MANSOURA JOURNAL OF CHEMISTRY
Official Journal of Faculty of Science, Mansoura University, Egypt
E-mail: scimag@mans.edu.eg ISSN: 2974-4938

Synthesis and antimicrobial activity of some new sulfathiazole derivatives

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Received:9/2/2020
Accepted:3/3/2020

Abstract: Diazotization of 3,5-diaminopyrazole derivative **2** to form diazonium salt **3,** which reacted with either 2-cyano-*N*-phenylacetamide (**4**) or 3,5-dimethyl phenol (**6**) to afford pyrazolo-4,5diazenyl derivatives **5** and **7**, respectively. Also, compound **1** was reacted with methyl iodide in potassium carbonate to give *N*-methyl-*N*-(4-(*N*-(thiazol-2-yl)sulfamoyl)phenyl)carbonohydrazonoyl dicyanide (**8**), which was treated with hydrazine hydrate to give α-cyanoarylhydrazones **9**. Moreover, the reaction of compound **1** with either thiourea or hydroxylamine hydrochloride afforded 4-(2-(4,6-diamino-2-thioxopyrimidin-5(2*H*)-ylidene)hydrazineyl)-*N*-(thiazol-2-yl)benzenesulfonamide(**10**)and4-(2-(3-amino-5-iminoisoxazol-4(5*H*)-ylidene)hydrazineyl)-*N*-(thiazol-2-yl)benzenesulfonamide (**11**), respectively. The newly prepared compounds were selected for their biological evaluation as antimicrobial activities.

keywords: Sulphathiazole; Pyrazole; Pyrimidine; Isoxazole; Antimicrobial activity

1.Introduction

Sulfathiazole ring systems are biologically active [1-4]. Sulfathiazole compounds show significant group of sulfur and nitrogen in a five member ring. It is important due to their anticancer, antiviral, antimicrobial, antibacterial, antifungal, antiinflammatory, antituberculosis, carbonic anhydrase inhibition, antimalarial, antiparasitic, anticonvulsant, and antidepressant activities [5-8]. On the other hand, Pyrazole derivatives are of significant attention as it has various activities as inhibitor of protein glycation, antioxidant as well as antiviral agents [9,10] and therapeutic activities [11-20].The present work has investigated the preparation of sulfathiazole derivatives and their antimicrobial agents [21-24].

2. Results and Discussion

2.1. Synthetic Chemistry

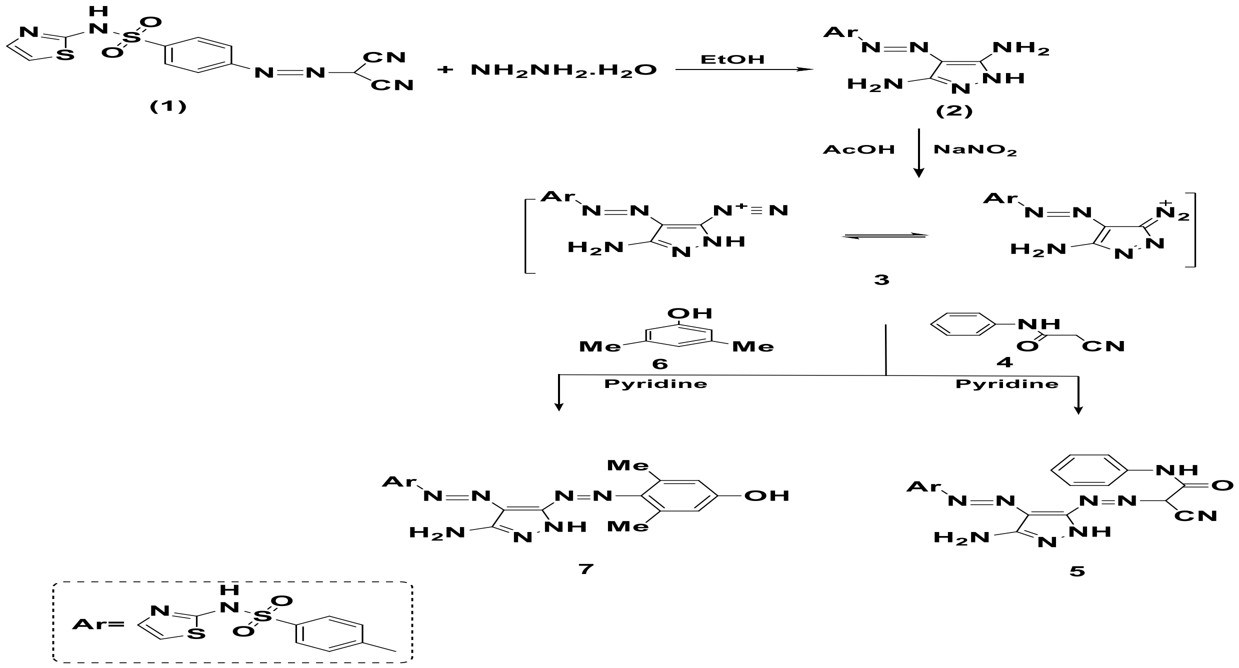
The above data encourage us to select 4-((3,5-diamino-1*H*-pyrazol-4-yl)diazenyl)-*N*-(thiazol-2-yl)benzenesulfonamide (**2**), which was previously prepared from our laboratory [25] as starting compound for the preparation of new polyfunctionally substituted fused heterocyclic compounds with anticipated biological activity.

Diazotization of 3,5-diaminopyrazole derivative **2** with sodium nitrite in acetic acid to form

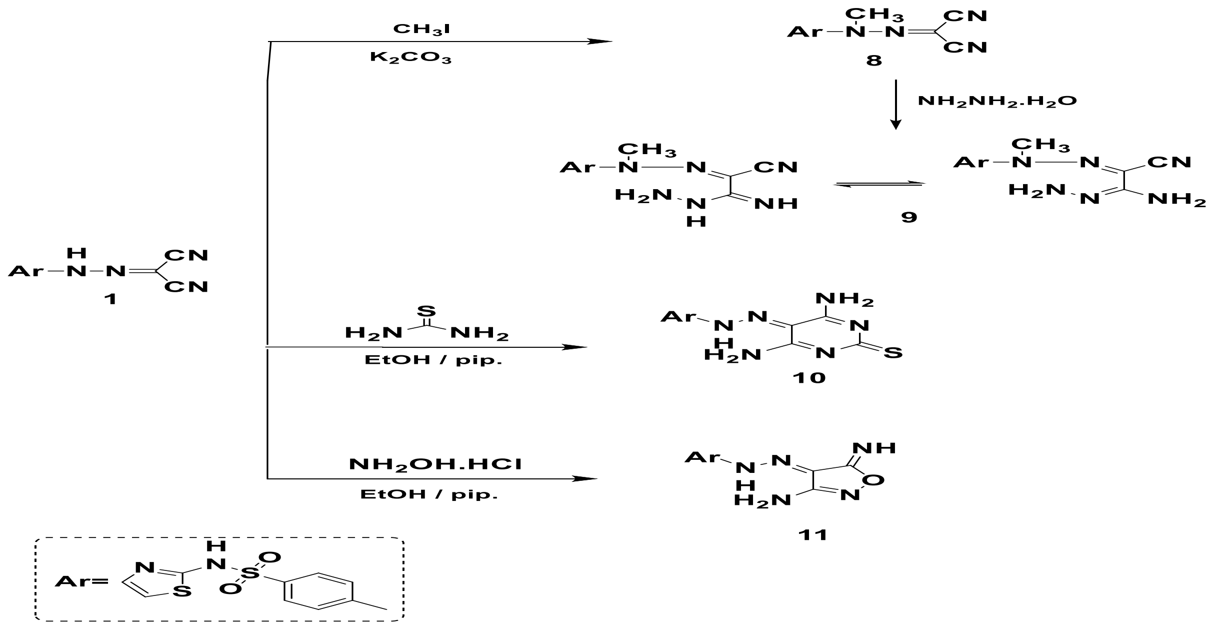
diazonium salt **3,** which reacted with 2-cyano-*N*-phenylacetamide (**4**) to give 2-*(*3-Amino-4-((4-(*N*-(thiazol-2-yl)sulfamoyl)phenyl)diazenyl)-1*H*-pyrazol-5-yl)diazenyl)-2-cyano-*N*-phenylacetamide (**5**). Also, diazonium salt **3** reacted with 3,5-dimethyl phenol (**6**) to afford 4-(3-Amino-5-((4-hydroxy-2,6-dimethylphenyl)diazenyl)-1*H*-pyrazol-4-yl)diazenyl)-*N*-(thiazol-2-yl)benzenesulfonamide (**7**). Structure of compounds **5** and **7** was established on the basis of elemental analysis and spectral data. (See experimental part).

Moreover, the significant biological and medicinal activities of the arylhydrazones of α-cyanoketone as antituberculosis and oxidative phosphorylation inhibitors have stimulated recent interest in the chemistry of this class of compounds. As a part of our program dealing with the synthesis and chemistry of α-cyanoarylhydrazones, we report here the synthesis of α-cyanoarylhydrazones **9** *via* treatment of hydrazine hydrate with *N*-methyl-*N*-(4-(*N*-(thiazol-2-

yl)sulfamoyl)phenyl)carbonohydrazonoyl dicyanide (**8**). The identity of compounds **8** and **9** was confirmed by their spectroscopicl data



Scheme 1. Synthetic route to pyrazolo-4,5diazenyl derivatives



Scheme 2. Synthetic route to pyrimidine and isoxazole derivatives

Furthermore, the reaction of compound **1** with different nucleophiles for example, thiourea and hydroxylamine hydrochloride afforded 4-(2-(4,6-diamino-2-thioxopyrimidin-5(*2H*)-ylidene)hydrazineyl)-*N*-(thiazol-2-yl)benzenesulfonamide (**10**) and 4-(2-(3-amino-5- iminoisoxazol-4(5*H*)-ylidene)hydrazineyl)-*N*-(thiazol-2-yl)benzenesulfonamide (**11**), individually. Structure **10** was based on the elemental analysis and spectroscopic studies. Hence, the IR spectrum of **10** showed the presence of two NH_2, two NH absorption bands at 3434-3400 cm^{-1}, C=S group at 1325 cm^{-1} and absence of CN groups. The mass spectra of compounds **10** and **11** revealed a molecular ion peaks correspond with their suggested structures.

2.2. Pharmacology

The prepared compounds were assessed against *the mentioned microrganisms as in table 1.*

Table 1. Minimal inhibitory concentration (MIC, μg/mL) and inhibition zone (mm) of the newly prepared compound

Compound No.	MIC in μg/mL, and inhibition zone (mm)				
	Bacteria			Fungi	
	Gram-positive bacteria		Gram-negative bacteria		
	B. subtilis	S. aureus	E. coli	P. aeruginosa	C. albicans
1	3.125 (40)	6.25 (37)	100 (15)	50 (19)	3.125 (36)
2	25 (27)	50 (15)	100 (15)	100 (16)	6.25 (28)
5	12.5 (32)	6.25 (38)	100 (15)	50 (19)	6.25 (30)
7	6.25 (37)	6.25 (37)	100 (15)	100 (15)	12.5 (32)
8	6.25 (38)	6.25 (37)	100 (15)	50 (19)	50 (20)
9	6.25 (38)	6.25 (37)	100 (15)	50 (19)	100 (16)
10	3.125 (40)	6.25 (37)	100 (15)	50 (19)	50 (20)
11	3.125 (41)	6.25 (38)	100 (15)	50 (19)	100 (16)
Chloramphenicol	3.125 (44)	3.125 (44)	6.25 (37)	6.25 (38)	NT
Cephalothin	6.25 (36)	6.25 (37)	6.25 (38)	6.25 (37)	NT
Cycloheximide	NT	NT	NT	NT	3.125 (42)

MIC: Minimal inhibitory concentration, values with SEM = 0.02 (The lowest concentration that inhibited the bacterial growth).

NT: Not tested.

The data were found according to the previously reported method [26-28].From table 1, in general, most of prepared compounds shown better activity against the Gram positive rather than Gram-negative bacteria.

structure–activity relationships (SAR`s):

- The structure of sulfathiazole is important for the broad spectrum of antimicrobial activity

- It is great attention to introduce electron-withdrawing group such as CN increases biological activity.

- In this view, the highest antimicrobial activity was shown by compounds **1**, **10** and **11** while the other compounds showed weak–moderate antimicrobial activity.

3. Experimental Methods

All spectroscopic data were recorded according to the methods previously reported [27]. Synthesis of 4-((3,5-diamino-1*H*-pyrazol-4-yl)diazenyl)-*N*-(thiazol-2-yl)benzenesulfonamide (**2**) and *N*-(4-(*N*-(thiazol-2-yl)sulfamoyl)phenyl)carbonohydrazonoyl dicyanide (**1**) according to the previously literature procedure [25].

General procedure for synthesis of compounds 5, 7:

Diazonium salt of **2** (10 mmol) was added dropwise in an ice cold solution of malononitrile, 2-cyanoacetohydrazide, *N*-phenyl acetamide and 3,5- dimethyl phenol (10 mmol) in pyridine and stirred for 1 hour, the reaction mixture cooled and the resulting solid was collected by filtration and recrystallized from ethanol.

2-((3-Amino-4-((4-(N-(thiazol-2-yl)sulfamoyl)phenyl)diazenyl)-1H-pyrazol-5-yl)diazenyl)-2-cyano-N-phenylacetamide (5)

Red powder; Yield (83%); mp 255-260 ^{0}C; IR (KBr) ν_{max}.cm^{-1}: 3444-3300 for NH_2, 3NH, 2220 (CN) 1678 (CO), 1565 for 2(N=N) groups. ^{1}H NMR (DMSO-d$_6$): δ_H ppm, 3.97 (s, 1H, CHCN), 6.27 (s, 2H, NH_2), 6.81 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.17-7.53 (m, 5H, Ar-H), 7.21 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.73 (d, 2H, Ar-H, *J*=8.5), 7.79 (d, 2H, Ar-H, *J*=8.5), 10.02 (s,1H, NHCO), 12.64 (s,1H, $NHSO_2$), 13.27 (s, 1H NH pyrazole ring). ^{13}C NMR (100 MHz, DMSO-d6): δ_C ppm, 54.5, 87.4, 112.3, 114.9, 121.7, 127.4, 128.9, 129.4, 130.6, 131.9, 137.5, 138.6, 139.8, 145.7, 152.8, 168.4, 171.9. MS: *m/z* (%) 535 (M^+, 0.8), 241 (6), 215 (7), 160 (40), 94 (24), 45 (100). Anal.Calcd for $C_{21}H_{17}N_{11}O_3S_2$ (535.56): C, 47.10; H, 3.20; N, 28.77%. Found, C, 47.19, H, 3.22, N, 28.83%.

4-(3-Amino-5-((4-hydroxy-2,6-dimethylphenyl)diazenyl)-1H-pyrazol-4-yl)diazenyl)-N-(thiazol-2-yl)benzenesulfonamide (7)

Red powder; Yield (78%); mp 245-250 ^{0}C; IR (KBr) ν_{max}.cm^{-1}: 3445, 3330 for NH_2, 2NH, 3300 for OH, 1550-1600 for 2(N=N) groups. ^{1}H NMR (DMSO-d$_6$): δ_H ppm, 2.36 (s, 6H, 2CH_3), 6.27 (s, 2H, NH_2), 6.60 (d, 2H, phenol ring), 6.81 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.21 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.73 (d, 2H, Ar-H, *J*=8.5), 7.79 (d, 2H, Ar-H, *J*=8.5), 9.19 (s, H, OH), 12.64 (s, 1H, $NHSO_2$), 13.27(s, 1H, NH pyrazole ring).^{13}C NMR (100 MHz, DMSO-d$_6$): δ_C ppm, 18.6, 87.8, 111.8, 112.2, 119.8, 127.4, 129.2, 131.9, 137.1, 138.4, 139.8, 145.7, 152.8, 156.4, 171.8. MS: *m/z* (%): 497 (M$^+$, 0.8), 394 (7), 284 (19), 259 (23), 151 (14), 109 (63), 91 (33), 85 (100), 42 (95). Anal.Calcd for $C_{20}H_{19}N_9O_3S_2$ (497.55): C, 48.28; H, 3.85; N, 25.34%. Found, C, 48.32, H, 3.80, N, 25.33%.

N-Methyl-N-(4-(N-(thiazol-2-yl)sulfamoyl)phenyl)carbonohydrazonoyl dicyanide (8)

To a solution of compound **7 (**0.3g, 1 mmol), in ethanol (25ml), K_2CO_3 (0.137g, 1 mmol) stirring for 1 hour and then add (0.14 ml, 1 mmol) of CH_3I, left the solution stirred for 12 hrs. The reaction mixture, then poured into crushed ice and little drops of HCl for acidification, the resulting solid was filtered off and recrystallized from ethanol to form compound **8.** Yellow powder; Yield (76%); mp 240-245 ^{0}C; IR (KBr) ν_{max}.cm^{-1}: 3300 for NH, 2232 (2CN), 1565-1600 for (N=N) and 1601 (C=N) groups. ^{1}H NMR (DMSO-d6):, δ_H ppm, 3.35 (s, 3H, CH_3), 6.81 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.21 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.73 (d, 2H, Ar-H, *J*=8.5), 7.79 (d, 2H, Ar-H, *J*=8.5), 12.45 (s, 1H, $NHSO_2$). ^{13}C NMR (100 MHz, DMSO-d6): δ_C ppm, 34.4, 84.6, 112.5, 127.6, 128.8, 130.1, 137.2, 147.2, 171.8. MS: *m/z* (%): 346 (M$^+$, 3.3), 332 (14), 283 (11), 267 (8), 200 (10), 191 (18), 156 (42), 93 (100), 80 (34).Anal.Calcd for $C_{13}H_{10}N_6O_2S_2$ (346.38) C, 45.08; H, 2.91; N, 24.26%. Found, C, 45.09, H, 2.95, N, 24.31%.

2-Amino-2-hydrazineylidene-N-methyl-N-(4-(N-(thiazol-2-yl)sulfamoyl)phenyl) acetohydrazonoyl cyanide (9)

To a solution of compound **8** (0.3g, 1 mmol), in ethanol (25ml), add hydrazine hydrate (0.05ml, 1 mmol), the reaction mixture was refluxed for 4 hours, then the reaction left to cool , poured into ice water, the precipitate, collected, , filtered, dried and recrystallized from EtOH/DMF to yield compound **9**. Orange powder; Yield (77%); mp. 255-260 ^{0}C; IR (KBr) ν_{max}.cm^{-1}: 3443, 3410 (2NH_2), 3333 (NH), 2215 (CN). ^{1}H NMR (DMSO-d6): δ_H ppm, 3.34 (s, 3H, CH_3), 5.80 (s, 2H, NH_2), 6.54 (s, 2H, NH_2), 6.81 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.21 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.73 (d, 2H, Ar-H, *J*=8.5), 7.79 (d, 2H, Ar-H, *J*=8.5), 12.46 (s, 1H, $NHSO_2$). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ_C ppm, 36.8, 108.6, 112.2, 114.8, 115.2, 129.3, 130.2, 137.3, 147.4, 152.9, 171.8. MS: *m/z* (%): 378.14 (M$^+$, 8), 336 (31), 314 (32), 275 (31), 257 (80), 152 (59), 110 (53), 83 (100). Anal.Calcd. for $C_{13}H_{14}N_8O_2S_2$ (378.43): C, 41.26; H, 3.73; N, 29.61%. Found C, 41.28; H, 3.77; N, 29.64%.

General procedure for the synthesis of 10 and 11:

To a solution of compound **2** (0.3g, 1 mmol), in ethanol (25ml), add thiourea (0.076g, 1 mmol) and hydroxyl amine HCl (0.07g, 1 mmol) containing a catalytic amount of pipridine (5 drops), the reaction mixture was refluxed for 4 hour. Then the reaction left to cool, poured into ice water, the precipitate, collected, filtered, dried and recrystallized from EtOH/few drops of DMF to yield **10** and **11,** respectively.

4-(2-(4,6-Diamino-2-thioxopyrimidin-5(2H)-ylidene)hydrazineyl)-N-(thiazol-2-yl) benzenesulfonamide (10)

Brown powder; Yield (68%); mp. 255-260 ^{0}C; IR (KBr) ν_{max}.cm^{-1}: 3434-3400, 1325 for (2NH_2), (2NH) and C=S groups, respectively. ^{1}H NMR (DMSO-d$_6$): δ_C ppm, 6.58 (s, 2H, NH_2), 6.61 (s, 2H, NH_2), 6.81 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.21 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.73 (d, 2H, Ar-H, *J*=8.5), 7.79 (d, 2H, Ar-H, *J*=8.5), 12.45 (s, 1H, $NHSO_2$), 12.86 (s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d6): δ_C ppm, 112.2, 116.8, 129.1, 130.6, 137.2, 138.3, 147.4, 162.8, 171.8, 230.0. MS: *m/z* (%):

408 (M^+, 1), 397 (11), 353 (17), 285 (19), 258 (27), 257 (62), 168 (20), 55 (92), 43 (100). Anal.Calcd. for $C_{13}H_{12}N_8O_2S_3$ (408.47): C, 38.23; H, 2.96; N, 27.43%. Found, C, 38.28; H, 2.93; N, 27.42%.

4-(2-(3-Amino-5-iminoisoxazol-4(5H)-ylidene)hydrazineyl)-N-(thiazol-2-yl) benzenesulfonamide (11)

Deep orange powder; Yield (73%); mp. 245-250 ^{0}C; IR (KBr) ν_{max}.cm^{-1}: 3444-3300, 1633 for NH_2, 3NH and N=N groups, respectively. ^{1}H NMR (DMSO-d$_6$): δ_C ppm, 6.62 (s, 2H, NH_2), 6.81 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.21 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.73 (d, 2H, Ar-H, *J*=8.5), 7.79 (d, 2H, Ar-H, *J*=8.5), 9.68 (s, 1H, NH isoxazole), 12.44 (s, 1H, $NHSO_2$), 12.87 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ_C ppm , 112.3, 116.8, 129.8, 130.2, 136.9 137.2, 147.4, 151.8, 158.9, 171.9. MS: *m/z* (%): 365, (M^+, 8), 244 (9), 239 (16), 229 (15), 207 (21), 119 (40), 97 (91), 66 (100). Anal.Calcd. for $C_{12}H_{11}N_7O_3S_2$ (365.39) C, 39.45; H, 3.03; N, 26.83%. Found, C, 39.47; H, 3.10; N, 26.86%.

Antimicrobial Studies

The antimicrobial evaluation was carried out according to the previously literature procedure [29].

In summary, the present work was a study to prepare and estimate the antimicrobial activity of some new sulphathiazole derivatives. From the activity data, compounds **10** and **11** displayed the highest antibacterial inhibition.

4. References

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