2-a]pyridine-2-carboxylic acid (4-chlorophenyl)amide **9a***

Buff crystals; (DMF); Yield 73%; m.p 279-281 ^{o}C; IR (KBr, cm^{-1}): υ 3445, 3361 (NH, NH_2), 3098 (Ar CH), 2209 (CN), 1634 (C=O) and 1596 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.63 (s, 3H, SCH_3), 7.39-7.90 (m, 9H, 4Ar-H, NH_2 & 3benzimidazole-H), 8.50 (d, 1H, *J*=8 Hz, benzimidazole-H), 10.51 (br, 1H, NH)); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.0 (SCH_3), 82.6 (Ar-C), 115.0 (CN), 119.5, 121.7, 122.3, 124.0, 125.0, 126.4, 127.0, 129.0,

135.5, 137.0, 138.0, 139.0, 154.9, 156.4 (Ar-C), 163.0 (C=O). Anal.Calcd.For. $C_{20}H_{14}ClN_5OS$ (407.88): C% 58.89; H% 3.46; N% 17.17. Found: C% 58.65; H% 3.15; N% 17.34.

2.2.2.2. 1-Amino-4-cyano-3-methylsulfanyl-benzo[4,5]imidazo[1,2-a]pyridine-2-carboxylic acid p-tolylamide ***9b***

Buff crystals; (DMF); Yield 71%; m.p 273-275 ^{o}C; IR (KBr, cm^{-1}): υ 3484, 3306 (NH_2, NH), 3100 (Ar C), 2206 (CN), 1648 (C=O) and 1590 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.30 (s, 3H, CH_3), 2.61 (s, 3H, SCH_3), 7.18 (d, 2H, *J*=8.4 Hz, Ar-H), 7.38 (t, 1H, *J*=6.4 Hz, benzimidazole-H), 7.57–7.64 (m, 3H, 2Ar-H & benzimidazole-H), 7.84 (m, 3H, NH_2 & benzimidazole-H), 8.49 (d, 1H, *J*=8Hz, benzimidazole-H), 10.47 (br, 1H, NH)); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.9 (SCH_3), 82.6 (Ar-C), 117.0 (CN), 119.5, 120.8, 121.9, 123.8, 124.9, 125.9, 127.6, 129.0, 130.0, 134.0, 136.4, 137.4, 138.0, 153.0, 155.8 (Ar-C), 163.9 (C=O). Anal.Calcd.For. $C_{21}H_{17}N_5OS$ (387.46): C% 65.10; H% 4.42; N% 18.08. Found: C% 65.35; H% 4.62; N% 18.26.

2.2.2.3. 1-Amino-4-cyano-3-methylsulfanyl-benzo[4,5]imidazo[1,2-a]pyridine-2-carboxylic acid m-tolylamide ***9c***

Buff solid; (DMF); Yield 73%; m.p 260-262 ^{o}C; IR (KBr, cm^{-1}): υ 3408, 3323 (NH_2, NH), 3062 (Ar C), 2222 (CN), 1642 (C=O) and 1545 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.33 (s, 3H, CH_3), 2.67 (s, 3H, SCH_3), 6.96 (d, 1H, *J*=7.2 Hz, Ar-H), 7.26 (t, 1H, *J*=7.6 Hz, benzimidazole-H), 7.46–7.52 (m, 2H, Ar-H & benzimidazole-H), 7.64-7.69 (m, 2H, Ar-H), 7.85 (d, 1H, *J*=8 Hz, benzimidazole-H), 8.27 (s, 2H, NH_2), 8.60 (d, 1H, *J*=8.4 Hz, benzimidazole-H), 10.71 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.0 (CH_3), 22.0 (SCH_3), 83.0 (Ar-C), 116.8 (CN), 117.5, 118.0, 118.9, 120.1, 121.2, 123.4, 124.8, 125.3, 127.5, 129.7, 136.7, 137.5, 138.8, 139.6, 155.2, 157.8 (Ar-C), 164.6 (C=O). Anal.Calcd.For. $C_{21}H_{17}N_5OS$ (387.46): C% 65.10; H% 4.42; N% 18.08. Found: C% 65.40; H% 4.25; N% 18.22.

2.2.3. Synthesis of 6-amino-5-(benzo[*d*]thiazol-2-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile ***13***

2-(Benzo[*d*]thiazole-2-yl)-3-(dimethylamino)acrylonitrile **11** (10 mmol) was added to a stirred solution of cyanoacetamide **12** (10 mmol) in dry 1,4-dioxane (30 ml) containing

potassium hydroxide (10 mmol) and the reaction mixture was refluxed for 1 hour. The solid precipitate was filtered off and then recrystallized from ethanol. Yellow solid; (DMF); Yield 75%; m.p > 350 ^{o}C; IR (KBr, cm^{-1}): υ 3451, 3202 (NH_2, NH), 2285 (CN), and 1659 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.13 (t, 1H, *J*=8 Hz, benzothiazole-H), 7.31 (t, 1H, *J*=8 Hz, benzothiazole-H), 7.61 (d, 1H, *J*=8 Hz, benzothiazole-H), 7.81 (d, 1H, *J*=8 Hz, benzothiazole-H), 8.18 (s, 1H, CHpyridone); ^{13}C NMR (100 MHz, DMSO-d_6): δ 74.4, 75.1 (Ar-C), 119.6 (CN), 119.5, 120.0, 121.1, 122.2, 125.7, 132.5, 144.6, 154.4, 167.1 (Ar-C), 168.9 (C=O). Anal.Calcd.For. $C_{13}H_8N_4OS$ (268.29): C% 58.20; H% 3.01; N% 20.88. Found: C% 58.51; H% 3.22; N% 20.81.

*2.2.4. General procedures for the synthesis of **15a-d***

2-(Benzo[*d*]thiazole-2-yl)-3-(dimethylamino)acrylonitrile **11** (10 mmol) was added to a stirred solution of 2-cyano-*N*-(aryl)acetamide **14a-d** (10 mmol) in dry 1,4-dioxane (30 ml) containing potassium hydroxide (10 mmol) and the reaction mixture was refluxed for 1 hour. The reaction was then cooled and poured onto iced water; the resulting precipitate was filtered off and recrystallized from ethanol.

*2.2.4.1. 6-Amino-5-(benzo[d]thiazole-2-yl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carbonitrile **15a***

Yellow crystals; (DMF); Yield 81%; m.p 318-320 ^{o}C; IR (KBr, cm $^{-1}$): υ 3374 (NH_2), 2205 (CN), and 1665 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.37-7.49 (m, 4H, 3Ar-H & benzothiazole-H), 7.58-7.67 (m, 3H, 2Ar-H & benzothiazole-H), 7.84 (d, 1H, *J*=8 Hz, benzothiazole-H), 8.06 (d, 1H, *J*=8 Hz, benzothiazole-H), 8.38 (s, 1H, CH pyridone); ^{13}C NMR (100 MHz, DMSO-d_6): δ 83.7, 90.0 (Ar-C), 115.0 (CN), 119.0, 121.2, 122.0, 123.5, 125.0, 126.4, 128.8, 130.0, 133.6, 145.8, 152.4, 160.5 (Ar-C), 165.3 (C=O). Anal.Calcd.For. $C_{19}H_{12}N_4OS$ (344.39): C% 66.26; H% 3.51; N% 16.27. Found: C% 66.38; H% 3.58; N% 16.45.

*2.2.4.2. 6-Amino-5-(benzo[d]thiazole-2-yl)-1-(4-chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile **15b***

Yellow crystals; (DMF); Yield 83%; m.p 316-318 ^{o}C; IR (KBr, cm^{-1}): υ 3432 (NH_2), 2209 (CN), and 1644 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.38-7.51 (m, 4H, 2Ar-H, 2benzothiazole-H), 7.71 (d, 2H, *J*=8 Hz, Ar-H), 7.88 (d, 1H, *J*=8 Hz, benzothiazole-H), 8.08

(d, 1H, *J*=8 Hz, benzothiazole-H), 8.43 (s, 1H, CH)); ^{13}C NMR (100 MHz, DMSO-d_6): δ 86.0, 89.4 (Ar-C), 116.0 (CN), 119.5, 120.3, 121.3, 122.8, 123.9, 125.0, 128.0, 129.0, 131.2, 147.5, 153.7, 159.7 (Ar-C), 160.0 (C=O). Anal.Calcd.For. $C_{19}H_{11}ClN_4OS$ (378.83): C% 60.24; H% 2.93; N% 14.79. Found: C% 60.56; H% 2.88; N% 14.64.

2.2.4.3. 6-Amino-5-(benzo[d]thiazole-2-yl)-2-oxo-1-(p-tolyl)-1,2-dihydropyridine-3-carbonitrile ***15c***

Yellow crystals; (DMF); Yield 86%; m.p 256-258 ^{o}C; IR (KBr, cm $^{-1}$): υ 3445 (NH_2), 3060 (Ar C), 2213 (CN), and 1669 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.43 (s, 3H, CH_3), 7.30 (d, 2H, *J*=8 Hz, Ar-H), 7.37-7.50 (m, 4H, 2Ar-H & 2benzothiazole-H), 7.86 (d, 1H, *J*=8 Hz, benzothiazole-H), 8.07 (d, 1H, *J*=8 Hz, benzothiazole-H), 8.40 (s, 1H, CHpyridone); ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.7 (CH_3), 81.9, 97.0 (Ar-C), 113.0 (CN), 119.9, 120.4, 121.7, 122.5, 124.6, 125.9, 129.2, 130.6, 132.6, 144.9, 151.0, 158.3 (Ar-C), 159.9 (C=O). Anal.Calcd.For. $C_{20}H_{14}N_4OS$ (358.42): C% 67.02; H% 3.94; N% 15.63. Found: C% 67.35; H% 3.83; N% 15.90.

2.2.4.4. 6-Amino-5-(benzo[d]thiazole-2-yl)-1-(naphthalene-1-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile ***15d***

Yellow crystals; (DMF); Yield 82%; m.p 296-298 ^{o}C; IR (KBr, cm $^{-1}$): υ 3419 (NH_2), 2210 (CN), and 1664 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.42-7.50 (m, 2H, naphthalene-H & benzothiazole-H), 7.57-7.77 (m, 5H, 4naphthalene-H & benzothiazole-H), 7.85 (d, 1H, *J*=8 Hz, benzothiazole-H), 8.09-8.15 (m, 2H, naphthaalene), 8.20 (d, 1H, *J*=8 Hz, benzothiazole-H), 8.56 (s, 1H, CHpyridone); ^{13}C NMR (100 MHz, DMSO-d_6): δ 82.0, 90.1 (Ar-C), 114.5 (CN), 119.7, 120.5, 121.9, 122.8, 123.5, 124.9, 125.9, 128.5, 129.3, 130.6, 131.8, 133.0, 147.0, 150.4, 157.8 (Ar-C), 159.0 (C=O). Anal.Calcd.For. $C_{23}H_{14}N_4OS$ (394.45): C% 70.03; H% 3.58; N% 14.20. Found: C% 70.22; H% 3.28; N% 14.05.

2.2.5. General procedures for the synthesis of ***21a-d***

2-(Benzo[*d*]thiazole-2-yl)-3-(dimethylamino)acrylonitrile **11** (10 mmol) was added to a stirred solution of 2-cyano-*N*-(4-alkylbenzylidine)acetohydrazide derivatives **16a-d** (10 mmol) in dry 1,4-dioxane (30 ml) containing potassium hydroxide (10 mmol) and the reaction mixture was refluxed for 2 hours. The solid precipitate was filtered off and then recrystallized from ethanol.

2.2.5.1. 8-(Benzo[d]thiazole-2-yl)-2-(4-fluorophenyl)-5-oxo-3,5-dihydro[1,2,4]triazolo[1,5-a]pyridine-6-carbonitrile ***21a***

Brown crystals; (DMF); Yield 73%; m.p > 350 ^{o}C; IR (KBr, cm $^{-1}$): υ 3404 (NH), 2204 (CN), and 1610 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.32-7.49 (m, 4H, 2Ar-H, 2benzothiazole-H), 7.92 (d, 1H, *J* = 8 Hz, benzothiazole-H), 8.10 (d, 1H, *J* = 8 Hz, benzothiazole-H), 8.34 (d, 2H, *J* = 8 Hz, Ar-H), 8.48 (s, 1H, CHpyridone); ^{13}C NMR (100 MHz, DMSO-d_6): δ 93.1, 100.0 (Ar-C), 114.6 (CN), 120.2, 121.8, 122.9, 123.4, 124.5, 125.9, 129.5, 130.2, 134.4, 149.9, 154.4, 156.2, 160.1 (Ar-C), 164.0 (C=O). Anal.Calcd.For. $C_{20}H_{10}FN_5OS$ (387.39): C% 62.01; H% 2.60; N% 18.08. Found: C% 62.35; H% 2.68; N% 18.05.

2.2.5.2. 8-(Benzo[d]thiazole-2-yl)-2-(4-chlorophenyl)-5-oxo-3,5-dihydro[1,2,4]triazolo[1,5-a]pyridine-6-carbonitrile ***21b***

Brown crystals; (DMF); Yield 75%; m.p > 350 ^{o}C; IR (KBr, cm^{-1}): υ 3415 (NH), 2207 (CN), and 1612 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.33 (t, 1H, *J*=8 Hz, benzothiazole-H), 7.47 (t, 1H, *J*=8 Hz, benzothiazole-H), 7.65 (d, 2H, *J*=8 Hz, Ar-H), 7.91 (d, 1H, *J*=8 Hz, benzothiazole-H), 8.10 (d, 1H, *J*=8 Hz, benzothiazole-H), 8.30 (d, 2H, *J*=8 Hz, Ar-H), 8.47 (s, 1H, CHpyridone); ^{13}C NMR (100 MHz, DMSO-d_6): δ 91.0, 102.5 (Ar-C), 115.9 (CN), 119.5, 120.9, 122.6, 123.9, 124.8, 127.5, 130.9, 131.7, 134.7, 151.0, 155.2, 157.0, 159.0 (Ar-C), 162.2 (C=O). Anal.Calcd.For. $C_{20}H_{10}ClN_5OS$ (403.84): C% 59.48; H% 2.50; N% 17.34. Found: C% 59.11; H% 2.10; N% 17.07.

2.2.5.3. 8-(Benzo[d]thiazole-2-yl)-2-(4-methoxyphenyl)-5-oxo-3,5-dihydro[1,2,4]triazolo[1,5-a]pyridine-6-carbonitrile ***21c***

Brown crystals; (DMF); Yield 70%; m.p > 350 ^{o}C; IR (KBr, cm $^{-1}$): υ 3423 (NH), 2195 (CN), and 1606 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.77 (s, 3H, OCH_3), 7.33-7.39 (m, 3H, 2Ar-H, benzothiazole-H), 7.47 (t, 1H, *J*=8 Hz, benzothiazole-H), 7.91 (d, 1H, *J*=8 Hz, benzothiazole-H), 8.11 (d, 1H, *J*=8 Hz, benzothiazole-H), 8.24 (d, 2H, *J*=8 Hz, Ar-H), 8.46 (s, 1H, CHpyridone); ^{13}C NMR (100 MHz, DMSO-d_6): δ 52.1 (OCH_3), 95.2, 102.4 (Ar-C), 117.7 (CN), 119.6, 120.9, 122.8, 123.9, 125.8, 127.6, 128.8, 132.9, 137.0, 152.5, 156.9, 158.5, 159.9 (Ar-C), 161.8 (C=O). Anal.Calcd.For. $C_{21}H_{13}N_5O2S$ (399.43): C% 63.15; H% 3.28; N% 17.53. Found: C% 63.35; H% 3.15; N% 17.44.

2.2.5.4. 8-(Benzo[d]thiazole-2-yl)-5-oxo-2-(p-tolyl)-3,5-dihydro-[1,2,4]triazolo[1,5-a] pyridine-6-carbonitrile ***21d***

Brown crystals; (DMF); Yield 72%; m.p > 350 ^{o}C; IR (KBr, cm^{-1}): υ 3374 (NH), 3121 (Ar C), 2205 (CN), and 1665 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.40 (s, 3H, CH_3), 7.33-7.39 (m, 3H, 2Ar-H, benzothiazole-H), 7.47 (t, 1H, *J*=8 Hz, benzothiazole-H), 7.92 (d, 1H, *J*=8 Hz, benzothiazole-H), 8.11 (d, 1H, *J*=8 Hz, benzothiazole-H), 8.20 (d, 2H, *J*=8 Hz, Ar-H), 8.47 (s, 1H, CHpyridone); ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.5 (CH_3), 97.2, 108.9 (Ar-C), 115.0 (CN), 119.0, 120.3, 122.0, 124.6, 125.3, 128.0, 129.4, 131.2, 135.4, 151.8, 155.4, 157.2, 158.5 (Ar-C), 160.7 (C=O). Anal.Calcd.For. $C_{21}H_{13}N_5OS$ (383.43): C% 65.78; H% 3.42; N% 18.27. Found: C% 65.94; H% 3.68; N% 18.20.

2.3. Biological evaluation

2.3.1. In vitro antibacterial and antifungal screening

Antimicrobial tests were carried out at the Microbiology Unit in Biochemistry Central Lab, Faculty of Science, Cairo University, Cairo, Egypt. At the honest, Agar-diffusion method was used for the determination of the preliminary antibacterial and antifungal activities of the synthesized compounds [36]. For the purpose of comparison against standard drugs, gentamicin, ampicillin and nystatin were also used. All the compounds and standard drugs were tested in vitro against *staphylococcus aureus* and *Streptococcus mutans* (Gram positive bacteria), *Escherichia coli*, *Pseudomonas aeruginosa* and *klebsiella pneumonia* (Gram negative bacteria) and *Candida albicans* fungal strains using nutrient agar medium. The results were all recorded for each tested compound as the average diameter of the inhibition zones of the microbial growth around the disks in mm ± SD, as summarized in Table 2. DMSO was used as solvent control. The compounds were tested at a concentration of 15 mg/ml against both bacterial and fungal strains.

2.3.2. Method of testing

The sterilized media was poured onto the sterilized Petri dishes (20-25 ml, each petri dish) and allowed to solidify at room temperature. Microbial suspension was prepared in sterilized saline equivalent to McFarland 0.5 standard solution (1.5x 10 5 CFU mL^{-1}) and its turbidity was adjusted to OD = 0.13 using spectrophotometer at 625 nm. Optimally, within 15 minutes after adjusting the turbidity of the inoculum suspension, a sterile cotton swab was dipped into

the adjusted suspension and was flooded on the dried agar surface then allowed to dry for 15 minutes with lid in place. Wells of 6 mm diameter was made in the solidified media with the help of sterile borer. 100 µL of the solution of the tested compound was added to each well with the help of micropipette. The plates were incubated at 37^{o}C for 24 hrs in case of antibacterial activity. This experiment was carried out in triplicate and zones of inhibition were measured in mm. scale.

2.4. Antiviral Evaluation

2.4.1. Cytotoxicity test

It was done according to literature [37,38]. Briefly, all samples (50 mg) were dissolved in 1 mL of DMSO. Decontamination of samples was done by adding 24_µL of 100× of antibiotic–antimycotic mixture to 1 mL of each sample. Then, bi-fold dilutions were done to 100_µL of original dissolved samples and 100 _µL of each dilutions were inoculated in Hep-2, Vero, BGM, FRHK4, and Huh 7.5 cell lines (obtained from the Holding Company for Biological Products & Vaccines VACSERA, Egypt) previously cultured in 96 multi well plates (Greiner-Bio one, Germany) to estimate the non-toxic dose of the tested samples. Cytotoxicity assay was done using cell morphology evaluation by inverted light microscope and cell viability test applying trypan blue dye exclusion method.

2.4.2. Cell morphology evaluation by inverted light microscopy

Hep-2, Vero, BGM, FRHK4, and Huh 7.5 cell cultures (2×10^5 cells/mL) were prepared separately in 96-well tissue culture plates (Greiner-Bio one, Germany). After 24 h incubation at 37 ^{o}C in a humidified 5% (v/v) CO_2 atmosphere cell monolayers were confluent, the medium was removed from each well and replenished with 100_µL of bi-fold dilutions of different samples tested prepared in DMEM (GIBCO BRL). For cell controls 100_µL of DMEM without samples was added. All cultures were incubated at 37 ^{o}C in a humidified 5% (v/v) CO_2 atmosphere for 72 h. Cell morphology was observed daily for microscopically detectable morphological alterations, such as loss of confluence, cell rounding and shrinking, and cytoplasm granulation and vacuolization. Morphological changes were scored [37].

2.4.3. Cell viability assay

It was done by trypan blue dye exclusion method [38]. Hep-2, Vero, BGM, FRHK4, and Huh 7.5 cell cultures (2×10^5 cells/mL) were grown in 12-well tissue culture plates (Greiner-Bio one, Germany). After 24 h incubation, the same assay described above for tested samples cytotoxicity was followed by applying 100_µL of tested samples dilutions (bifold dilutions) per well. After 72 h the medium was removed, cells were trypsinized and an equal volume of 0.4% (w/v). Trypan blue dye aqueous solution was added to cell suspension. Viable cells were counted under the phase contrast microscope.

2.4.4. Determination of adenovirus 7, HAV HM175, Coxsackievirus B4, and Herpes simplex virus type 1 Titers using plaque assay

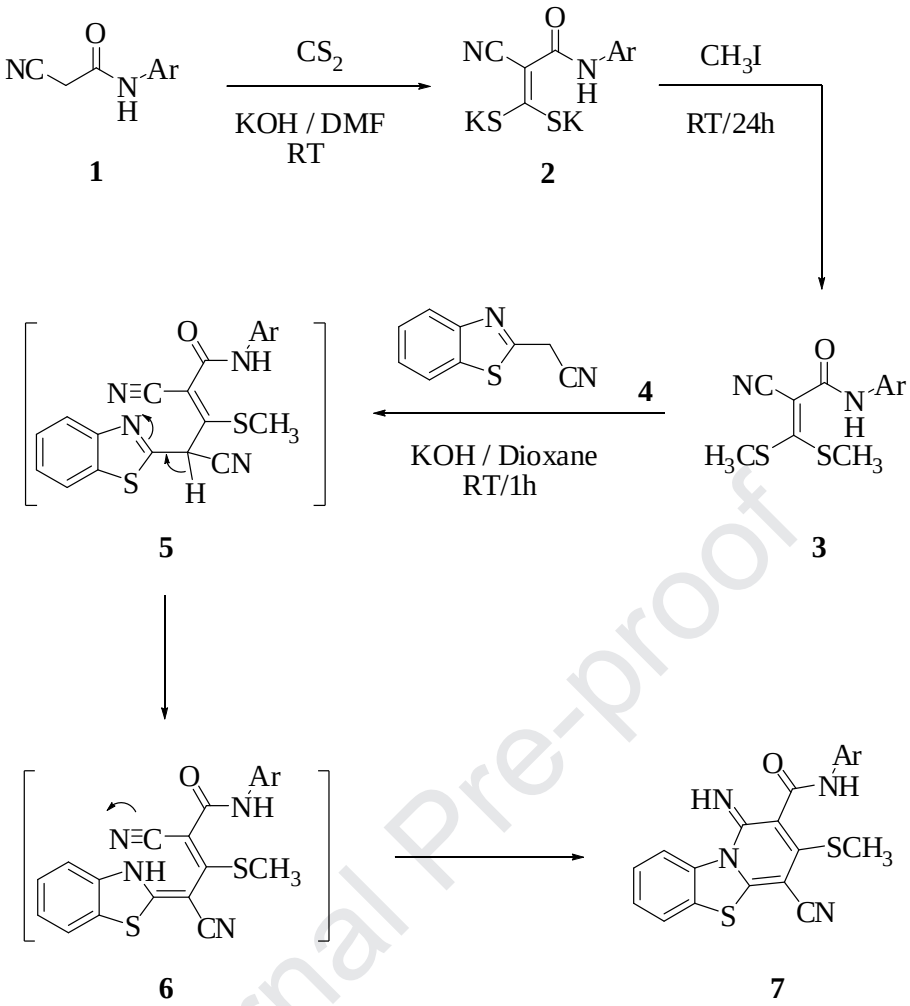
Non-toxic dilutions were mixed (100µl) with 100µl of different doses of Herpes simplex virus type 1, adenovirus 7, HAV HM175 and Coxsackievirus B4 ($1X10^5$, $1X10^6$, $1X10^7$). The mixture was incubated for 1/2 hr in 37 °C. The inoculation of (100µl) 10 fold dilutions of treated and untreated adenovirus 7, HAV HM175, Coxsackievirus B4 and Herpes simplex virus type 1 was carried out separately into Hep-2, FRHK4, BGM, and Vero cell lines respectively in 12 multi well- plates. After 1 hr of incubation for adsorption at 37 °C in a 5% CO_2-water vapor atmosphere without constant rocking. The plates were rocked intermittently to keep the cells from drying. After adsorption, 1 mL of 2X media (Dulbecco´s Modified Eagle Medium, Gibco-BRL (DMEM) plus 1ml 1% agarose was added to each well, the plates were incubated at 37 °C in a 5% CO_2-water vapor atmosphere. After the appropriate incubation period, the cells were stained with 0.4% crystal violet after formaline fixation, and the number of plaques counted. The viral titers were then calculated, and expressed as plaque-forming units per milliliter (pfu/mL) [39].

2.4.5. Antiviral bioassay of tested materials against ED-43/SG-Feo (VYG) replicon of Hepatitis C virus genotype 4a:

ED-43/SG-Feo (VYG) replicon of HCV genotype 4a was treated with the non-toxic dose of the tested compounds. HCV RNA was quantified in algal extracts treated Huh 7.5 infected cells using qRT-PCR (Taqman probe kit, Qiagen) and according to the manufacturer's instructions to show a dose-dependent decrease in sub genomic RNA copies according to the literature [40].

3. Results and Discussion

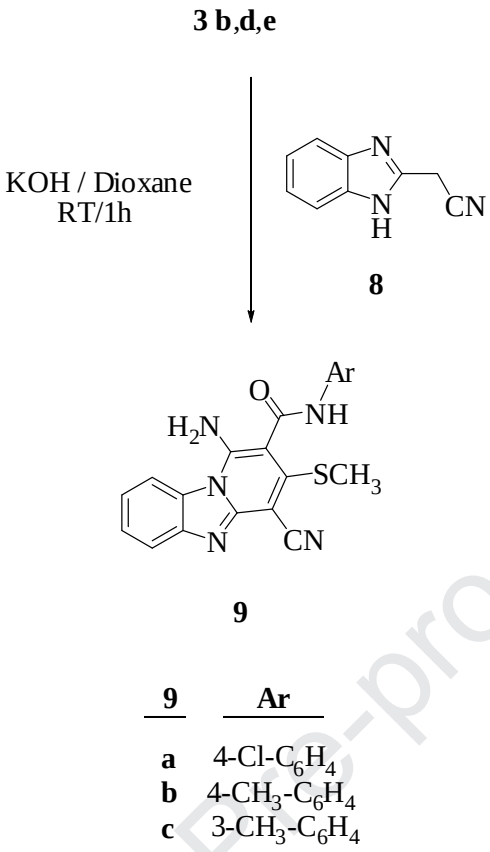
Initially, compound *N*-aryl-2-cyano-3,3-bis(methylthio)acrylamide **3a-f** was synthesized using the procedure reported in the literature [41]. The synthesized compounds **3a-f** were reacted with benzothiazoleylacetonitrile **4** in the presence of potassium hydroxide in 1,4-dioxane at room temperature for one hour to afford the 4-cyano-1-imino-3-(methylthio)-*N*-aryl-1-*H*-pyrido[1,2-*a*]benzothiazole-2-carboxamide **7a-f,** Scheme 1. The structures of these derivatives were established on the basis of elemental analysis and spectral data (IR), ^{1}H NMR and ^{13}C NMR. For instance, the IR spectra of compound **7b** showed characteristic bands at 3439 and 3260 cm^{-1} for NH groups, a band at 2201 cm^{-1} associated with the cyano group, and a peak at 1644 cm^{-1} for the carbonyl group. The ^{1}H NMR spectrum of **7b** revealed a singlet peak at δ 2.54 ppm for the protons of SCH_3 group, and two broad peaks at δ 8.27 and 10.79 ppm for two protons of two NH groups. The ^{13}C NMR showed a signal at δ 12.7 ppm for the SCH_3 carbon and a signal at δ 118.9 ppm for the CN carbon. Moreover, signals appeared at δ 158.1 ppm were attributed to the carbonyl group. The corresponding data of these compounds confirmed the fused structures of compounds **7a-f**. The reaction is assumed to proceed via Micheal addition of the active methylene group of compound **4** to the double bond of compound **3** followed by the elimination of CH_3SH to form the intermediate acyclic adduct **5.** Tautomerism occurred through proton transfer in an intramolecular fashion from the methylene group to the nitrogen atom of the benzothiazole ring to produce intermediate **6**. The later cyclized by the addition of NH proton to the cyano group to yield the novel pyrido[1,2-*a*]benzothiazole derivatives **7a-f**.



7	Ar	7	Ar
a	C_6H_5	**d**	4-CH_3-C_6H_4
b	4-Cl-C_6H_4	**e**	3-CH_3-C_6H_4
c	3-Cl-C_6H_4	**f**	2-CH_3-C_6H_4

Scheme 1. Synthesis of 4-cyano-1-imino-3-methylsulfanyl-benzo[4,5]thiazo[1,2-*a*]pyridine--2-carboxylic acid arylamides **7a-f**

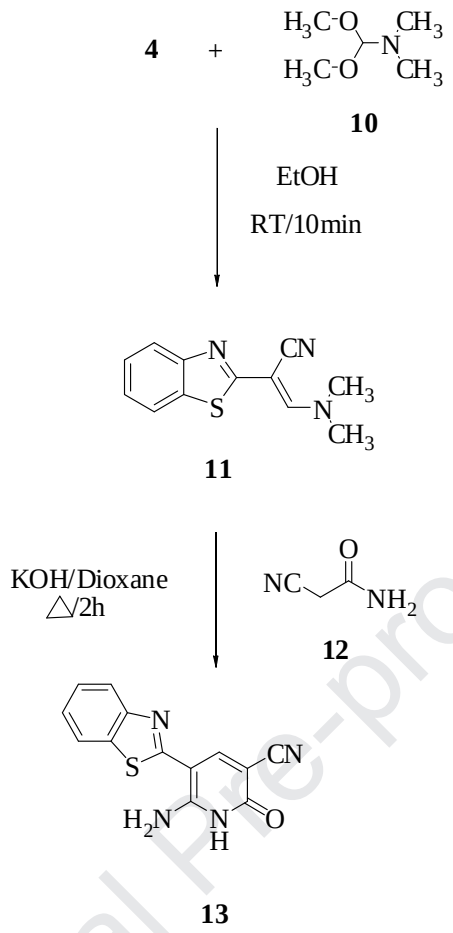
The course of the reaction between *N*-aryl-2-cyano-3,3-bis(methylthio)acrylamide derivatives **3** and benzothiazole-2-yl-acetonitrile **4** prompted us to investigate similar reaction between compound **3** and 2-benzoimidazole-2-yl-acetonitrile **8** under similar conditions. The products obtained were shown to form via the same mechanism to afford the methylthiobenzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxamide **9a-c,** Scheme 2. The structure of the synthesized fused pyridine derivatives were also confirmed by elemental analysis and spectral data.



9	Ar
a	4-Cl-C_6H_4
b	4-CH_3-C_6H_4
c	3-CH_3-C_6H_4

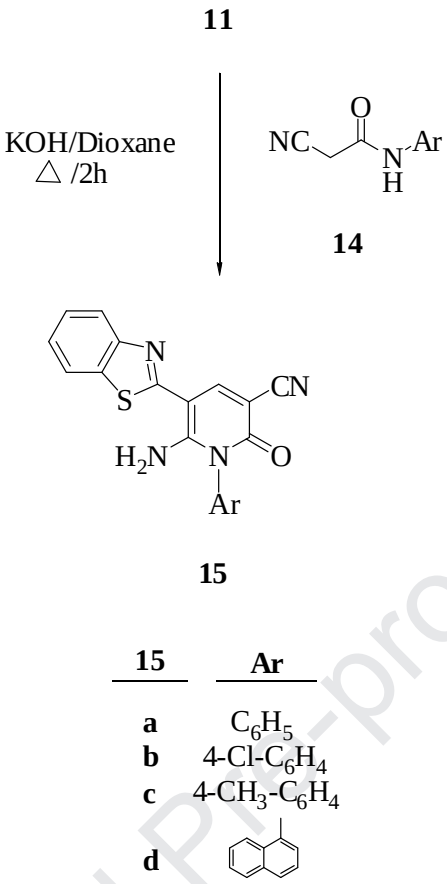
Scheme 2. Synthesis of 1-amino-4-cyano-3-methylsulfanyl-benzo[4,5]imidazo[1,2-*a*]pyridine-2-carboxylic acid arylamides **9a-c**

Furthermore, reaction of benzothiazole-2-yl-acetonitrile **4** with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) **10** in ethyl alcohol at room temperature for 10 minutes afforded the 2-(benzo[*d*]thiazol-2-yl)-3-(dimethylamino)acrylonitrile **11** in high yield [42]. The latter was further reacted with cyanoacetamide **12** in presence of potassium hydroxide in 1,4-dioxane under reflux conditions to afford substituted 2-pyridylbenzothiazole **13,** Scheme 3. The reaction proceeded via Micheal addition followed by the elimination of $NH(CH_3)_2$ and intermolecular cyclization through the addition of NH_2 proton to the cyano group as to produce the substituted 2-pyridylbenzothiazole **13**. According to IR spectra of compound **13**, the bands of NH_2 and NH groups were observed at 3451 and 3202 cm^{-1}, respectively, while the bands of CN and carbonyl group observed at 2285 and 1659 cm^{-1}, respectively.



Scheme 3. Synthesis of 6-amino-5-(benzo[*d*]thiazol-2-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile **13**

In order to further investigate the scope of this reaction and to establish whether the reaction of 2-(benzo[*d*]thiazol-2-yl)-3-(dimethylamino)acrylonitrile **11** with aryl cyanoacetamides could be extended to provide a general approach for the synthesis of *N*-substituted 2-pyridylbenzothiazole, the reaction of compound **11** with other functionalized cyanoacetamides was investigated. The reaction of compound **11** with *N*-aryl-2-cyanoacetamides **14a-d** and potassium hydroxide in 1,4-dioxane under reflux afforded *N*-substituted 2-pyridylbenzothiazole **15a-d**, Scheme 4.



15	Ar
a	C_6H_5
b	4-Cl-C_6H_4
c	4-CH_3-C_6H_4
d	

Scheme 4. Synthesis of 6-amino-1-aryl-5-(benzo[*d*]thiazole-2-yl)-2-oxo-1,2-dihydropyridines **15a-d**

The structures of the newly synthesized compounds **15a-d** were also established on the basis of their elemental analysis and spectral data. For example, ^{1}H NMR spectrum of compound **15c** showed a singlet signal at δ 2.43 ppm for the protons of the CH_3 group, doublet at δ 7.30 ppm for the two protons of 4-tolyl group, two doublets at δ 7.86 and 8.07 ppm for two protons of benzothiazole ring and singlet peak at δ 8.40 ppm for the CH proton. In order to establish the chemical structure of these derivatives, X-ray crystallographic studies of compound **15c** was performed. X-ray analysis confirmed the exclusive presence of **15c** in the solid state, Fig. 1.

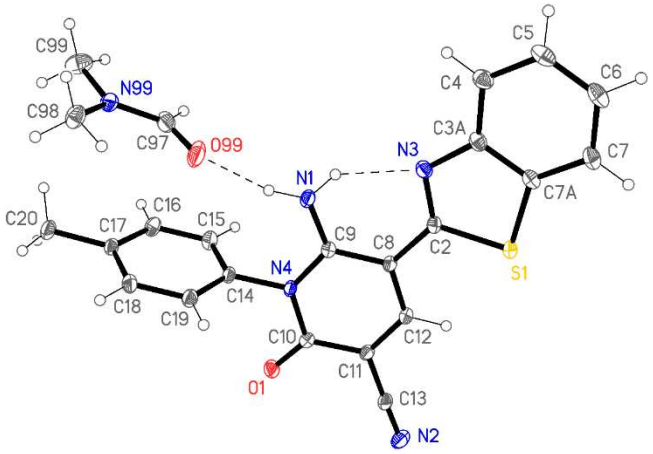
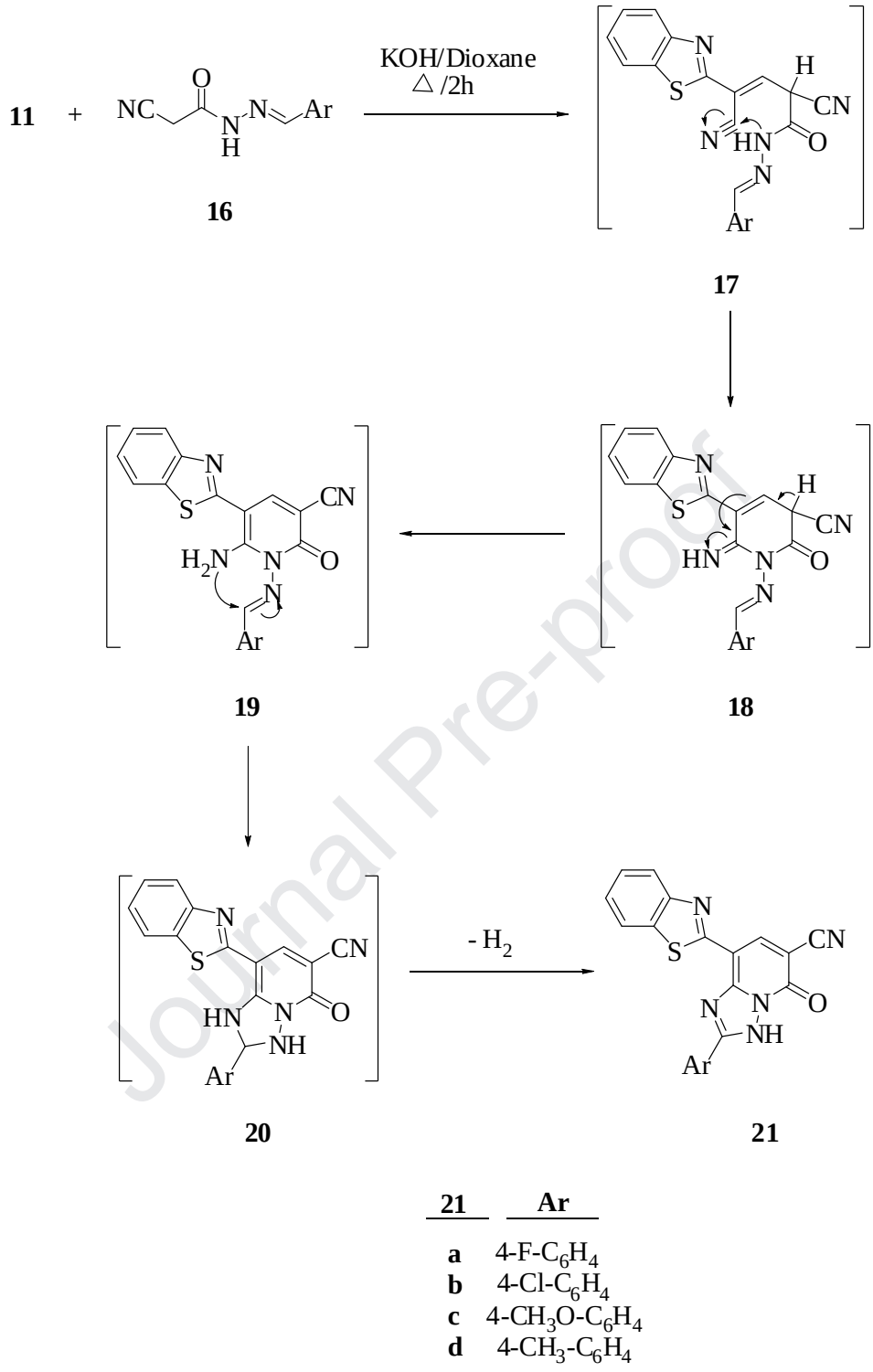


Fig. 1 Molecular structure of compound **15c**

Moreover, compound **11** was allowed to react with 2-cyano-*N*′-(4-substituted benzylidene)acetohydrazide **16a-d** to afford 2-aryl-8-(benzo[*d*]thiazole-2-yl)-5-oxo-3,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridine-6-carbonitrile **21a-d**, Scheme 5. The most probable reaction pathway involved the addition of the active methylene group of the 2-cyano-*N*′-(4-substituted benzylidene)acetohydrazide **16a-d** to the double bond of compound **11** to form intermediate Michael adducts with the subsequent elimination of the $HN(CH_3)_2$ group to yield the intermediate **17a-d**. Intramolecular cyclization through the addition of the NH group to the cyano group forming the intermediate **18a-d** followed by additional intramolecular cyclization involving the bonding of the amino group to the ylidene carbon, which is followed by the hydrolysis and the removal of H_2 molecule to finally yield the novel 2-aryl-8-(benzo[*d*]thiazole-2-yl)-5-oxo-3,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridine-6-carbonitrile **21a-d**. Elemental analysis and spectral data of compounds **21a-d** were consistent with its proposed structure. For example, IR spectra of compound **21d** showed bands for stretching vibrations of NH group at 3374 cm^{-1}, CN group at 2205 cm^{-1}, and carbonyl group at 1665 cm^{-1}. The ^1H NMR spectrum of compound **21d** showed a singlet signal at δ 2.40 ppm, which indicated the presence of CH_3 protons, a multiplet at δ 7.33-7.39 ppm assigned for the aromatic protons and a singlet peak at δ 8.47 ppm of the CH proton.



21	Ar
a	4-F-C_6H_4
b	4-Cl-C_6H_4
c	4-CH_3O-C_6H_4
d	4-CH_3-C_6H_4

Scheme 5. Synthesis of 2-aryl-8-(benzo[*d*]thiazole-2-yl)-5-oxo-3,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridines **21a-d**

Interestingly, some of the synthesized compounds showed fluorescence properties which prompted us to study its photophysical properties. The photophysical properties of **7b**, **7d-f**, **9b**, **13**, **15a-d** are summarized in Fig. 2-4 and Table 1. Fig. 2 shows the absorption

spectra of the examined compounds **7b**, **7d-f**, **9b**, **13**, **15a-d** in ethanol. It can be clearly observed that the absorption spectrum of **15c** exhibited strong absorption band at 379 nm with other two weak absorption bands at 326 and 480 nm. It is most likely that the absorption bands at 326 and 379 nm arise from π–π^* transition, while the absorption band at the longer wavelength of 480 nm arise from the n- π^* transition.

Similar observations were recorded for the other derivatives **15a-d**. The absorption maxima were listed in Table 1. Upon excitation, the samples with 370 nm absorbance, the fluorescence spectra of the examined compounds in ethanol showed strong emission bands in the range of 418-425 nm as shown in Fig. 3 and Table 1. From the listed values, it is clearly seen that the fluorescence maxima are slightly change (1-5 nm) with changing the substituents of **15a-d** suggesting minor effect of the substituents in the fluorescence behavior.

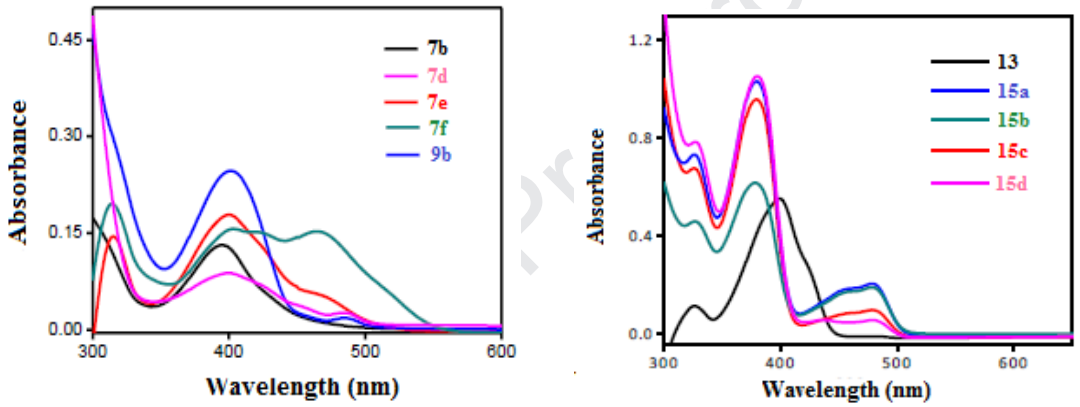


Fig. 2 UV-vis absorption spectra of **7b**, **7d-f**, **9b**, **13**, **15a-d** in ethanol

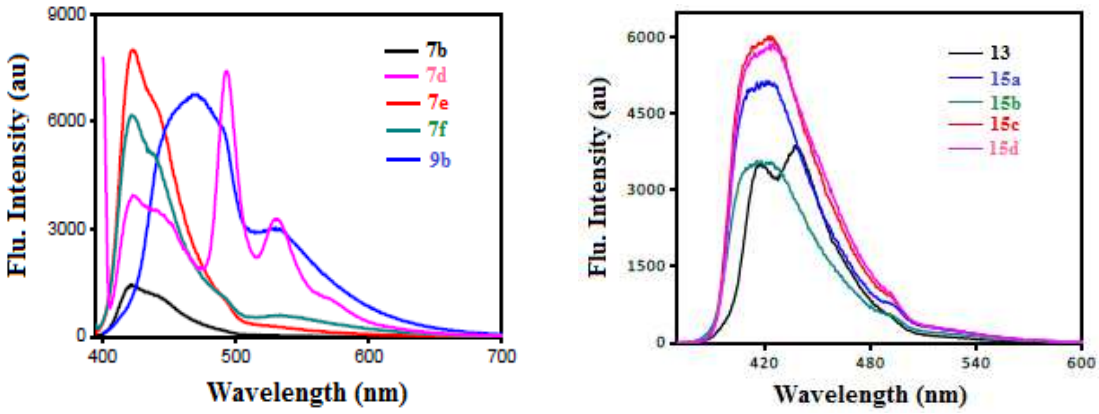


Fig. 3. Fluorescence spectra of **7b**, **7d-f**, **9b**, **13**, **15a-d** in ethanol; λ_{ex} = 370 nm

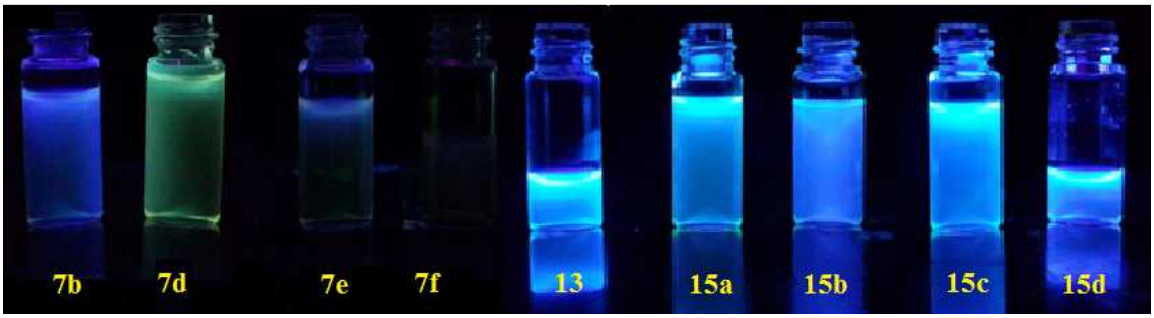


Fig. 4. Fluorescent images of **7b**, **7d-f**, **9b**, **13**, **15a-d** in ethanol when excited with 370 nm light

To check the ability of the examined compounds to be utilized as fluorescent materials in laser devices and optoelectronic applications, the fluorescence quantum yields were determined. In general, the quantum yield of photo-excited fluorescence (F_F) is defined as the ratio of the number of photons emitted and the number of photons absorbed. The fluorescence quantum yields of the examined compounds in ethanol were calculated by the steady-state comparative method using Coumarin 460 as a standard (Φ_{st} = 0.73, ethanol) [22] according to the following equation:

$$\Phi_F = \Phi_{st} \frac{S_x}{S_{st}} * \frac{A_{st}}{A_x} * \frac{n^2_x}{n^2_{st}} \qquad (1)$$

Where Φ_F is the emission quantum yield of the samples, Φ_{st} is the emission quantum yield of the standard, A_{st} and A_x represent the absorbance of the standard and sample at the excitation wavelength, respectively, while S_{st} and S_x are the integrated emission band areas of the standard and sample, respectively, and n_{st} and n_x the solvent refractive index of the standard and sample, x and st refer to the unknown and standard, respectively. This method relies on the fact that the unknowns of equation (1) should be quantitatively the same for different fluorescent solutions as compared under identical conditions of excitation i.e. at the same excitation wavelength with the same aperture settings (slit widths). By comparing the intensity of fluorescence from a sample with that from a material whose QY is known, it is straightforward to estimate Q_F.

Table 1: Fluorescent properties of synthesized compounds **7b**, **7d-f**, **9b**, **13**, **15a-d**

Compd. No.	λ_{max}^{abs}	λ_{max}^{flu}	Φ_f
7b	395	421	**0.10**
7d	399, 484	422, 492, 531	**0.02**
7e	315, 400, 468	423	**0.03**

7f	314, 403, 464	422, 490, 534	**0.01**
9b	402, 488	470, 530	**0.01**
13	326, 399	418, 438	**0.29**
15a	326, 378, 480	421	**0.28**
15b	327, 378, 481	419	**0.24**
15c	326, 379, 480	421	**0.29**
15d	328, 381, 482	425	**0.26**

Fluorescence quantum yields of **13** and **15a-d** were determined to be 0.29, 0.28, 0.24, 0.29 and 0.26, respectively. The considerably smaller value of **15b** compared to other samples (**15a,c,d**) may rationalized by the presence of the electron withdrawing chlorine atom. In general, the determined fluorescence quantum yields values are in an excellent agreement with the fluorescent images obtained by irradiation at 360 nm, Fig. 4. Accordingly, it is clear that the newly synthesized *N*-substituted 2-pyridylbenzothiazole compounds **13** and **15a-d** showed remarkably higher quantum yield values than those of pyrido[2,1-*b*]benzothiazole **7b**, **7d-f** and pyrido[2,1-*b*]benzoimidazole compounds **9b**. Such relatively high fluorescence quantum yields of *N*-substituted 2-pyridylbenzothiazoles suggest the usefulness of these compounds as fluorescent probes in different optoelectronic applications.

The antimicrobial activities of the newly synthesized compounds were evaluated *in-vitro* against different bacterial strains such as *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus mutans* as well as against *Candida albicans* fungal strain. The synthesized compounds of benzothiazole-substituted pyridines such as **7a**, **7f**, **9a**, **9b**, **13**, **15a**, **15d**, **21a**, **21b**, and **21d** showed some activities against tested bacterial and fungal strains while other compounds such as **7b**, **7d**, **7e**, **15b** and **15c** showed no reactivity toward all tested bacteria, Table 2. Interestingly, compound **21a** was found to be the most potent among all synthesized compounds towards Klebsiella pneumonia strain (Inhibition Zone 24.3±0.6 mm) with comparable performance to that of gentamicin, Table 2. It also showed moderate activities towards Staphylococcus aureus (Inhibition Zone 20.3±0.6 mm) and Streptococcus mutans (Inhibition Zone 20.3±0.5 mm) as compared to ampicillin. Alternatively, compound **9b** was the most potent among all synthesized compounds toward *Streptococcus mutans* (Inhibition Zone 21.3±1.5 mm). It was found that other compounds such as **9a**, **13**, **15a**, and **21d** have exhibited relatively low activities toward *Staphylococcus aureus* when compared to ampicillin. In addition, some of

synthesized compounds such as **9a**, **9b**, **15a**, and **21d** showed activity against *Candida albicans* as compared to Nystatin.

The structure-activity relationship (SAR) evaluated for the synthesized compounds revealed that substituted benzene ring with methyl group at the ortho position **7f** had some activities toward *Escherichia coli*, *Klebsiellla pneumonia* and *Streptococcus mutans* while derivatives with methyl group at the para and meta positions such as compounds **7d** and **7e**, respectively, showed no activity toward all tested bacterial and fungi strains. Surprisingly, substituted benzene ring with electron withdrawing group such as chlorine atom at the para and meta positions, compound **7b** and **7c**, respectively, exhibited no activity toward all tested bacterial and fungi strains. Moreover, replacing the benzothiazole moiety with a benzoimidazole one in the presence of the methyl group at the para position of the benzene ring, compound **9b**, led to increasing the potency against *Escherichia coli*, *Klebsiellla pneumonia*, *Streptococcus mutans* and *Candida albicans* strains. Interestingly, the presence of the chlorine atom at the para position of the benzene ring such as compound **9a** showed an activity toward *Staphylococcus aureus* and *Candida albicans* strains only. Compound **13**, which contains the *N*-unsubstituted 2-pyridylbenzothiazole ring was shown to be more potent than *N*-substituted 2-pyridylbenzothiazole derivatives **15a-d** against *Pseudomonas aeruginosa* and *Staphylococcus aureus* strains. Only compound **15a** with a phenyl group at the *N*-position of 2-pyridylbenzothiazole showed some activity toward fungi strain, *Candida albicans*, while compound **15d** with naphthyl group at the *N*-position of 2-pyridylbenzothiazole showed some activity toward *Klebsiellla pneumonia* stain as compared with other *N*-substituted 2-pyridylbenzothiazole derivatives **15a-c**. Triazolo-pyridone derivative with fluorine atom at the para position of the benzene ring, compound **21a,** was more potent than other derivatives containing - in place of the fluorine atom - a chlorine atom or a methyl group, compounds **21b** and **21d**, respectively. Interestingly, the presence of the methyl group as an electrondonating group at the para position of the benzene ring, compound **21d**, rendered the compound more potent than similar derivatives with a chlorine atom (an electron withdrawing group) at the same position, compound **21b**, against *Klebsiellla pneumonia, Staphylococcus aureus* and *Candida albicans.*

Table 2: Antibacterial inhibition zone in mm ± standard deviation of synthesized compounds

Compd No.	Diameter of the inhibition zone (mm)		
	Gram (-ve) bacteria	Gram (+ve) bacteria	Fungi

	Escherichia coli *(ATCC:3008)*	Klebsiella pneumonia *(ATCC:4415)*	Pseudomonas aeruginosa *(ATCC:27853)*	Staphylococcus aureus *(ATCC:6538)*	Streptococcus mutans *(ATCC:25175)*	Candida albicans *(ATCC:10231)*
7a	NA[a]	10.7±1.1	NA	NA	NA	NA
7b	NA	NA	NA	NA	NA	NA
7d	NA	NA	NA	NA	NA	NA
7e	NA	NA	NA	NA	NA	NA
7f	13.0±0.0	14.7±0.6	NA	NA	14.3±0.6	NA
9a	NA	NA	NA	11.7±0.5	NA	12.7±0.5
9b	12.7±0.5	14.7±0.5	NA	NA	21.3±1.5	12.7±2.0
13	NA	NA	11.3±0.5	13.3±0.5	NA	NA
15a	NA	NA	NA	10.7±0.5	NA	11.7±0.6
15b	NA	NA	NA	NA	NA	NA
15c	NA	NA	NA	NA	NA	NA
15d	NA	16.0±1.1	NA	NA	NA	NA
21a	16.7±1.0	24.3±0.6	NA	20.3±0.6	20.3±0.5	NA
21b	NA	15.3±0.6	NA	NA	13.0±1.0	NA
21d	NA	17.3±1.5	NA	14.7±0.6	13.7±1.2	11.7±0.5
Gentamicn	35.0±0.5	35.0±0.5	30.0±0.5	-	-	-
Ampicillin	-	-	-	30.0±1.0	35.0±0.5	-
Nystatin	-	-	-	-	-	20.0±0.5

[a] NA = No activity

The antiviral activities of the newly synthesized benzothiazole-substituted pyridines derivatives were evaluated *in-vitro* against Herpes simplex virus type 1, Coxsackievirus B4, Hepatitis A virus HM 175, ED-43/SG-Feo (VYG) replicon of Hepatitis C virus genotype 4a and Adenovirus type 7. In order to determine the appropriate doses for the antiviral studies, the newly synthesized compounds were subjected to a cytotoxicity evaluation using cell line FRHK-4, Hep2, BGM, Vero and Huh 7.5 as the specific hosts to the various studied viruses. The non-toxic doses of the synthesized compounds showed no significant differences, which ranged between 70 and 120 µg/ml, Table 3. Even though the non-toxic doses reached 120 µg/ml, the synthesized compounds showed low level of activity against studied viruses with reduction percent less than 50%, Table 4.

Table 3. Non-toxic doses of synthesized compounds on FRHK-4, Hep2, BGM, Vero, and Huh 7.5 cell lines.

Compd No.	Nontoxic dose on **FRHK-4** cell line (µg/mL)	Nontoxic dose on **Hep2** cell line (µg/mL)	Nontoxic dose on **BGM** cell line (µg/mL)	Nontoxic dose on **Vero** cell line (µg/mL)	Nontoxic dose on **Huh 7.5** cell line (µg/mL)

7a	100	100	100	100	100
7b	90	90	90	90	90
7d	100	100	100	100	100
7e	90	90	90	90	90
7f	100	100	100	100	100
9a	90	90	90	90	90
9b	70	70	70	70	70
9c	80	80	80	90	80
13	90	90	90	90	90
15a	90	90	90	90	90
15b	120	120	110	120	120
15c	100	100	100	100	100
15d	100	100	90	100	90
21a	80	80	80	80	80
21b	90	90	90	90	90
21c	90	90	90	90	90
21d	110	110	110	110	110

Table 4. Antiviral activity of non-toxic doses of synthesized compounds against Herpes Simplex Virus, Coxsackievirus B4, Hepatitis A virus HM 175, HCVcc genotype 4 & Adenovirus type 7.

Compd No.	**Mean % of Reduction**				
	Herpes Simplex Virus	**Coxsackievirus B4**	**Hepatitis A virus HM 175**	**HCVcc genotype 4**	**Adenovirus type 7**
7a	10	10	10	10	10
7b	10	10	10	10	10
7d	20	20	16.7	13.3	10
7e	10	20	10	10	10
7f	20	20	13.3	10	10
9a	10	10	10	10	10
9b	10	10	10	10	10
9c	10	13.3	10	10	10
13	10	10	10	10	10
15a	10	10	10	10	10
15b	10	10	10	10	10
15c	10	10	10	10	10
15d	10	10	10	10	10
21a	10	16.7	10	10	10
21b	10	10	10	10	10
21c	10	10	10	10	10
21d	10	10	10	10	10

4. Conclusion:

In conclusion, eighteen novel compounds of pyrido[2,1-*b*]benzothiazole and *N*-substituted 2-pyridylbenzothiazole derivatives were synthesized. Pyrido[2,1-*b*]benzothiazole derivatives were synthesized via the reaction of *N*-aryl-2-cyano-3,3-bis(methylthio)acrylamide and benzothiazoleylacetonitrile while *N*-substituted 2-pyridylbenzothiazole derivatives were synthesized by reacting 2-(benzo[*d*]thiazol-2-yl)-3-(dimethylamino)acrylonitrile with cyanoacetamide, aryl cyanoacetamides or 2-cyano-*N*′-(4-substituted benzylidene)acetohydrazide. The structures of all the compounds were confirmed by ^{1}H NMR, ^{13}C NMR, IR and elemental analyses. The newly synthesized *N*-substituted 2-pyridylbenzothiazole derivatives exhibited remarkable fluorescence properties. The strong absorption bands at 326 and 379 nm most probably arise from the π–π^{*} transition, while the absorption band at the longer wavelength of 480 nm arise from the n-π^{*} transition. Upon excitation, samples with 370 nm absorbance showed strong fluorescence emission bands in the range of 418-425 nm. It can be readily concluded that the fluorescence maxima may slightly change in response to changing the aryl groups of the compounds suggesting a minor effect of the substituents on the fluorescence behavior. Fluorescence quantum yields of these compounds were also evaluated and determined to be in the range of 0.25-0.29.

In addition, the antimicrobial activities against *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus mutans* and *Candida albicans* strains have been also tested and some of examined compounds showing some activities against the tested bacterial and fungal strains. The newly synthesized compounds were also evaluated for their antiviral activity against HSV-1, COB4, HAV HM 175, ED-43/SG-Feo (VYG) replicon of HCV genotype 4a and HAdV7 and showed low level of activity against examined viruses with viral reduction percent of less than 50%.

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Table 1: Fluorescent properties of synthesized compounds **7b**, **7d-f**, **9b**, **13**, **15a-d**

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15a	326, 378, 480	421	**0.28**
15b	327, 378, 481	419	**0.24**
15c	326, 379, 480	421	**0.29**
15d	328, 381, 482	425	**0.26**

Table 2: Antibacterial inhibition zone in mm ± standard deviation of synthesized compounds

Compd No.	Diameter of the inhibition zone (mm)					
	Gram (-ve) bacteria			Gram (+ve) bacteria		Fungi
	Escherichia coli *(ATCC:3008)*	Klebsiella pneumonia *(ATCC:4415)*	Pseudomonas aeruginosa *(ATCC:27853)*	Staphylococcus aureus *(ATCC:6538)*	Streptococcus mutans *(ATCC:25175)*	Candida albicans *(ATCC:10231)*
7a	NA[a]	10.7±1.1	NA	NA	NA	NA
7b	NA	NA	NA	NA	NA	NA
7d	NA	NA	NA	NA	NA	NA
7e	NA	NA	NA	NA	NA	NA
7f	13.0±0.0	14.7±0.6	NA	NA	14.3±0.6	NA
9a	NA	NA	NA	11.7±0.5	NA	12.7±0.5
9b	12.7±0.5	14.7±0.5	NA	NA	21.3±1.5	12.7±2.0
13	NA	NA	11.3±0.5	13.3±0.5	NA	NA
15a	NA	NA	NA	10.7±0.5	NA	11.7±0.6
15b	NA	NA	NA	NA	NA	NA
15c	NA	NA	NA	NA	NA	NA
15d	NA	16.0±1.1	NA	NA	NA	NA
21a	16.7±1.0	24.3±0.6	NA	20.3±0.6	20.3±0.5	NA
21b	NA	15.3±0.6	NA	NA	13.0±1.0	NA
21d	NA	17.3±1.5	NA	14.7±0.6	13.7±1.2	11.7±0.5
Gentamicn	35.0±0.5	35.0±0.5	30.0±0.5	-	-	-
Ampicillin	-	-	-	30.0±1.0	35.0±0.5	-
Nystatin	-	-	-	-	-	20.0±0.5

[a] NA = No activity

Table 3. Non-toxic doses of synthesized compounds on FRHK-4, Hep2, BGM, Vero, and Huh 7.5 cell lines.

Compd No.	Nontoxic dose on **FRHK-4** cell line (µg/mL)	Nontoxic dose on **Hep2** cell line (µg/mL)	Nontoxic dose on **BGM** cell line (µg/mL)	Nontoxic dose on **Vero** cell line (µg/mL)	Nontoxic dose on **Huh 7.5** cell line (µg/mL)
7a	100	100	100	100	100
7b	90	90	90	90	90
7d	100	100	100	100	100
7e	90	90	90	90	90
7f	100	100	100	100	100
9a	90	90	90	90	90
9b	70	70	70	70	70
9c	80	80	80	90	80
13	90	90	90	90	90
15a	90	90	90	90	90
15b	120	120	110	120	120
15c	100	100	100	100	100
15d	100	100	90	100	90
21a	80	80	80	80	80
21b	90	90	90	90	90
21c	90	90	90	90	90
21d	110	110	110	110	110

Table 4. Antiviral activity of non-toxic doses of synthesized compounds against Herpes Simplex Virus, Coxsackievirus B4, Hepatitis A virus HM 175, HCVcc genotype 4 & Adenovirus type 7.

Compd No.	Mean % of Reduction				
	Herpes Simplex Virus	**Coxsackievirus B4**	**Hepatitis A virus HM 175**	**HCVcc genotype 4**	**Adenovirus type 7**
7a	10	10	10	10	10
7b	10	10	10	10	10
7d	20	20	16.7	13.3	10
7e	10	20	10	10	10
7f	20	20	13.3	10	10
9a	10	10	10	10	10
9b	10	10	10	10	10
9c	10	13.3	10	10	10
13	10	10	10	10	10
15a	10	10	10	10	10
15b	10	10	10	10	10
15c	10	10	10	10	10
15d	10	10	10	10	10
21a	10	16.7	10	10	10
21b	10	10	10	10	10
21c	10	10	10	10	10
21d	10	10	10	10	10

Synthesis of novel pyrido[2,1-*b*]benzothiazole and *N*-substituted 2-pyridylbenzothiazole derivatives showing remarkable fluorescence and biological activities

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Highlights:

- Synthesis of pyrido[2,1-*b*]benzothiazole and *N*-substituted 2-pyridylbenzothiazole derivatives have been
- The new *N*-substituted 2-pyridylbenzothiazole derivatives exhibited significant fluorescence properties.
- The potency of the synthesized compounds as antimicrobial and antiviral agency were evaluated.