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Synthesis, characterization and *in vitro* biological screening of 4-hydroxy naphthalen-1-yl, naphtho[1,2-*b*]furan, benzo[*h*]chromene and 5,6-dihydropyridazine derivatives containing sulfonamide moiety

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Abstract: In this study, a series of 4-((4-hydroxynaphthalen-1-yl)diazenyl)benzenesulfonamides have been prepared by subsequent diazotization of sulfonamide derivatives and coupling with 1-naphthol in alkaline medium. Cyclization of 4-((4-hydroxynaphthalen-1-yl)diazenyl)benzenesulfonamides with cinnamic acid in the presence of a basic catalyst afforded the novel naphtho[1,2-*b*]furans. Also, 4-((4-hydroxynaphthalen-1-yl)diazenyl)benzenesulfonamides can be cyclized with *α*-cyanocinnamonitriles to afford 2-amino-3-cyano-4-phenyl-4*H*-benzo[*h*]chromenes. 4-(4-amino-3,5-dicyano-6-iminopyridazin-1(6H)-yl)benzenesulfonamides were obtained at room temperature by treatment of 2-amino-1,1,3-tricyanopropene with a diazonium salt of sulfonamide derivatives. The structures of newly synthesized compounds were confirmed by analytical data and spectroscopic techniques. The antimicrobial activity of the obtained compounds was assessed *in vitro* by qualitative and quantitative (minimum inhibitory concentration) (MIC) assays.

Keywords: sulfonamide; azobenzene; naphtho[1,2-*b*]furan; benzo[*h*]chromene; pyridazine.

Introduction

Substituted azobenzene have attracted considerable attention based on their various physical and chemical properties, such as bright colors, good stability, low flammability, and rapid, reversible photo-isomerization [1-4]. Aromatic azo compounds are widely used in the chemical industry as dyes, pigments [5,6], food additives 7, indicators [3], radical reaction initiators [8] and therapeutic agents [9,10]. Also, azobenzenes have shown promising applications in photo-optical media [11], photo-switches [12], photo-mechanical systems [13], micro patterning [14], nonlinear optical media [15], molecular shuttles [16], nanotubes [17], and in the manufacture of protective eye glasses and filters [18].

Naphthofuran derivatives have also been reported to possess diverse biological activities, including anti-tyrosinase, antioxidant and antibacterial [19]. Naphtho[1,2-*b*]furans are very important structural units found in diverse natural and synthetic products 20. They possess a broad spectrum of biological activities and have been used as precursors for the synthesis of bioactive materials. Naphtho[1,2-*b*]furan-4,5-dione (NFD, Fig. 1), a 1,2-furanonaphtho quinone, was originally isolated from *avicennia marina* belonging to the family *Avicenniaceae* and can be synthesized by a chemical process. NFD was found to show potent cytotoxicity against human cancer cell lines, including KB (human epidermoid carcinoma, IC50 = 3.05 ± 0.195 µM), HeLa (human cervical carcinoma,IC50 = 2.85 ± 0.210 µM) and HepG2 (human hepatocellular carcinoma, IC50 = 3.00 ± 0.040 µM) cell lines [21].

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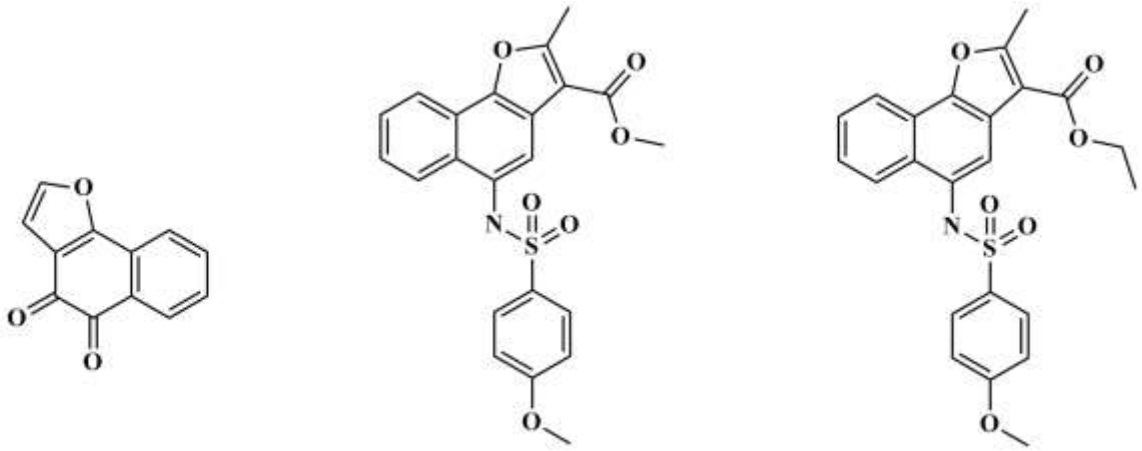
Recently, Chen et al. [22] discover, *N*-(naphtha [1,2-*b*]furan-5-yl) benzene sulfonamides (Fig. 1), as novel selective inhibitors of triple-negative breast cancer (TNBC).

Chromene derivatives are very an important class of heterocyclic compounds, widely distributed in natural products. Chromene and its derivatives have also been recognized as one type of 'privileged medicinal scaffolds' due to their unique pharmacological and biological activities [23]. Dong et al. [24,25] designed and prepared a series of 4-amino-2*H*-benzo[*h*]-chromen-2-one and 4-amino-7,8,9,10-tetrahydro-2*H*-benzo[*h*]chromen-2-one derivatives based on the potent anticancer agents neo-tanshinlactone and its 4-ethyl analogue [26].

Sulfonamides are another important compounds family for the medicinal industry, and they are now extensively used drugs for the treatment or conservation of different illnesses [27]. In clinical medicine, they have been used as anticancer [28], antimicrobial [29], antiobesity [30], carbonic anhydrase [31] and acetylcholinesterase inhibitor agents for Alzheimer's disease [32].

In view of the above-mentioned benefits and in continuation of our interest in biologically active compounds [33-37], we report herein the synthesis of some novel 4-((4-hydroxynaphthalen-1-yl)diazenyl)-benzene sulfonamides**3a-e**, naphtho[1,2-*b*]-furans **6a-c**,benzo[*h*]chromenes**8a,b** and 4-(4-amino-3,5-dicyano-6-imino-5,6-dihydropyridazin-1(4*H*)-yl)-benzenesulfonamides **13a-e** containing a sulfonamido moiety to evaluate their antimicrobial biological activity.



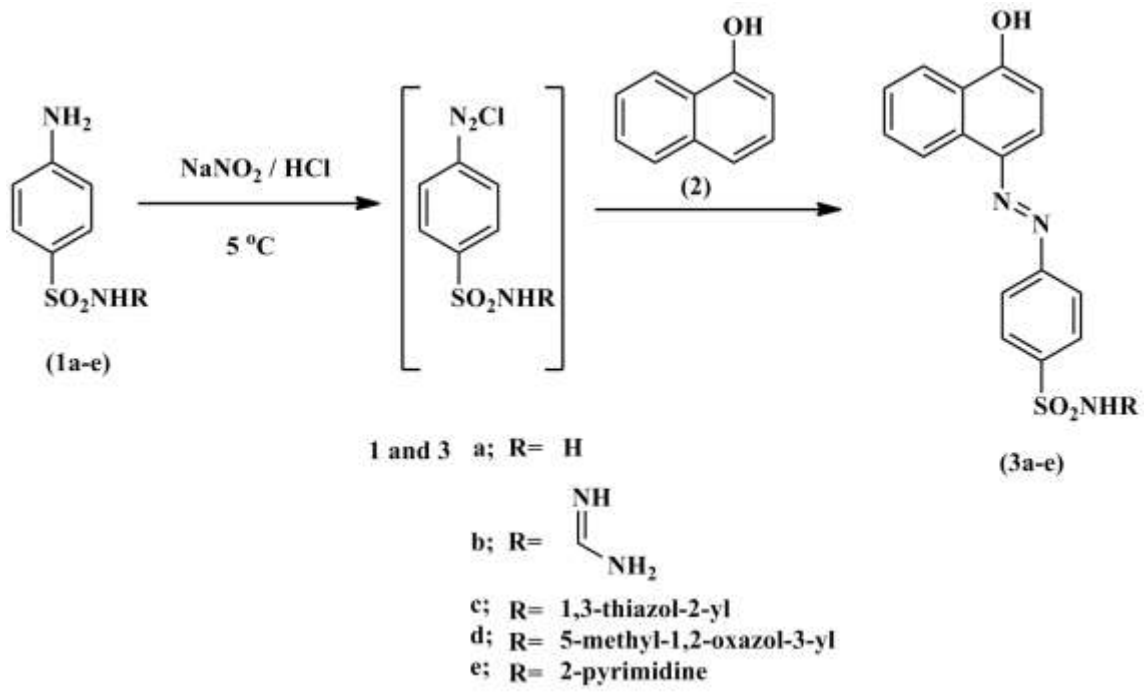
Naphtho[1,2-*b*]furan-4,5-dione (NFD) N-(naphtho[1,2-*b*]furan-5-yl) benzenesulfonamides

Figure 1.

Results and Discussion

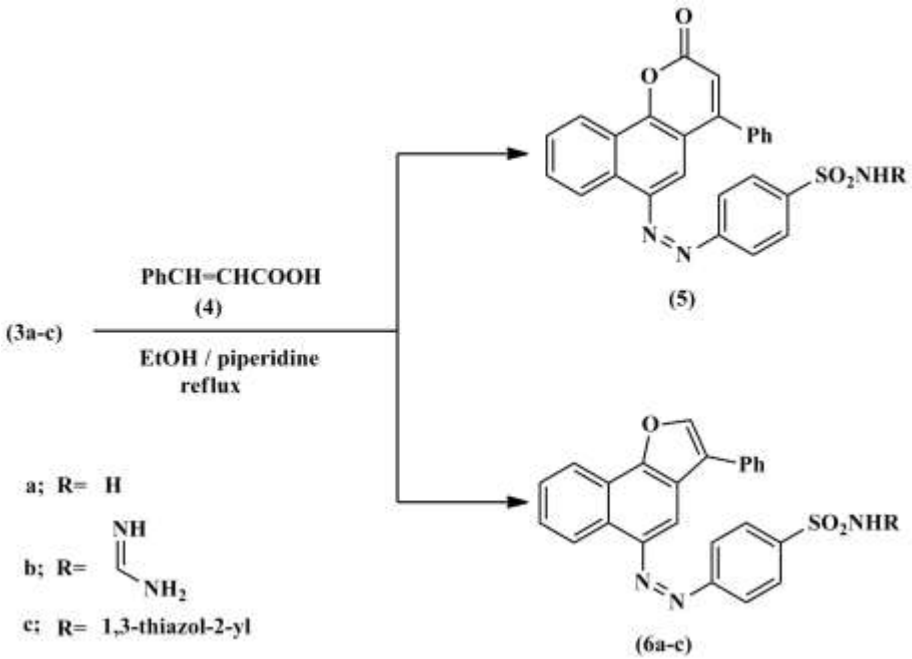
Syntheses and characterizations of the compounds

A series of 4-((4-hydroxynaphthalen-1-yl)diazenyl)benzenesulfonamides **3a-e** were synthesized by coupling of diazonium salt of sulfonamide derivatives **1a-e** with 1-naphthol **2** in presence of 10% sodium hydroxide (Scheme 1). Diazotization was carried out in the presence of nitrosyl chloride at 0-5 ºC. The structure of compounds **3a-e** was determined by their elemental analysis and spectral data. Elementary analysis indicated that sulfur was present. The infrared spectra of all isolated compounds were consistent with the assumed structures. The infrared spectra of compounds 3**a-e** showed the presence of absorption band at 3357-3448 cm^{-1} which is characteristic of the hydroxyl group beside two absorptions bands for azo and sulfone groups. The representative ^{1}HNMR spectrum of compound **3a** (DMSO-d_6) shown 7.1, 7.75, 8.35, 8.80 (4d, 4H, naphtho-H), 7.47, 7.58 (2m, 2H, naphtho-H), 7.94, 8.24 (2d, 4H, AB-system), 8.10 (s, 2H, NH_2 exchangeable with D_2O), 12.36 (br, 1H, OH exchangeable with D_2O). The molecular ion peak of compound **3c** was observed at m/z 410 (42.83%) corresponding to the molecular formula $C_{19}H_{14}N_4O_3S_2$, and the base peak was found in the spectrum at m/z 65. The enolic–OH groups of all the compounds were chemically detected by the treatment with a $FeCl_3$ solution, which gives characteristic color.



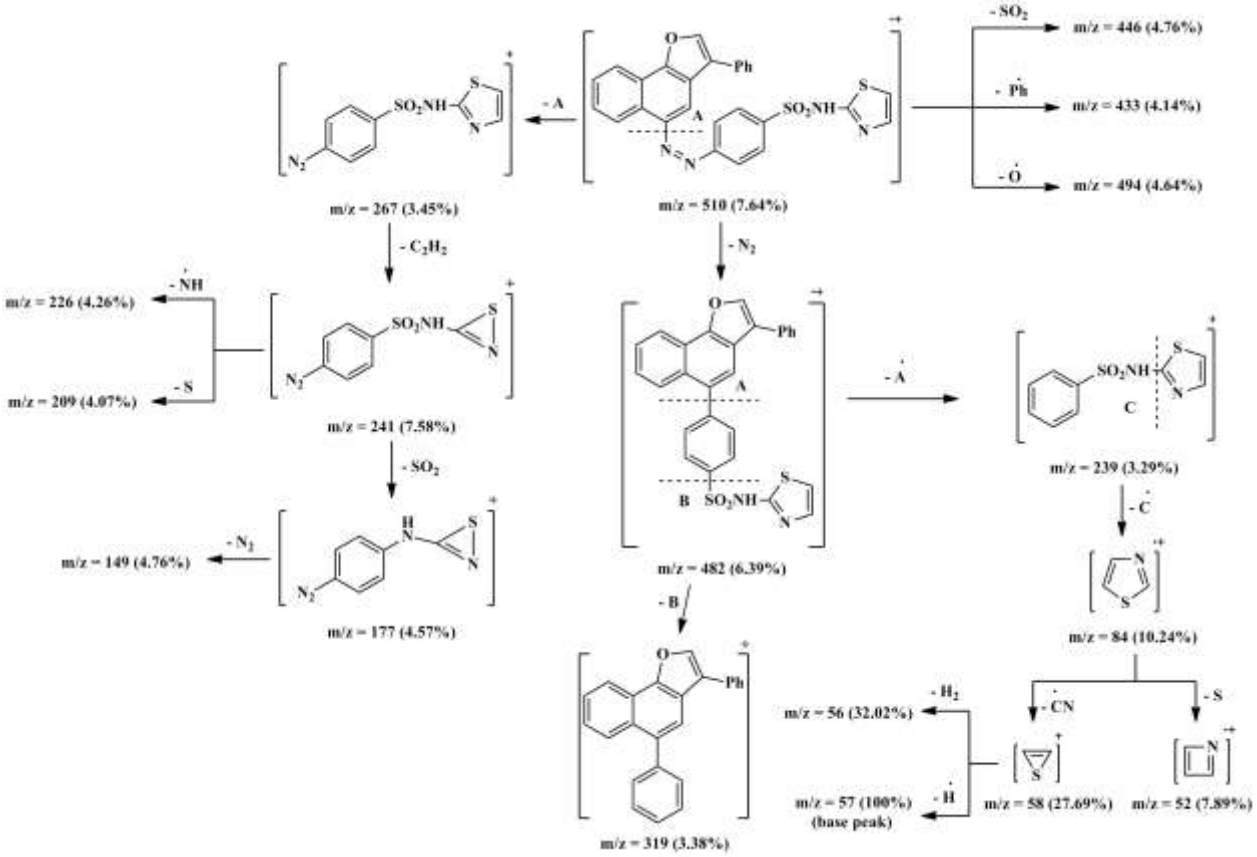
Scheme 1. Synthesis of 4-((4-hydroxynaphthalen-1-yl)diazenyl)benzenesulfonamides **3a-e**

The reactivity of 4-((4-hydroxynaphthalene-1-yl)diazenyl)benzenesulfonamides **3** towards some carbon electrophiles was investigated. Thus, it has been found that the reaction of 4-((4-hydroxynaphthalen-1-yl)diazenyl)benzenesulfonamides **3a-c** with cinnamic acid **4** in refluxing *N*,*N*-dimethylformamide (DMF) containing catalytic amounts of piperidine gave naphtho[1,2-*b*]furans **6a-c** rather than the expected naphthopyran **5** (Scheme 2).



Scheme 2. Synthesis of naphtho[1,2-*b*]furans **6a-c**

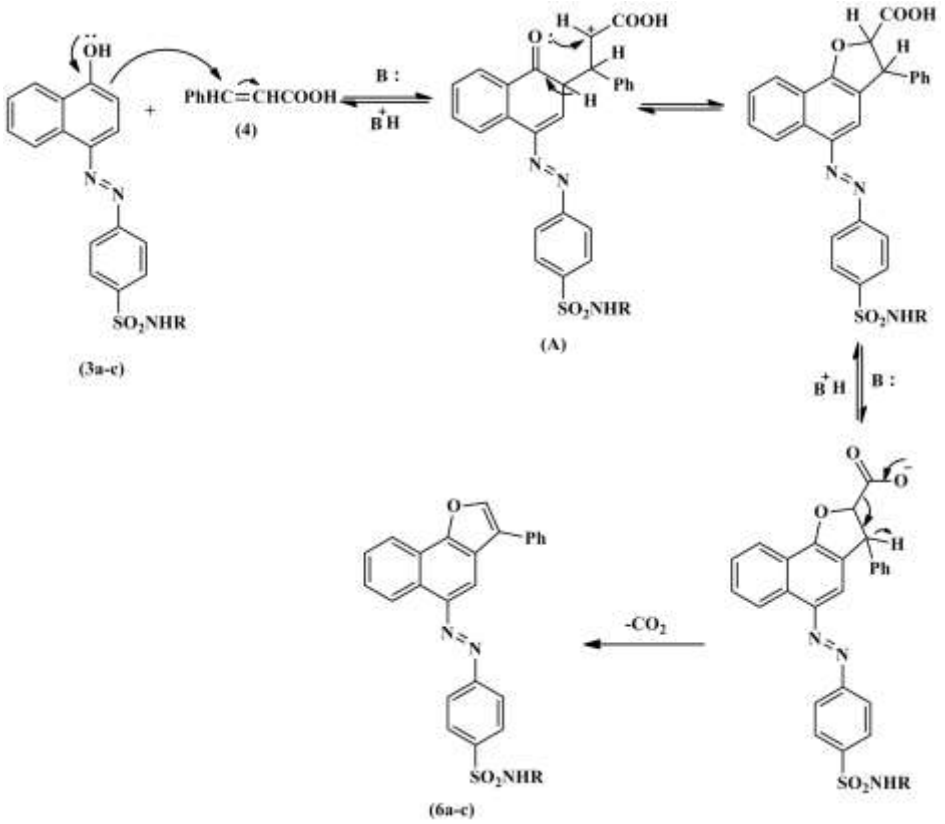
The structures of compounds **6a-c** were established by spectroscopic tools as well as elemental analyses data. The infrared spectra of compounds **6a-c** indicated the absence of the hydroxyl and carbonyl absorption bands. The ^{1}H NMR spectrum of compound **6a** (DMSO-d_6) 7.25-7.62 (m, 7H, Ph-H and naphtho-H), 8.20 (s, 1H, furan-H), 8.32, 8.39(2d, 2H, naphtho-H), 8.45, 8.50(2s, 3H, naphtho-H and NH_2, exchangeable with D_2O), 7.98, 8.55 (2d, 4H, AB-system). The mass spectrum of compound **6b** showed a molecular ion peak at m/z 469 (12.15%) compatible with molecular formula $C_{25}H_{19}N_5O_3S$. The base peak was found in the spectrum at m/z 55. Also, the mass spectrum of compound **6c** showed a molecular ion peak atm/z 510 (7.64%) corresponding to the molecular formula $C_{27}H_{18}N_4O_3S_2$. The molecular ion of compound **6c** underwent fragmentation to produce a peak of m/z 57, corresponding to the base peak (Scheme 3).



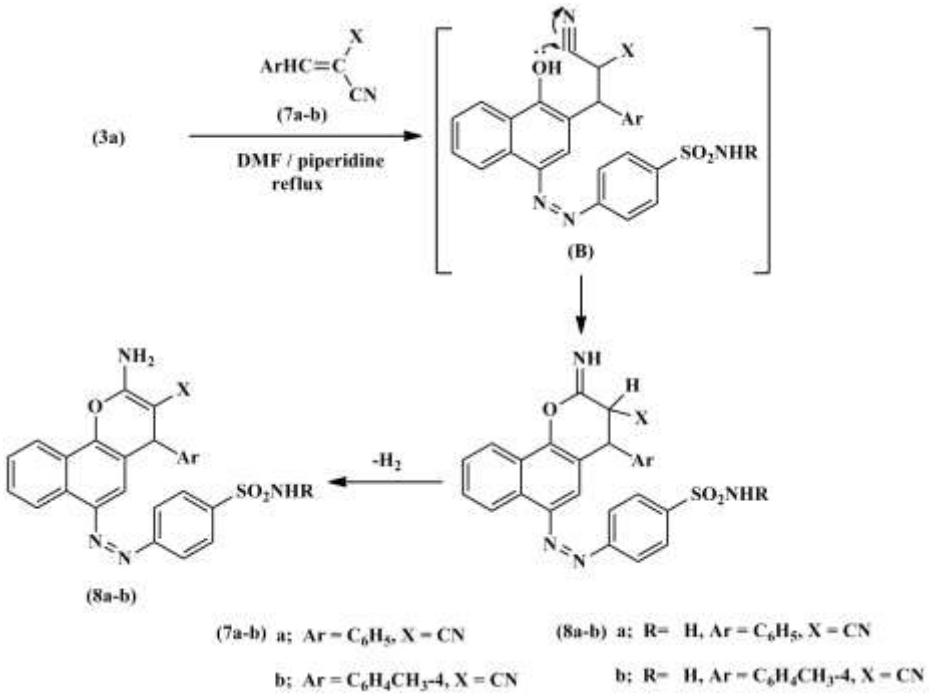
Scheme 3. Fragmentation pattern of naphtho[1,2-*b*]furan **6c**

The formation of 6 from the reaction of 3 with **4** is assumed to proceed via initial addition naphtholate anion (C-2) in **3** to the activated double bond in **4** to yield the non-isolable intermediate *Michael* adduct (**A**) followed by intramolecular cyclization and subsequent decarboxylation to afford the naphthofurans **6** (Scheme 4).

The reaction of compound **3a** with *α*-cyanocinnamonitriles was investigated. Thus, the reaction of compound **3a** with *α*-cyanocinnamonitriles **7** in refluxing DMF in the presence of piperidine afforded 2-amino-3-cyano-4-phenyl-4*H*-benzo[*h*]chromenes **8a,b.** The structure of **8** was supported by elemental analysis and spectral data**.** The infrared spectra of compounds **8a, b** displayed absorption bands for NH_2, C≡N, N=N and SO_2 functions. The mass spectrum of compound **8a** showed a molecular ion peak at m/z 481 (1.64%) corresponding to the molecular formula $C_{26}H_{19}N_5O_3S$. The formation of **8** from the reaction of **3a** with 7 is assumed to proceed via initial addition of naphtholate anion (C-2) in **3a** to the activated double bond in **7** to yield the non-isolable intermediate *Michael* adduct (**B**) followed by intramolecular cyclization through nucleophilic addition of the hydroxyl group to the cyano group and tautomerization [38] to afford benzochromene **8** (Scheme 5) .

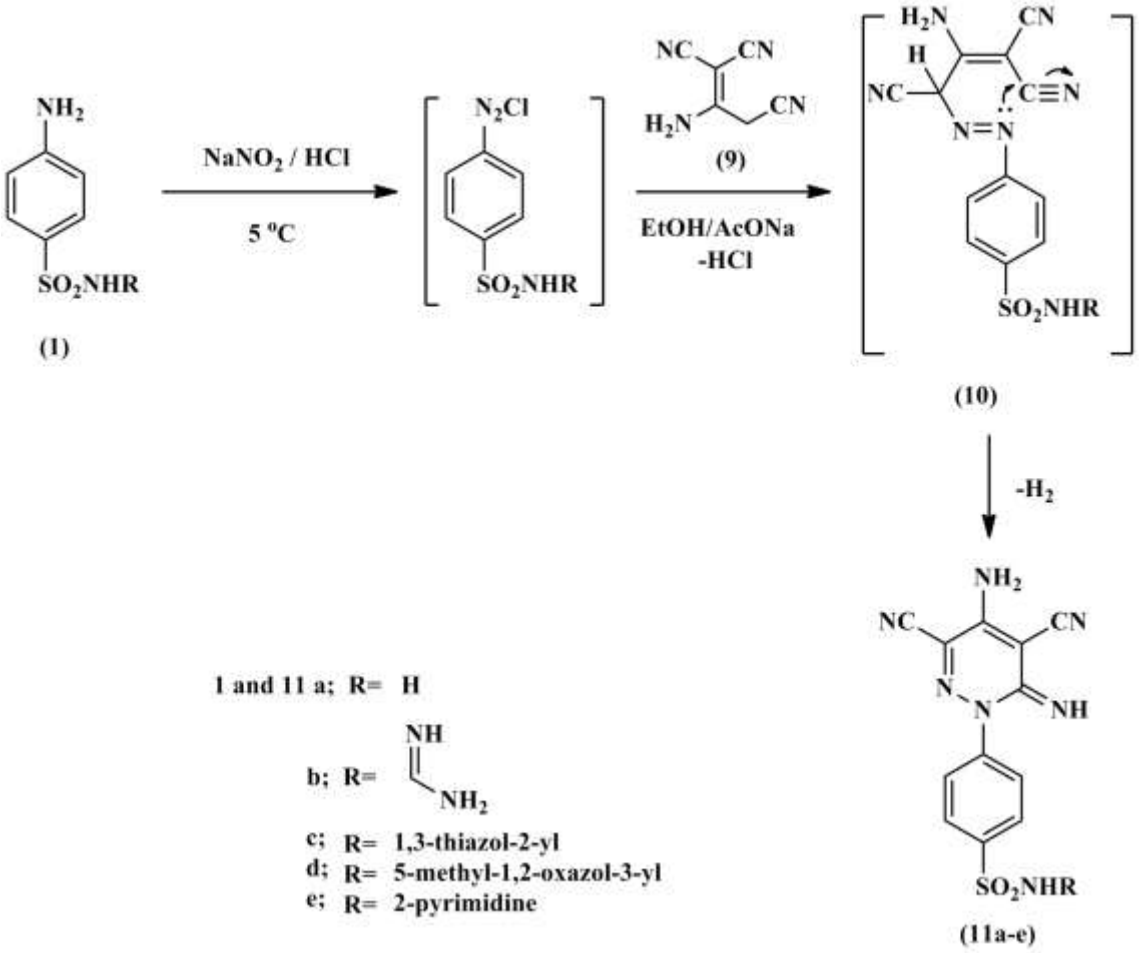


Scheme 4. Formation of naphtho[1,2-*b*]furans **6**



Scheme 5. 2-amino-3-cyano-4-phenyl-4*H*-benzo[*h*]chromenes **8a-b**

Pyridazine and its derivatives have been extensively investigated because of their important role especially in medicinal chemistry, a large variety of biological activities being described: antibacterial, antifungus, antituberculosis, antiviral, anti-inflammatory, anticancer, cardiovascular disorders [39]. Thus, treatment of 2-amino-1,1,3-tricyanopropene **9** with a diazonium salt of sulfonamide derivatives **1a-e** at room temperature gave 4-(4-amino-3,5-dicyano-6-iminopyridazin-1(6H)-yl)benzenesulfonamide derivatives **11**a-e, via intramolecular cyclization of **10** through nucleophilic addition of the nitrogen atom to the cyano group and tautomerization [40] (Scheme 6).



Scheme 6. 4-(4-amino-3,5-dicyano-6-imino-5,6-dihydropyridazin-1(4*H*)- yl)benzenesulfonamides **11**a-e

Antimicrobial activity and minimal inhibition concentration

The newly synthesized compounds were evaluated for their *in-vitro* antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis* as examples of Gram-positive bacteria, *Proteus vulgaris*and *Escherichia coli* as examples of Gram-negative bacteria, using two standard antibiotics, Ampicillin, and Gentamycin as reference drugs and antifungal potential against a representative panel of fungal strains i.e. *Aspergillus fumigatus* (*filamentous fungi*), and *Candida albicans* (yeast), using one standard antibiotic, Amphotericin B as reference drug. The compounds were tested for their activity at a concentration of 10 mg/mL using inhibition zone diameter in mm as a criterion for the antimicrobial activity, and the results are shown in (Table 1). Based on the results, the newly synthesized compounds tested displayed variable *in-vitro* antimicrobial activities under these screening conditions. Interestingly, the tested compounds exhibited significant antifungal activities against the filamentous fungus (*Aspergillus fumigatus*) and unicellular yeast (*Candida albicans*). The highest antifungal activity was detected for compound **3b** followed by **3a, 3e, 3d, 3c,** respectively. However, compound **3e** exhibited the highest activity against Gram-positive bacteria, *Staphylococcus aureus* as compared with the standard antibiotic, Ampicillin,

followed by **3b, 3a, 8a** and **3d**, respectively. On the other hand, compound **3b** exhibited the highest activity against Gram-positive bacteria, *Bacillus subtilis* followed by **3a, 3e, 3d** and **6a,** respectively. Moreover, the tested Gram-negative bacteria; *Proteus vulgaris* was highly susceptible to compound **3e** followed by, **3d**, **8a**, **3b**, **3a**, **6a** and **6b** as compared with the standard antibiotic, Gentamycin. The order of activity against *Escherichia coli* was **3e >3b >3a >3d > 6a > 8a >3c >6c >6b >8b.**

Table 1. *In-vitro* antimicrobial activities of the synthesized compounds tested at 10 mg/mL by well diffusion agar assay and expressed as inhibition zone diameter (mm) in the form of mean ± standard deviation.

Compound	Fungi		Gram positive bacteria		Gram negative bacteria	
	C. albicans **ATCC 10231**	***A. fumigatus*** **RCMB 002568**	***S. Aureus*** **RCMB 010012**	***B. subtilis*** **NRRL B-543**	***Proteus vulgaris*** **ATCC 13315**	***E. coli*** **ATCC 25955**
3a	33.5±1.6	29±0.7	20.3±0.5	18.4±0.8	15.8±1.4	**21.2±0.4**
3b	34.1±1.7	30.7±1.5	21.6±1.3	20.2±0.6	16.1±0.7	**22.6±0.8**
3c	13±0.7	20.3±1.1	15.8±0.5	8.1±0.2	12.4±0.6	**13.1±0.4**
3d	14.2±0.6	26±1.2	17.1±0.8	15.4±0.7	17.1±0.8	**20.4±1.6**
3e	26.1±1.2	27.4±0.8	22.3±1.4	16±0.8	18.9±1.6	**23.4±0.9**
6a	17.1±0.7	15.7±0.9	16.3±1.1	15.2±1.4	14.7±1.3	**17.5±1.2**
6b	0	0	13.4±0.9	9.2±0.5	14.5±0.8	**10.1±0.7**
6c	11.4±0.9	0	13.3±0.8	10.2±0.6	13.5±0.7	**11.6±0.5**
8a	14.5±1.1	16±0.8	18.2±0.9	14±0.6	16.4±0.8	**15.1±1.3**
8b	14.6±0.8	12.9±0.3	10.2±0.4	11.5±0.7	10.9±0.4	**9.7±0.5**
11a	0	0	0	8.6±0.8	0	**0**
11b	0	0	0	0	0	**0**
11c	0	0	9.8±0.6	0	0	**0**
11d	0	0	8.7±0.5	0	0	**0**
11e	0	0	0	10.2±0.6	0	**0**
Amphotricin B	25.7±1.3	24.8±1.4	-	-	-	-
Ampicillin	-	-	27.8±0.6	26.4±0.7	-	-
Gentamycin	-	-	-	-	**25.7±0.9**	**29.6±1.3**

Amphotericin B, ampicillin and gentamycin were used as standard drugs against the tested fungi, Gram-positive and Gram-negative bacteria, respectively.

The antimicrobial activities of the synthesized compounds were also tested to determine the minimum inhibitory concentration as shown in Table 2. Moreover, compound **3b** showed the highest activity (MIC values ranged from 4.9 to 312.5 µg/ml), followed by **3a** (MIC 4.9-625 µg/ml), **3e** (MIC 9.8-625 µg/ml), and **3d** (MIC 9.8-625 µg/ml).

Table 2. The antibacterial activities of the synthesized compounds expressed as minimum inhibitory concentration (µg/ml).

Compound	Fungi		Gram positive bacteria		Gram negative bacteria	
	***C. albicans* ATCC 10231**	***A. fumigatus* RCMB 002568**	***S. aureus* RCMB 010012**	***B. subtilis* NRRL B-543**	***Proteus vulgaris* ATCC 13315**	*E. coli* ATCC 25955
3a	4.9	4.9	39	156	625	**39**
3b	4.9	4.9	156	156	312.5	**39**
3c	1250	156	625	5000	1250	**625**
3d	625	9.8	312.5	625	312.5	**156**
3e	9.8	9.8	39	625	156	**39**
6a	312.5	625	625	625	625	**312.5**
6b	NA*	NA	625	5000	625	**2500**
6c	1250	NA	625	2500	625	**2500**
8a	625	625	312.5	625	625	**625**
8b	625	1250	2500	1250	2500	**2500**
Amphotricin B	9.8	2.44	-	-	-	-
Ampicillin	-	-	1.22	0.6	9.76	**9.76**
Gentamycin	-	-	**9.76**	**4.88**	**0.6**	**1.22**

* NA: No activity

Conclusion

A series of novel 4-((4-hydroxynaphthalen-1-yl)diazenyl) benzenesulfonamides, naphtho[1,2-*b*]furans, benzo[*h*]chromenes and 4-(4-amino-3,5-dicyano-6-imino-5,6-dihydropyridazin-1(4*H*)-yl)benzenesulfonamides were synthesized to evaluate their antimicrobial biological activity with the hope of discovering new structure leads serving as antimicrobial agents.

Experimental

All analyses were done at the Microanalytical Center, Cairo University, Cairo (Egypt). Melting points (uncorrected) were determined in open capillaries on a Gallenkamp melting point apparatus (Sanyo Gallenkamp, Southborough, UK). IR spectra (KBr discs) were recorded using a Shimadzu FT-IR 8400S spectrophotometer (Shimadzu, Kyoto, Japan), Infrared (IR) Spectra were recorded as KBr disks. NMR Spectra were recorded on a Bruker spectrophotometer (Bruker, Karlsruhe, Germany). ^{1}H spectrum was run at 400 MHz in deuterated dimethylsulfoxide (DMSO-d_6). Chemical shifts are expresses in values (ppm) relative to TMS as an internal standard. Mass spectral data were given by a GCMS-QP1000 EX-spectrometer (Shimadzu, Kyoto, Japan) at 70 eV. All reagents used were of the Analytical grade. Compounds α-cyanocinnamonitriles **7** [41] and 2-amino-1,1,3-tricyanopropene **9** [42] have been synthesized as previously reported.

General Procedure for Synthesis of 4-((4-hydroxynaphthalen-1-yl)diazenyl)benzene-sulfonamides 3a-e:

Sulfonamide (0.01 mole) was suspended in water (50 ml). Hydrochloric acid (10 ml, 36%) was added dropwise to this well stirred. The mixture was gradually heated up to 70 ˚C till clear solution obtained. The solution was cooled to 0-5 ˚C in an ice bath. A solution of $NaNO_2$ (0.5 mg) in water (5ml) previously cooled to 0 ˚C, was then added over a period 5 minutes with

stirring. 1-naphthol (0.01 mole) was dissolved in 10% NaOH (10 ml) and then put ice to cool to 5 ºC. Then, diazonium salt solution was added occasionally stirring very slowly to the 1-naphthol solution. The reaction mixture was left to complete for 15 min and occasional stirring; then the formed precipitate was filtered and dried in air and then recrystallized from proper solvent to give **3**.

4-((4-hydroxynaphthalen-1-yl)diazenyl)benzene-sulfonamide 3a.

Brown crystals (ethanol), Yield:85%, m.p.254-256 ˚C; IR(KBr, cm^{-1}): 3357 (OH), 3300, 3249 (NH_2),1622 (C=C), 1594 (N=N), 1356, 1147 (S=O);
^{1}HNMR (DMSO-d_6, ppm): 7.24, 7.72, 7.98, 8.16(4d, 4H), 7.55, 7.62(2m, 2H), 7.88, 8.26 (2d, 4H), 7.36 (s, 2H, NH_2, exchangeable with D_2O), 9.45 (s, 1H, OH, exchangeable with D_2O);
Anal. Calcd. for $C_{16}H_{13}N_3O_3S$: C, 58.70; H, 4.00; N, 12.84; S, 9.80. Found: C, 58.52; H, 3.89; N, 12.58; S, 9.65.

N-carbamimidoyl-4-((4-hydroxynaphthalen-1-yl)diazenyl)benzenesulfonamide 3b.

Brown crystals (ethanol), Yield:83%, m.p.246-248 °C; IR(KBr, cm-1): 3441 (OH), 3329 (NH_2), 3272, 3223 (2NH), 1633 (C=C), 1596 (N=N), 1355, 1165 (S=O);
^{1}HNMR (DMSO-d_6, ppm): 7.28, 7.72,8.14 (3d, 3H), 7.49-7.57(2m, 2H), 7.82, 788 (2d, 4H), 6.75 (s, 2H, NH_2, exchangeable with D_2O), 7.61, 7.80 (2s, 2H, 2NH, exchangeable with D_2O), 10.03(s, 1H, OH, exchangeable with D_2O); Anal. Calcd. for $C_{17}H_{15}N_5O_3S$: C, 55.27; H, 4.09; N, 18.96; S, 8.68. Found: C, 55.12; H, 3.95; N, 18.76; S, 8.42.

4-((4-hydroxynaphthalen-1-yl)diazenyl)-N-(thiazol-2-yl)benzenesulfonamide 3c.

Brown crystals (ethanol), Yield: 86%, m.p.202-204 °C; IR(KBr, cm-1): 3415 (OH), 3274 (NH), 1627 (C=C), 1594 (N=N), 1317, 1138 (S=O);
^{1}HNMR (DMSO-d_6, ppm): 7.30, 7.75, 8.13, 8.15(4d, 4H), 7.58, 7.71 (2m, 2H), 7.86, 7.92(2d, 4H), 6.73, 7.26 (2d, 2H, H-thiazole), 12.74 (br, H, NH, exchangeable with D_2O), 10.05 (s, 1H, OH, exchangeable with D_2O);
MS: 410 (M^+; 42.83 %), 393 (3.17), 382 (28.92 %), 346 (62.87 %), 247 (17.45 %), 219 (4.18 %), 92 (93.25 %), 76(19.77%), 65 (100 %).
Anal. Calcd. for $C_{19}H_{14}N_4O_3S_2$: C, 55.60; H, 3.44; N, 13.65; S, 15.62. Found: C, 55.46; H, 3.28; N, 13.47; S, 15,42.

4-((4-hydroxynaphthalen-1-yl)diazenyl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide 3d.

Brown crystals (ethanol), Yield: 80%, m.p.242-244 ˚C; IR(KBr, cm-1): 3448 (OH), 3107 (NH), 2924 (CH-aliph.), 1632 (C=C), 1595 (N=N), 1327, 1139 (S=O);
^{1}HNMR (DMSO-d_6, ppm): 2.36 (s, 3H, CH_3), 6.25 (s, 1H, H-oxazole), 7.25, 7.68, 8.04, 8.12(4d, 4H), 7.51, 7.63 (2m, 2H), 7.88, 7.97(2d, 4H), 11.26 (s, H, NH, exchangeable with D_2O), 10.02 (s, 1H, OH, exchangeable with D_2O);
Anal. Calcd. for $C_{20}H_{16}N_4O_4S$: C, 58.81; H, 3.95; N, 13.72; S, 7.85. Found: C, 58.64; H, 3.79; N, 13.54; S, 7.68.

4-((4-hydroxynaphthalen-1-yl)diazenyl)-N-(pyrimidin-2-yl)benzenesulfonamide 3e.

Dark brown crystals (ethanol), Yield:7 8%, m.p. 132-134 °C;
IR(KBr, cm-1): 3377 (OH), 3225 (NH), 1625 (C=C), 1581 (N=N), 1316, 1155 (S=O);
^{1}HNMR (DMSO-d_6, ppm): 6.99, 8.36(m, d,3H, H-pyrimidine), 7.23, 7.69, 8.06, 8.15 (4d, 4H), 7.52, 7.60 (2m, 2H), 7.91, 7.98 (2d, 4H), 11.30 (s, H, NH, exchangeable with D_2O), 9.98 (s, 1H, OH, exchangeable with D_2O);
Anal. Calcd. for $C_{20}H_{15}N_5O_3S$: C, 59.25; H, 3.73; N, 17.27; S, 7.91. Found: C, 58.94; H, 3.64; N, 17.13; S, 7.64.

General Procedure for Synthesis of naphtho[1,2-b]furans 6a-c.

To a mixture of compound 3 (0.01 mole) and cinnamic acid **4** (0.01 mole) in DMF (10 ml), a few drops piperidine was added. The reaction mixture was refluxed for 2 h. After cooling, the precipitate was filtered and recrystallized from proper solvent to give **6.**

4-((3-phenylnaphtho[1,2-b]furan-5-yl)diazenyl)-benzenesulfonamide 6a.

Brown crystals (ethanol), Yield: 79%, m.p.180-182 °C; IR(KBr, cm-1):3266 (NH_2), 1624 (C=C), 1594 (N=N), 1316, 1155 (S=O);
^{1}HNMR (DMSO-d_6, ppm): 7.28-7.55 (m, d, 5H, Ph-H), 8.18 (s, 1H, furan-H), 8.32(s, 1H), 8.20, 8.52(2d, 2H), 7.42, 7.56 (2m, 2H), 7.90, 8.06(2d, 4H), 7.30(s, 2H, NH_2, exchangeable with D_2O);
Anal. Calcd. for $C_{24}H_{17}N_3O_3S$: C, 67.43; H, 4.01; N, 11.23; S, 7.50. Found: C, 67.28; H, 3.87; N, 11.14; S, 7.38.

N-carbamimidoyl-4-((3-phenylnaphtho[1,2-b]furan-5-yl)diazenyl)benzenesulfonamide 6b.

Dark brown crystals (ethanol), Yield: 82%, m.p.205-207 °C;
IR(KBr, cm-1): 3440 (NH_2), 3328, 3271 (2NH), 1632 (C=C), 1595 (N=N), 1307, 1131 (S=O);
^{1}HNMR (DMSO-d_6, ppm): 7.32-7.58 (m, d, 5H, Ph-H), 8.17(s, 1H, furan-H), 8.32(s, 1H), 8.17, 8.43 (2d, 2H), 7.60, 7.67 (2m, 2H), 7.88, 7.96(2d, 4H), 6.74(s, 2H,

NH_2, exchangeable with D_2O), 7.75, 8.08(2s, 2H, 2NH, exchangeable with D_2O).
MS: 469 (M^+; 12.15 %), 453 (8.95 %), 426 (10.10 %), 398 (6.67 %), 392(6.67%), 362 (14.58 %), 198 (11.76 %), 135 (8.31 %), 57 (81.71 %), 55 (100 %).
Anal. Calcd. for $C_{25}H_{19}N_5O_3S$: C, 63.95; H, 4.08; N, 10.22; S, 6.83. Found: C, 63.78; H, 3.97; N, 10.10; S, 6.65.

4-((3-phenylnaphtho[1,2-b]furan-5-yl)diazenyl)-N-(thiazol-2-yl)benzenesulfonamide 6c.

Dark brown crystals (ethanol), Yield: 84%, m.p.193-195°C;
IR(KBr, cm-1): 3247 (NH), 1628 (C=C), 1593 (N=N), 1311, 1137 (S=O);
^{1}HNMR (DMSO-d_6, ppm): 6.73, 7.19 (2d, 2H, thiazole-H), 7.35-7.58 (m, d, 5H, Ph-H), 8.12 (s, 1H, furan-H), 8.26(s, 1H), 8.14, 8.44 (2d, 2H), 7.43, 7.59 (2m, 2H), 7.93, 8.02 (2d, 4H), 12.64(s, H, NH, exchangeable with D_2O);
MS: 510 (M^+; 7.64 %), 494 (4.64 %), 482 (6.39 %), 446 (4.76 %), 433 (4.14 %), 319 (3.38 %), 267 (3.45 %), 241 (7.58 %), 239 (3.29 %), 226 (4.26 %), 209 (4.07 %), 177 (4.57 %), 149 (4.76 %), 84 (10.24 %), 58 (27.69), 57 (100 %), 56 (32.02 %), 52 (7.89 %). Anal. Calcd. for $C_{27}H_{18}N_4O_3S_2$: C, 63.51; H, 3.55; N, 10.97; S, 12.56. Found: C, 63.38; H, 3.39; N, 10.75; S, 12.32.

General Procedure for Synthesis of benzo[h]chromenes 8a,b.

To a mixture of compound 3 (0.01 mole) and *α*-cyanocinnamonitrile **7**(0.01 mole) in DMF (10 ml), a few drops triethylamine was added. The reaction mixture was refluxed for 1 h. After cooling, the precipitate was filtered and recrystallized from proper solvent to give **8.**

4-((2-amino-3-cyano-4-phenyl-4H-benzo[h]chromen-6-yl)diazenyl)benzenesulfonamide 8a.

Brown crystals (ethanol), Yield: 84%, m.p.90-92 °C;
IR(KBr, cm-1): 3355, 3270 ($2NH_2$), 3054 (CH-arom.), 2190 (CN), 1631 (C=C), 1593 (N=N), 1357, 1156 (S=O); ^{1}HNMR(DMSO-d_6, ppm): 4.90 (s, 1H, 4H-pyran), 7.23-7.32 (m, d, 5H, Ph-H), 7.88(s, 1H), 8.12, 8.27(2d, 2H), 7.49, 7.56(2m, 2H), 7.90, 8.25(2d, 4H), 6.88, 7.21 (2s, 4H, $2NH_2$, exchangeable with D_2O);
MS: 481 (M^+; 1.64 %), 465 (1.53%), 455 (1.55%), 452 (25.81%), 401 (2.42%), 404 (4.62%), 373 (12%), 327 (8.13%), 297 (100 %), (269 (39.18%), 219 (1.11%), 65 (26.78%).

Anal. Calcd. for $C_{26}H_{19}N_5O_3S$: C, 64.85; H, 3.98; N, 14.54; S, 6.66. Found: C, 64.63; H, 3.74; N, 14.24; S, 6.39.

4-((2-amino-3-cyano-4-(p-tolyl)-4H-benzo[h]-chromen-6-yl)diazenyl)benzenesulfonamide 8b.

Brown crystals (ethanol), Yield: 87%, m.p.135-137 °C;
IR(KBr, cm-1): 3424, 3385 ($2NH_2$), 3034 (CH-arom), 2870 (CH-aliph), 2186 (CN), 1631 (C=C), 1594 (N=N), 1358, 1153 (S=O);
^{1}HNMR (DMSO-d_6, ppm): 2.35 (s, 3H, CH_3), 4.82 (s, 1H, 4H-pyran), 7.13, 7.21 (2d, 4H, Ph-CH3), 7.87(s, 1H), 8.13, 8.38(2d, 2H), 7.51, 7.54(2m, 2H), 8.15, 7.81(2d, 4H), 6.89, 7.23 (2s, 4H, $2NH_2$, exchangeable with D_2O);
Anal. Calcd. for $C_{27}H_{21}N_5O_3S$: C, 65.44; H, 4.27; N, 14.13; S, 6.47. Found: C, 65.38; H, 4.09; N, 13.95; S, 6.28.

General Procedure for Synthesis of 4-(4-amino-3,5-dicyano-6-iminopyridazin-1(6H)-yl)benzene-sulfonamides 11a-e:

Sulfonamide (0.01 mole) was suspended in water (50 ml). Hydrochloric acid (10 ml, 36%) was added drop wise to this well stirred. The mixture was gradually heated up to 70 °C till clear solution obtained. The solution was cooled to 0-5 °C in an ice bath. A solution of $NaNO_2$ (0.5 gm) in water (5ml) previously cooled to 0 °C, was then added over a period 5 minutes with stirring. 2-Amino-1,1,3-tricyanopropene 9 (0.01 mole) was dissolved in ethanol (10 ml) in the presence of sodium acetate (1 gram) and then put ice to cool to 5 °C. Then, diazonium salt solution was added occasionally stirring very slowly to the 2-Amino-1,1,3-tricyanopropene solution. The reaction mixture was left to complete for 3h and occasional stirring; then the formed precipitate was filtered and dried in air and then recrystallized from proper solvent to give **11**.

4-(4-amino-3,5-dicyano-6-iminopyridazin-1(6H)-yl)benzenesulfonamide 11a:

Yellow crystals (ethanol), Yield: 88%, m.p.158- 160 °C;
IR(KBr, cm-1): 3378, 3312 ($2NH_2$), 3211 (NH), 2219, 2199 (2C≡N), 1620 (C=N), 1326, 1159 (S=O);
^{1}HNMR (DMSO-d_6, ppm): 6.65, 7.20 (2br., 4H, $2NH_2$, exchangeable with D_2O), 7.80, 8.21(2d, 4H, AB-system), 9.85(br., 1H, NH, exchangeable with D_2O).
Anal. Calcd. for $C_{12}H_9N_7O_2S$: C, 45.71; H, 2.88; N, 31.10; S, 10.17. Found: C, 45.56; H, 2.64; N, 30.94; S, 10.04.

4-(4-amino-3,5-dicyano-6-iminopyridazin-1(6H)-yl)-N-carbamimidoylbenzenesulfon amide 11b

Yellow crystals (ethanol), Yield: 82%, m.p.>300 °C;
IR(KBr, cm-1): 3450-3211 ($NH+NH_2$), 2220, 2202 (2C≡N), 1620 (C=N), 1352, 1138 (S=O);
^{1}HNMR (DMSO-d_6, ppm): 6.85, 7.10(2br., 4H, $2NH_2$, exchangeable with D_2O), 7.63, 7.95 (2d, 4H, AB-

system), 7.55, 8.52, 10.10(3br., 3H, 3NH, exchangeable with D_2O).
Anal. Calcd. for $C_{13}H_{11}N_9O_2S$:C, 43.69; H, 3.10; N, 35.28; S, 8.97. Found: C, 43.46; H, 2.92; N, 35.13; S, 8.87.

4-(4-amino-3,5-dicyano-6-iminopyridazin-1(6H)-yl)-N-(thiazol-2-yl)benzenesulfon amide 11c

Yellow crystals (ethanol), Yield: 85%, m.p.>300 ˚C;
IR(KBr, cm-1): 3430 (NH_2), 3320, 3214 (2NH), 2216, 2201 (2C≡N), 1622 (C=N), 1330, 1147 (S=O);
^{1}HNMR (DMSO-d_6, ppm): 6.84, 7.77 (2d, 2H, thiazole), 7.70, 7.95 (2d, 4H, AB-system), 6.70 (s, 2H, NH_2, exchangeable with D_2O), 9.85, 12.16 (2br., 2H, 2NH, exchangeable with D_2O).
Anal. Calcd. for $C_{15}H_{10}N_8O_2S_2$: C, 45.22; H, 2.53; N, 28.12; S, 16.10. Found: C, 45.22; H, 2.53; N, 28.12; S, 16.10.

4-(4-amino-3,5-dicyano-6-iminopyridazin-1(6H)-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide 11d:

Yellow crystals (ethanol), Yield: 80%, m.p.>300 ˚C;
IR(KBr, cm-1): 3311 (NH_2), 3225, 3192 (2NH), 2217, 2199 (2C≡N), 1618 (C=N), 1330, 1159 (S=O);
^{1}HNMR (DMSO-d_6, ppm): 2.35 (s, 3H, CH_3), 6.15 (s, 1H, oxazole-H), 7.72, 8.12(2d, 4H, AB-system), 7.52(s, 2H, NH_2, exchangeable with D_2O), 9.76, 11.18(2s, 2H, 2NH, exchangeable with D_2O);
Anal. Calcd. for $C_{16}H_{12}N_8O_3S$: C, 48.48; H, 3.05; N, 28.27; S, 8.09. Found: C, 48.26; H, 2.97; N, 28.12; S, 7.95.

4-(4-amino-3,5-dicyano-6-iminopyridazin-1(6H)-yl)-N-(pyrimidin-2-yl)benzenesulfonamide 11e

Yellow crystals (ethanol), Yield: 88%, m.p.>300 ˚C;
IR(KBr, cm-1): 3434 (NH_2), 3228, 3213 (2NH), 2216, 2201 (2C≡N), 1621 (C=N), 1339, 1155 (S=O);
^{1}HNMR (DMSO-d_6, ppm): 6.98, 8.42(m, d, 3H, H-pyrimidine), 7.68, 8.15 (2d, 4H, AB-system), 7.90(s, 2H, NH_2 exchangeable with D_2O), 9.65, 11.26(2s, 2H, 2NH, exchangeable with D_2O);
Anal. Calcd. for $C_{16}H_{11}N_9O_2S$: C, 48.85; H, 2.82; N, 32.05; S, 8.15. Found: C, 48.64; H, 2.59; N, 31.97; S, 7.98.

Biological evaluation

All microbial strains were provided from the culture collection of the Regional Center for Mycology and Biotechnology (RCMB), Al-Azhar University, Cairo, Egypt. The antimicrobial activity was investigated on a dozen of newly synthesized compounds in order to increase the selectivity of these derivatives towards test microorganisms using the agar diffusion method using Mueller-Hinton agar medium for bacteria and Sabouraud's agar medium for fungi [43,44]. Briefly, 100 µl of the test bacteria/fungi were grown in 10 mL of fresh media until they reached a count of approximately 10^8 cells/ml for bacteria or 10^5 cells/mL for fungi. All the newly synthesized compounds were weighed and dissolved in dimethyl sulfoxide to prepare extract stock solution.

One hundred µL of each sample at 5 mg/mL was added to each well (10 mm diameter holes cut in the agar gel). The plates were incubated for 24-48 h at 37 °C (for bacteria and yeast) and 48 h at 28 °C (for filamentous fungi). After incubation, the microorganism's growth was observed. Ampicillin and Gentamycin were used as standard antibacterial drugs while amphotericin B was used as a standard antifungal drug. The resulting inhibition zone diameters were measured in millimeters and used as a criterion for the antimicrobial activity. If an organism is placed on the agar, it will not grow in the area around the well if it is susceptible to the chemical. This area of no growth around the disc is known as a Zone of inhibition. The size of the clear zone is proportional to the inhibitory action of the compound under investigation. Solvent controls (DMSO) were included in every experiment as negative controls. DMSO was used for dissolving the tested compounds and showed no inhibition zones, confirming that it does not influence the growth of the tested microorganisms. The active compounds were further investigated to determine their antimicrobial activity expressed regarding minimum inhibitory concentration (MIC) using the modified agar well diffusion method that mentioned above. Different concentrations of each active compound were tested and compared with standard drugs**.** The MIC was then determined as the lowest concentration inhibiting the growth of the organism after 24-48 h [43,45].

Conflict of interest

The authors declare that they have no conflict of interest.

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