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synthesis and antimicrobial evaluation of some new pyrazolo[1,5-*a*]pyrimidine and pyrazolo[1,5-*a*]quinazoline derivatives bearing sulfathiazole nucleus

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Abstract Treatment of 4-((3,5-diamino-1*H*-pyrazol-4-yl)diazenyl)-*N*-(thiazol-2-yl)benzenesulfonamide (**1**) with malononitrile, 2-(ethoxymethylene)malononitrile, ethyl 2-cyano-3-ethoxyacrylate and diethyl 2-(ethoxymethylene)malonate afforded pyrazolo[1,5-*a*]pyrimidine derivatives **2-5**. Also, compound **1** was react with ethyl 3,5-diphenylcyclohexanone-2-acetate **(6)** afford pyrazolo[5,1-*b*]quinazoline derivative **7**. Moreover, the reaction of aminopyrazole **1** with enaminones **8**, **10** in glacial acetic acid gave pyrazolo[1,5-*a*]pyrimidine derivative **9** and pyrazolo[1,5-*a*]quinazoline derivative **11**. Furthermore, the reaction of aminopyrazole **1** with enaminonitriles **12**, **14** gave pyrazolo[1,5-*a*]pyrimidine derivatives **13** and **15**, respectively. The newly prepared compounds were screened for their biological evaluation as antimicrobial activities**.**

keywords: Sulphathiazole; Benzenesulfonamide ; Pyrazolopyrimidine; Biological activity.

1.Introduction

Sulfathiazole and its related compounds are biologically active derivatives [1-4]. Sulfathiazole compounds have broad spectrum of biological activity [5]. Sulfathiazole is one the most potent sulfonamides and is a typical example of bacteriostatic drug family, which acts as inhibitor to p-aminobenzoic acid substrate for the dihydropteroate synthase enzyme, which acts as catalyst in the formation of folate intermediate [6]. Moreover pyrazole moiety has important to prepared different heterocyclic compounds with different biological applications, especially as inhibitor of protein glycation, antioxidant as well as antiviral agents [9-10].Pyrazole ring system attracted important attention as it has diverse therapeutic activities [11-20].The aim of the present work is to synthesize some new pyrazoloprimidine and sulfathiazole derivatives to form new pharmacophore for antimicrobial agents [21-24].

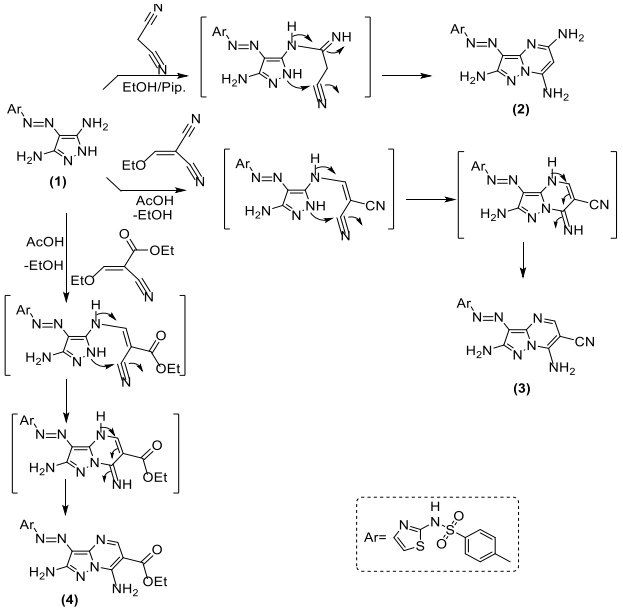
2. Results and Discussion

The above data encourage us to select 4-((3,5-diamino-1*H*-pyrazol-4-yl)diazenyl)-*N*-(thiazol-2-yl)benzenesulfonamide (**1**), 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.

Treatment of 3,5-diaminopyrazole derivative **1** with malononitrile in ethanol and a catalytic amount of piperidine afforded *N*-(thiazol-2-yl)-4-((2,5,7-triaminopyrazolo[1,5-*a*] pyrimidin-3-yl) diazenyl)benzenesulfonamide (**2**). Compound **2** was stablished based on spectral and analytical data . The ^{1}H NMR spectrum referred signals at δ 5.86, 6.57, 7.05, 7.16 and 12.53 ppm due to fused pyrimidine H-5, three NH_2 and $NHSO_2$ protons, respectively. The MS spectrum displayed m/z=430 referred to chemical structure ($C_{15}H_{14}N_{10}O_2S_2$).

Reaction of **1** with 2-(ethoxymethylene)malononitrile in glacial ethanoic acid gave 4-((2,7-diamino-6-cyanopyrazolo[1,5-*a*]pyrimidin-3-yl)diazenyl)-*N*-(thiazol-2-yl) benzenesulfonamide (**3**). Absorption bands at 3423-3268, 3233 and 2218 cm^{-1} corresponding to two amino, imino and cyano groups were shown in its IR spectrum. The ^{1}H NMR spectrum displayed singlets at δ 6.56, 7.06, 8.56 and 12.55 ppm due to two NH_2, fused pyrimidine H-5 and $NHSO_2$ protons, respectively. The MS displayed m/z=440 due to correct structure ($C_{16}H_{12}N_{10}O_2S_2$).

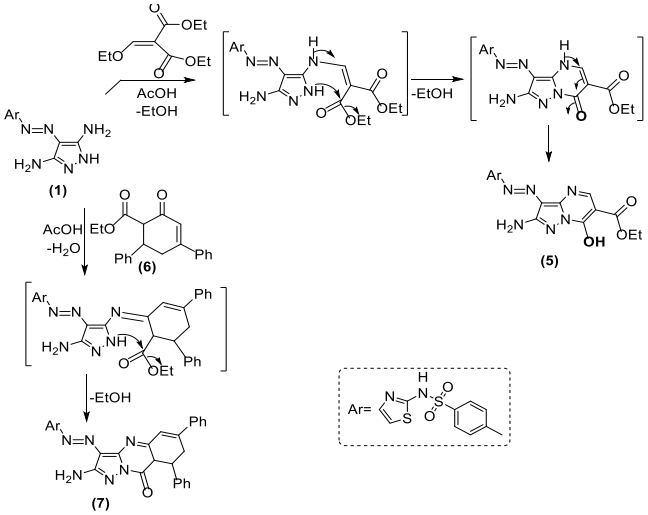
Also, reaction of compound **1** with ethyl 2-cyano-3-ethoxyacrylate in glacial ethanoic acid gave ethyl 2,7-diamino-3-((4-(*N*-(thiazol-2-yl)sulfamoyl)phenyl)diazenyl)pyrazolo[1,5-*a*] pyrimidine-6-carboxylate (**4**). The ^{1}H NMR spectrum referred signals at δ 1.23, 4.18, 6.46, 7.10, 8.76 and 12.56 ppm due to ester, two NH_2, fused pyrimidine H-5 and $NHSO_2$ protons, respectively. The MS displayed m/z=487 due to its correct structure ($C_{18}H_{17}N_9O_4S_2$).



Scheme 1. Reaction of compound **1** with bifuctional reagents.

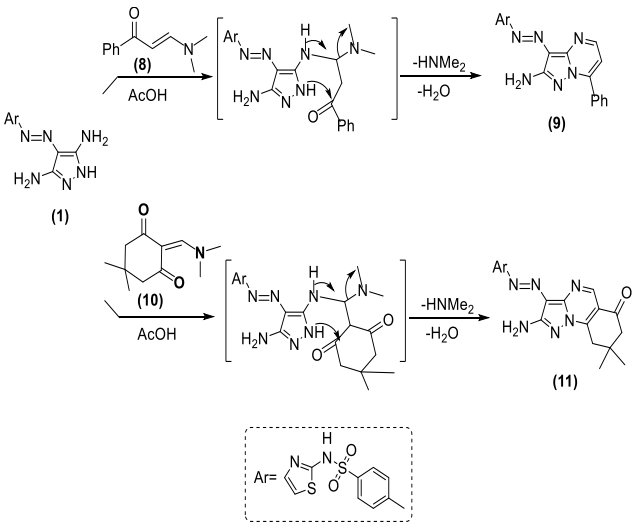
In the same manner, reaction of compound **1** with diethyl 2-(ethoxymethylene)malonate in ethanoic acid gave ethyl 2-amino-7-hydroxy-3-((4-(*N*-(thiazol-2-yl)sulfamoyl)phenyl)diazenyl) pyrazolo[1,5-*a*]pyrimidine-6-carboxylate (**5**). The IR spectrum of 5 displayed frequencies at 3487, 3421-3265, 3233 and 1728 cm^{-1} corresponding to OH, amino, NH and CO groups, respectively. It's ^{1}H NMR spectrum revealed singlet signals at δ 1.18, 4.06, 6.37, 8.61 and 12.46 ppm owing to ester, amino, pyrimidine H-5 and $NHSO_2$ protons, respectively. The MS displayed *m/z* = 488 due to the molecular formula ($C_{18}H_{16}N_8O_5S_2$).

Moreover, treatment of compound **1** with ethyl 3,5-diphenylcyclohexanone-2-acetate (**6**) to give 4-((2-amino-9-oxo-6,8-diphenyl-7,8,8a,9-tetrahydropyrazolo[5,1-*b*]quinazolin-3-yl)diazenyl)-*N*-(thiazol-2-yl)benzenesulfonamide (**7**). The IR spectrum of 7 displayed frequencies at 3421-3362, 3285 and 1676 cm^{-1} corresponding to NH_2, NH and CO groups, respectively. It's ^{1}H NMR spectrum referred singlets at δ 2.66, 3.06, 3.38, 6.54, 6.82 and 12.45 ppm due to CH_2, CHPh, methine , CH= NH_2 and $NHSO_2$ protons, respectively. MS referred at *m/z* = 620 due to the chemical structure ($C_{31}H_{24}N_8O_3S_2$).



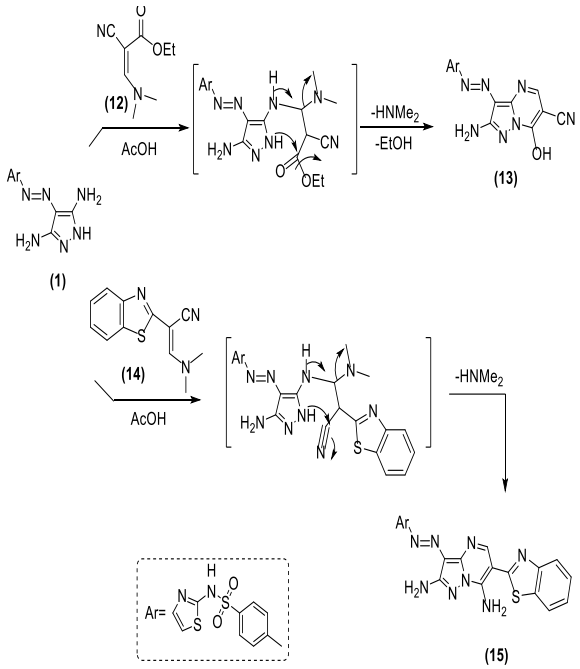
Scheme 2. Reaction of 3,5-diaminopyrazole with ethoxy diethylmalonate and β-ketoester

Moreover, the reaction of aminopyrazole **1** with either 3-(dimethylamino)-1-phenylprop-2-en-1-one (**8**) or 2-((dimethylamino)methylene)-5,5-dimethylcyclohexane-1,3-dione (**10**) in refluxing glacial acetic acid gave pyrazolo[1,5-*a*]pyrimidine derivative **9** and pyrazolo[1,5-*a*]quinazoline derivative **11**. The structures **9** and **11** were established on the basis of their correct elemental and spectral analyses. The mass spectroscopic measurements of compounds **9** and **11** revealed *m/z* = 476 (M^+, 45%) and 496 (M^+, 27%), respectively, which are in agreement with their chemical formulas.



Scheme 3. Reaction of 3,5-diaminopyrazole with enaminones

Furthermore, the reaction of aminopyrazole **1**.with.either.ethyl.2cyano3(dimethylamino)acrylate (**12**) or 2-(benzo[*d*]thiazol-2-yl)-3-(dimethylamino)acrylonitrile (**14**) in refluxing glacial acetic acid gave pyrazolo[1,5-*a*]pyrimidine derivatives **13** and **15**, respectively. The structures **13** and **15** were established on the basis of their correct elemental and spectral analyses. The infrared of **13** displayed that frequencies at 3466, 3413-3314, 3256 and 2223 cm^{-1} corresponding to OH, amino, imino and cyano functions, respectively. It's ^1H NMR spectrum displayed singlets at δ 6.81, 8.87, 12.42 and 12.83 ppm due to NH_2, fused pyrimidine H-5, $NHSO_2$ and hydroxyl protons, respectively. The mass spectrum revealed *m/z* = 441 owing to the chemical structure ($C_{16}H_{11}N_9O_3S_2$). The ^1H NMR spectrum of **15** showed singlets at δ 6.81, 6.89, 8.88 and 12.44 ppm due to two amino, pyrimidine H-5 and $NHSO_2$ protons, respectively. The MS displayed at *m/z* = 548 owing to the molecular formula ($C_{22}H_{16}N_{10}O_2S_3$).



Scheme 4. Reaction of 3,5-diaminopyrazole with enaminonitriles

2.2. Pharmacology

The synthesized 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 synthesized compounds

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	25 (27)	50 (15)	100 (15)	100 (16)	6.25 (28)
2	6.25 (38)	6.25 (37)	100 (15)	50 (19)	50 (20)
3	3.125 (45)	6.25 (38)	25 (25)	12.5(33)	3.125 (40)
4	3.125 (41)	6.25 (37)	100 (15)	100 (16)	6.25 (25)
5	3.125 (44)	6.25 (37)	100 (14)	50 (20)	25 (19)
7	12.5 (32)	50 (20)	100 (15)	100 (15)	6.25 (30)
9	6.25 (37)	6.25 (37)	100 (15)	100 (15)	12.5 (32)
11	6.25 (38)	6.25 (30)	100 (14)	100 (15)	6.25 (26)
13	3.125 (41)	6.25 (37)	100 (15)	100 (16)	6.25 (25)
15	6.25 (37)	6.25 (38)	25 (25)	100 (15)	25 (19)
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 results were obtained according to the previously reported method [26-28].From table 1, in general, most of tested compounds

displayed better activity against the Gram positive rather than Gram-negative bacteria.

structure–activity relationships (SAR`s):

The presence of a basic skeleton sulfathiazole is necessary for the broad spectrum of antimicrobial activity.

- It is interesting to point out that introducing electron-attracting group such as CN increases biological activity.

- In this view, the highest antimicrobial activity was displayed by compounds **3**, **4**, **5** and **13** 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 *N*-(thiazol-2-yl)-4-((2,5,7-triaminopyrazolo[1,5-*a*]pyrimidin-3-yl)diazenyl) benzenesulfonamide (2).

A mixture of **1** (3.64 g, 0.01 mol), malononitrile (0.66 g, 0.01 mol) in refluxing ethanol (30 mL) with few drops of pipredine (0.5mL)was refluxed 8-10 hr.The solid product obtained on cooling was recrystallized from a mixture of DMF/EtOH (1:1) to form **2**. Orange solid; 84 % yield; m.p. 270-272 ^{o}C. IR (ν_{max},cm^{-1}): 3433-3289 ($3NH_2$), 3218 (NH), 1535 (N=N); ^{1}H NMR (DMSO-d_6): δ_H ppm, 5.86 (s, 1H, pyrimidine H-5), 6.57, 7.05, 7.16 (s, 6H, $3NH_2$), 7.31 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.64 (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), 12.53 (s, 1H, $NHSO_2$); MS: *m/z* (%): 430 (M^+, 25); Anal.Calcd for $C_{15}H_{14}N_{10}O_2S_2$ (430.47): C, 41.85; H, 3.28; N, 32.54%. Found C, 41.79; H, 3.21; N, 32.52%.

Synthesis of pyrazolo[1,5-*a*]pyrimidines (3–5 and 7) : General procedure

In glacial acetic acid-ethanol mixture (30 mL, 1:1) compound **1** (3.64 g, 0.01 mol) and 2-(ethoxymethylene)malononitrile (1.22 g, 0.01 mol) or ethyl 2-cyano-3-ethoxyacrylate (1.69 g, 0.01 mol) or diethyl 2-(ethoxymethylene)malonate (2.16 g, 0.01 mol) or ethyl 3,5-diphenylcyclohexaone-2-acetate (**6**)(3.20 g, 0.01 mol) were refluxed 8-10 hr . The solid product obtained after cooling was recrystallized from a mixture of DMF/EtOH (1:1) to give compounds **3-5** and **7**.

4-((2,7-Diamino-6-cyanopyrazolo[1,5-*a*]pyrimidin-3-yl)diazenyl)-*N*-(thiazol-2-yl) benzenesulfonamide (3).

Reddish solid; 81 % yield ; m.p. 260-262 ^{o}C. IR (ν_{max},cm^{-1}): 3423-3268 ($2NH_2$), 3233 (NH), 2218 (CN), 1538 (N=N); ^{1}H NMR (DMSO-d_6): δ_H ppm, 6.56, 7.06 (s, 4H, $2NH_2$), 7.32 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.66 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.71 (d, 2H, Ar-H, *J*=8.5), 7.76 (d, 2H, Ar-H, *J*=8.5), 8.56 (s, 1H, pyrimidine H-5),12.55 (s, 1H, $NHSO_2$); MS: *m/z* (%): 440 (M^+, 36); Anal.Calcd for $C_{16}H_{12}N_{10}O_2S_2$ (440.46): C, 43.63; H, 2.75; N, 31.80% . Found C, 43.55; H, 2.70; N, 31.76%.

Ethyl 2,7-diamino-3-((4-(*N*-(thiazol-2-yl)sulfamoyl)phenyl)diazenyl)pyrazolo[1,5-*a*] pyrimidine-6-carboxylate (4).

Brownish solid; 73 % yield ; m.p. 246-248 ^{o}C. IR (ν_{max},cm^{-1}): 3468-3353 ($2NH_2$), 3254 (NH), 1718 (CO), 1539 (N=N); ^{1}H NMR (DMSO-d_6): δ_H ppm, 1.23 (t, 3H, CH_3), 4.18 (q, 2H, CH_2), 6.46, 7.10 (s, 4H, $2NH_2$), 7.33 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.65 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.74 (d, 2H, Ar-H, *J*=8.5), 7.78 (d, 2H, Ar-H, *J*=8.5), 8.76 (s, 1H, pyrimidine H-5), 12.56 (s, 1H, $NHSO_2$); MS: *m/z* (%): 487 (M^+, 16); Anal.Calcd for $C_{18}H_{17}N_9O_4S_2$ (487.51): C, 44.35; H, 3.51; N, 25.86%. Found C, 44.26; H, 3.45; N, 25.82%.

Ethyl 2-amino-7-hydroxy-3-((4-(*N*-(thiazol-2-yl)sulfamoyl)phenyl)diazenyl)pyrazolo[1,5-*a*] pyrimidine-6-carboxylate (5).

Brownish crystals; 68 % yield; m.p. > 300 ^{o}C. IR (ν_{max},cm^{-1}): 3487 (OH), 3421-3265 (NH_2), 3233 (NH), 1728 (CO), 1537 (N=N); ^{1}H NMR (DMSO-d_6): δ_H ppm, 1.18 (t, 3H, CH_3), 4.06 (q, 2H, CH_2), 6.37 (s, 2H, NH_2), 7.33 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.62 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.71 (d, 2H, Ar-H, *J*=8.5), 7.78 (d, 2H, Ar-H, *J*=8.5), 8.61 (s, 1H, pyrimidine H-5), 12.46 (s, 1H, $NHSO_2$), 12.84 (s, 1H, OH); MS: *m/z* (%): 488 (M^+, 12); Anal.Calcd for $C_{18}H_{16}N_8O_5S_2$ (488.50): C, 44.26; H, 3.30; N, 22.94%. Found C, 44.22; H, 3.27; N, 22.86%.

4-((2-Amino-9-oxo-6,8-diphenyl-7,8,8a,9-tetrahydropyrazolo[5,1-*b*]quinazolin-3-yl)diazenyl)-*N*-(thiazol-2-yl)benzenesulfonamide (7).

Orange yellow crystals; yield 80 %; m.p. 292-294 ^{o}C. IR (ν_{max},cm^{-1}): 3421-3362 (NH_2), 3285 (NH), 1676 (CO), 1533 (N=N); ^{1}H NMR (DMSO-d_6): δ_H ppm, 2.66 (m, 2H, CH_2), 3.06 (m, 1H, CHPh), 3.38 (d, 1H,CH), 6.54 (s, 1H, CH=), 6.82 (s, 2H, NH_2), 6.89-7.31 (m, 10H, Ar-H), 7.37 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.62 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.74 (d, 2H, Ar-H, *J*=8.5), 7.77 (d, 2H, Ar-H, *J*=8.5), 12.45 (s, 1H, $NHSO_2$); MS: *m/z* (%): 620 (M^+, 33); Anal.Calcd for $C_{31}H_{24}N_8O_3S_2$ (620.71): C, 59.99; H, 3.90; N, 18.05%. Found C, 59.92; H, 3.86; N, 18.00%.

General procedure for the reaction of compound 1 with enaminones and enaminonitriles

To a mixture of compound **1** (3.64 g, 0.01 mol) in glacial ethanoic acid (30 mL) and 3-(dimethylamino)-1-phenylprop-2-en-1-one (**8**) (1.75 g, 0.01 mol) or 2-((dimethylamino)methylene)-5,5-dimethylcyclohexane-1,3-dione (**10**) (1.95 g, 0.01 mol) or ethyl 2-cyano-3-(dimethylamino)acrylate (**12**) (1.68 g, 0.01 mol) or 2-(benzo[d]thiazol-2-yl)-3-(dimethylamino)acrylonitrile (**14**) (2.29 g, 0.01 mol) was added then boiled for 4 hr then left to cool. The obtained product was filtered off and recrystallization from a mixture of DMF/EtOH (1:1) to give compounds **9, 11, 13** and **15**.

4-((2-Amino-7-phenylpyrazolo[1,5-*a*]pyrimidin-3-yl)diazenyl)-*N*-(thiazol-2-yl) benzenesulfonamide (**9**).

Orange crystals; yield 86 %; m.p. 296-298 ^{o}C. IR (ν_{max},cm^{-1}): 3416-3355 (NH_2), 3275 (NH), 1536 (N=N); ^{1}H NMR (DMSO-d_6): δ_H ppm, 6.84 (s, 2H, NH_2), 7.07-7.53 (m, 5H, Ar-H), 7.33 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.61 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.72 (d, 2H, Ar-H, *J*=8.5), 7.75 (d, 2H, Ar-H, *J*=8.5), 8.91 (d, 1H, *J* = 6.2 Hz, pyrimidine H-5), 8.14 (d, 1H, *J* = 6.2 Hz, pyrimidine H-6),12.46 (s, 1H, $NHSO_2$); MS: *m/z* (%): 476 (M^+, 45); Anal.Calcd for $C_{21}H_{16}N_8O_2S_2$ (476.53): C, 52.93; H, 3.38; N, 23.51%. Found C, 52.85; H, 3.35; N, 23.44%.

4-((2-Amino-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydropyrazolo[1,5-*a*]quinazolin-3-yl)diazenyl)-*N*-(thiazol-2-yl)benzenesulfonamide (**11**).

Orange yellow crystals; yield 74 %; m.p. > 300 ^{o}C. IR (ν_{max},cm^{-1}): 3421-3338 (NH_2), 3268 (NH), 1689 (CO), 1538 (N=N); ^{1}H NMR (DMSO-d_6): δ_H ppm, 1.12 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 2.43 (s, 2H, CH_2), 2.61 (s, 2H, CH_2), 6.85 (s, 2H, NH_2), 7.32 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.64 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.73 (d, 2H, Ar-H, *J*=8.5), 7.77 (d, 2H, Ar-H, *J*=8.5), 8.41 (s, 1H, quinazoline H-5), 12.45 (s, 1H, $NHSO_2$); MS: *m/z* (%): 496 (M^+, 27); Anal.Calcd for $C_{21}H_{20}N_8O_3S_2$ (496.56): C, 50.80; H, 4.06; N, 22.57%. Found C, 50.77; H, 3.99; N, 22.53%.

4-((2-Amino-6-cyano-7-hydroxypyrazolo[1,5-*a*]pyrimidin-3-yl)diazenyl)-*N*-(thiazol-2-yl)benzenesulfonamide (13).

Yellow crystals; yield 71 %; m.p. 288-290 ^{o}C. IR (ν_{max},cm^{-1}): 3466 (OH), 3413-3314 (NH_2), 3256 (NH), 2223 (CN), 1536 (N=N); ^{1}H NMR (DMSO-d_6): δ_H ppm, 6.81 (s, 2H, NH_2), 7.31 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.63 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.73 (d, 2H, Ar-H, *J*=8.5), 7.76 (d, 2H, Ar-H, *J*=8.5), 8.87 (s, 1H, pyrimidine H-5), 12.42 (s, 1H, $NHSO_2$), 12.83 (s, 1H, OH); MS: *m/z* (%): 441 (M^+, 18); Anal.Calcd for $C_{16}H_{11}N_9O_3S_2$ (441.44): C, 43.53; H, 2.51; N, 28.56%. Found C, 43.45; H, 2.49; N, 28.50%.

4-((2,7-Diamino-6-(benzo[d]thiazol-2-yl)pyrazolo[1,5-*a*]pyrimidin-3-yl)diazenyl)-*N*-(thiazol-2-yl)benzenesulfonamide (15). Yellowish brown crystals; yield 82 %; m.p. > 300 ^{o}C. IR (ν_{max},cm^{-1}): 3421-3311 ($2NH_2$), 3282 (NH), 1538 (N=N); ^{1}H NMR (DMSO-d_6): δ_H ppm, 6.81 (s, 2H, NH_2), 6.89 (s, 2H, NH_2), 7.21-8.25 (m, 4H, Ar-H), 7.343 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.65 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.73 (d, 2H, Ar-H, *J*=8.5), 7.76 (d, 2H, Ar-H, *J*=8.5), 8.88 (s, 1H, pyrimidine H-5), 12.44 (s, 1H, $NHSO_2$); MS: *m/z* (%): 548 (M^+, 52); Anal.Calcd for $C_{22}H_{16}N_{10}O_2S_3$ (548.62): C, 48.17; H, 2.94; N, 25.53%. Found C, 48.11; H, 2.91; N, 25.44%.

In summary, synthesis of polyfunctionally substituted pyrazolo[1,5- a]pyrimidine derivatives and we expected to hybrid two valuable scaffolds (pyrazolopyrimidine and sulfathiazole) in the same molecule to get new pharmacophore for active antimicrobial agents.

4. References

1 Anacona, J. R.; Rodriguez, J. L.; Camus, (2014) *J. Spectrochim Acta Part A, 129*, 96.

2 Al-Masoudi, W. A.; Mahmood, H. Y.; Faaz, R. A.; Aledany, A. H.(2015) *Int. J. Sci. Technol*., *143*, 1.

3 Nikoofard, H.; Sargolzaei, M.; Faridbod, F. Acta (2017), Chim. Slov., *64*, 842.

4 Rouf, A.; Tanyeli, C(2015). *Eur. J. Med. Chem.* , *97*, 911.

5 Khan, F. A.; Mushtaq, S.; Naz, S.; Farooq, U.; Zaidi, A.; Bukhari, S. M.; Rauf, A.; Mubarak, M. S(2018),. Curr. Org. Chem. *22*, 818.

6 Nasr, T.; Bondock, S.; Eid, S(2014),. *Eur. J. Med. Chem. 84*, 491.

7 Petri, W. A.(2011), *Pharmacol. Basis. Therapeut. 12e*, 1463.

8 Skold, O. (2000), mechanisms and trends, Drug Resist. Updat. *3*, 155.

9 Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, (2011), A. Chem. Rev. 111, 6984.

10 Ansari, A.; Ali, A.; Asif, M. (2017), *New J. Chem. 41*, 16.

11 Steinbach, G.; Lynch, P. M.; Robin, K. S. P.; Wallace, M. H.; Hawk, E.; Gordon, G. B.; Wakabayashi, N.; Saunders, B.; Shen, Y.; Fujimura, T.; Su, L.-K.; Levin, A. B. (2000) *N. Engl. J. Med.*, *342*, 1946.

12 Uslaner, J. M.; Parmentier-Batteur, S.; Flick, R. B.; Surles, N. O.; Lam, J. S.; McNaughton, C. H. (2009), Neuropharmacology *57*, 531.

13 Friedrich, G.; Rose, T.; Rissler, K. (2002), *J. Chromatogr. B 766*, 295.

14 Hampp, C.; Hartzema, A. G.; Kauf, T. L. (2008),*Value Health 11*, 389.

15 Prakash, O.; Kumar, R.; Parkash, (2008),*V. Eur J Med Chem 43*, 435.

16 Foks, H.; Pancechowska-ksepko, D.; Kedzia, A.; Zwolska, Z.; Janowiec, M.; Augustynowicz-Kopec, E (2005),. *IL Farmaco 60*, 513.

17 Kuettel, S.; Zambon, A.; Kaiser, M.; Brun, R.; Scapozza, L.; Perozzo, R(2007),. *J Med Chem 50*, 5833.

18 Yan, R.-Z.; Liu, X.-Y.; Xu, W.-F.; Pannecouque, C.; Witvrouw, MDe Clercq E. Arch Pharm Res, (2006) *29*, 957.

19 Diana, P.; Carbone, A.; Barraja, P.; Martorana, A.; Gia, O.; Dallavia, L.; Cirrincione, G. Bioorg (2007) Med Chem Lett, 17, 6134.

20 Farag, A. M.; Mayhoub, A. S.; Barakat, S. E. Bayomi, A. H. Bioorg 2008,Med Chem 16, 881.

21 Elsherbiny, H. E.; Fadda, A. A.(2018), *J. Heterocycl. Chem. 55*, 2251.

22 Elsherbiny, H. E.; Fadda, A. A(2018.) Acta Chim. Slov., *65*, 853.

23 Khaled, S. M.; Elsherbiny, H. E. (2018) Heterocycles, , *96*, 1897.

24 Elsherbiny, H. E.; Khaled, S. M. Poly (2019)**,**Cyclic Aromatic Compound https://doi.org/10.1080/10406638.2019.1653941.

25 Elsherbiny, H. E.; Fadda, A. A.; El-Saadaney, A. M. Acta Chim. Slov. In press.

26 Rahman, A. U.; Choudhary, M. I.; Thomsen, W. J (2001);.Bioassay Techniques for drug development, the Netherlands: Harwood Academic Publishers; p 16.

27 Fadda, A. A.; Afsah, E. M.; Awad, R. S. *Eur. J. Med. Chem.* 2013, *60*, 421.

28 Abo-Melha, H.; Fadda, A. A (2012),. *J. Spectrochim. Acta Part A. 89*, 123.