PREPARATION OF SOME NOVEL 3,5-DIAMINOPYRAZOLE, PYRAZOLO-[1,5-a][1, 3, 5]TRIAZINE AND PYRAZOLO[1,5-a]-PYRIMIDINE DERIVATIVES CONTAINING SULFONAMIDO MOIETIES AS ANTIMICROBIAL AGENTS

Mohamed S. A. El-Gaby,[a]* Nadia M. Taha,[b] Jehane A. Micky,[b] Marwa A. M. Sh. El-Sharief

[a]*Department of Chemistry, Faculty of Science, Al–Azhar University at Assiut, Assiut 71524, Egypt*
[b]*Department of Chemistry, Faculty of Science (Girl's), Al–Azhar University, Nasr City, Cairo, Egypt.*

Received 10-09-2001

Abstract

Various sulfa drugs were coupled with active methylene compounds to give various hydrazones **2a-e.** The reactivity of hydrazones **2a-e** towards hydrazines was investigated. Thus , a novel series of 3, 5– diaminopyrazoles **3, 5, 6, 7a,** and **b** and **9a, b** were obtained by treatment of **2** with hydrazines. Pyrazolo[1,5-a][1,3,5] triazine derivatives **10, 11** and **12** were synthesized by interaction of aminopyra-zole **9a** with triethyl orthoformate, acetic anhydride and benzoyl chloride , respectively. When aminopyrazole **6** and **8** were allowed to react with ketene dithioacetal **13**, the novel pyrazolo[1,5-a] pyrimidine **15a,b** were obtained. Structures of the new compounds were established by their elemental analysis and spectral data. Some of the synthesized compounds were tested in vitro for their antimicrobial activity.

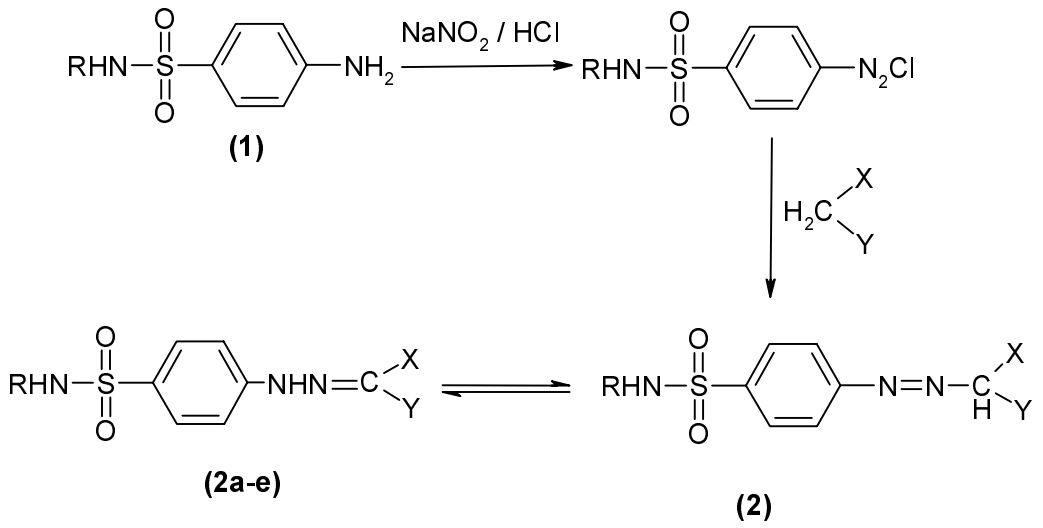
Introduction

A considerable number of sulfonamides were found to have antibacterial,[1] insulin releasing,[2] carbonic anhydrase inhibitory,[3] antiinflammatory,[4] anticancer,[5] activities. Aminopyrazoles possess a wide variety of biological activities.[6-8] Also, 3- amino or 5-aminopyrazoles are used as a starting materials for the preparation of purine analogues as pyrazolo[1,5–a]pyrimidines. Substituted pyrazolo[1,5-a]pyrimidine was synthesized as anticancer, antipyretic, hypotensive and anxiety agents.[9] In addition, pyrazolotriazines are applied as herbicides.[10] Having the above facts in mind and in continuation of our efforts to synthesize heterocyclic compounds containing sulfonamido moiety,[11-13] we were interested to prepare 3,5–diaminopyrazole, pyrazolo [1,5–a][1,3,5]triazine and pyrazolo[1,5–a]pyrimidine derivatives containing sulfona-mido moieties to investigate their antimicrobial activity of them.

Results and Discussion

Hydrazones **2a-e** were synthesized by diazotization of sulfonamides **1** at 5-10 °C in hydrochloric acid followed by coupling with active methylene compounds in the presence of sodium acetate at room temperature, Scheme (1) . On the basis of spectral data, compounds **2** exist in hydrazone form **2a-e**. The ^{1}H-NMR spectrum of **2b** recorded in deuterated dimethylsulfoxide showed a signal at δ 11.46 ppm which could be assigned to NH group, in addition to a multiple at δ 7.61-7.92 ppm which was assigned to aromatic protons and SO_2NH group.

Scheme (1)



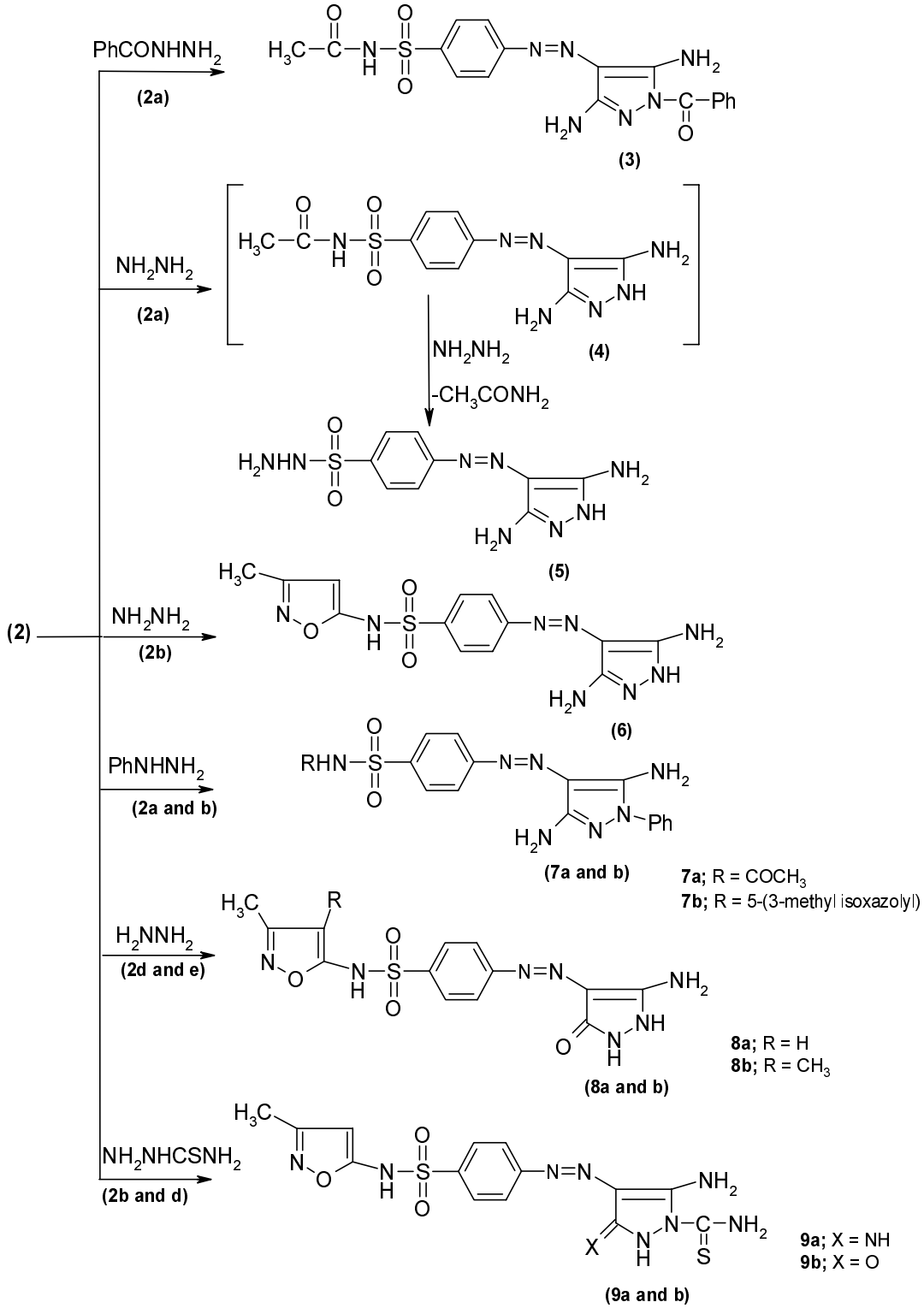
	X	Y	R
2a	CN	CN	$COCH_3$
b	CN	CN	5-(3-methyl) isoxazolyl
c	C N	CN	5-(3,4- dimethyl) isoxazolyl
d	CN	COOEt	5-(3-methyl) isoxazolyl
e	CN	COOEt	5-(3,4- dimethyl) isoxazolyl

It was reported that, β-enaminonitriles reacted with hydrazine to afford pyrazole derivatives.[14] The reactivity of the enaminonitriles **2a-e** with hydrazines (namely, benzoyl hydrazine, hydrazine, phenyl hydrazine and thiosemicarbazide) was investigated.Thus, condensation of hydrazone **2a** with benzoyl hydrazine in dioxane under reflux furnished the 3,5-diaminopyrazole derivative **3**. The structure of **3** was

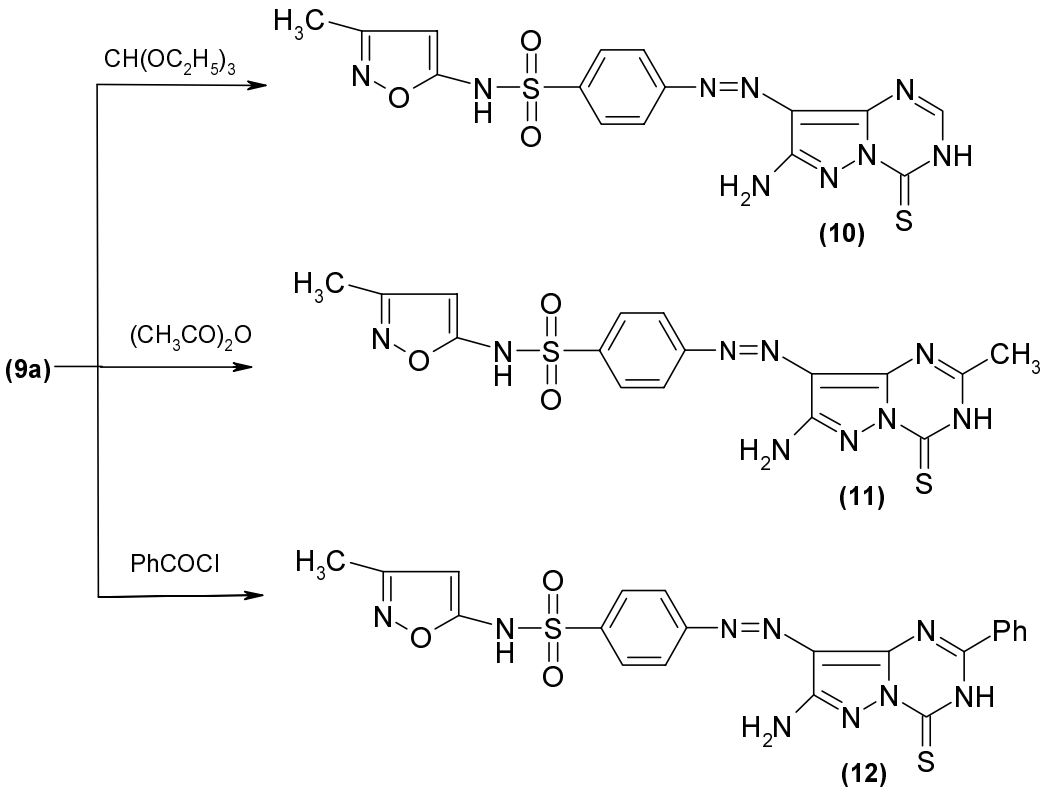
inferred from its elemental analysis and spectral data. The IR spectrum revealed characteristic bands for NH_2, C=O, N=N and SO_2 functional groups. ^{1}H-NMR spectrum of **3** in DMSO-d_6 showed a signal at δ 1.96 ppm assignable to $COCH_3$ group, a multiplet at δ 7.51- 8.01 ppm assigned for aromatic protons and amino group and a broad singlet at. δ 8.60 ppm assignable to amino group. On the other hand, when hydrazone **2a** was allowed to react with hydrazine hydrate in ethanol under reflux, the novel sulfonylhydrazide **5** was obtained. Structure of **5** was readily established on the basis of analytical and spectral data. ^{1}HNMR spectrum of **5** in DMSO–d_6 showed the absence of $COCH_3$ fragment and the presence of two broad singlet at δ 6.00–6.50 (2 NH_2) and 7.31 ppm (NH_2). The formation of **5** was proceeded via initial formation of pyrazole **4** followed by nucleophilic attack of hydrazine molecule on sulfonyl group and elimination of acetamide molecule. 3,5–Diaminopyrazole **6** was obtained by refluxing of compound **2b** with hydrazine for 5 min. Also, hydrazones **2a** and **b** were subjected to react with phenyl hydrazine to yield the novel substituted pyrazoles **7a** and **b** in good yields. 3–Amino–5– pyrazolinone derivatives **8a** and **b** were synthesized by reacting **2d** and **e** with hydrazine hydrate in ethanol. Thiosemicarbazide was reacted smoothly with hydrazones **2b** and **d** in dioxane containing a catalytic amount of triethylamine to give thiocarbamoyl derivatives **9a** and **b** Scheme (2). The mass spectrum of **9a** revealed a molecular ion peak M^+ at m/z = 421 (22%) corresponding to molecular formula $C_{14}H_{15}N_9O_3S_2$.

The starting material **9a** was proved to be a versatile starting material for the synthesis of some novel pyrazolo[1,5-a] [1,3,5]triazines. Thus, cyclocondensation of **9a** with triethyl orthoformate as carbon donor moiety under boiling condition yielded the novel pyrazolo[1,5-a][1,3,5]triazine derivative **10**. The structure **10** was proved by the presence of a signal at δ 8.21 ppm characteristic for the triazine proton in the ^{1}HNMR spectrum. Also, upon treatment of **9a** with acetic anhydride afforded the pyrazolotriazine **11**. In the same manner, **9a** reacted with benzoyl chloride in pyridine under reflux, furnishing the corresponding pyrazolotriazine derivative **12**, Scheme (3).

Scheme (2)


PhCONHNH2
(2a)
(3)
NH2NH2
(2a)
(4)
NH2NH2
-CH3CONH2
(5)
(2)
NH2NH2
(2b)
(6)
PhNHNH2
(2a and b)
(7a and b)
7a; R = COCH3
7b; R = 5-(3-methyl isoxazolyl)
H2NNH2
(2d and e)
8a; R = H
8b; R = CH3
(8a and b)
NH2NHCSNH2
(2b and d)
9a; X = NH
9b; X = O
(9a and b)

Scheme (3)

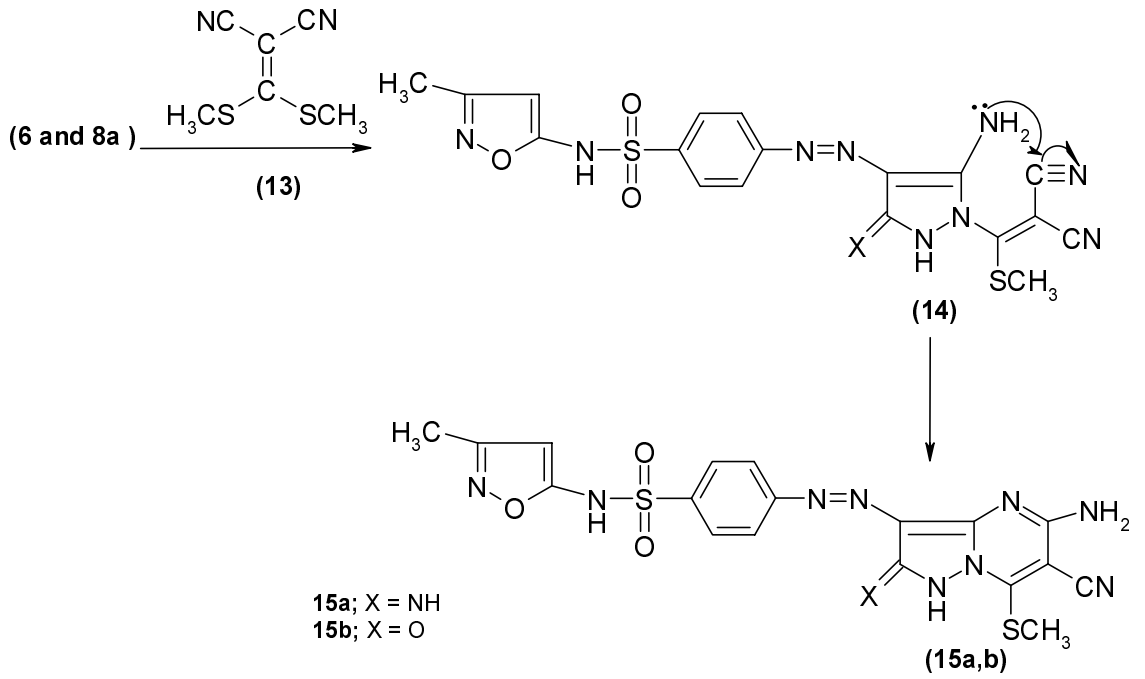


Ketene dithioacetals and related compounds are well known as useful starting materials for the synthesis of heterocycles.[15] The reactivity of aminopyrazoles **6 and 8a** towards ketene dithioacetals was also investigated. Thus, [bis(methylsulfanyl) methylidene]malononitrile **13** was reacted with aminopyrazoles **6** and **8a** under reflux in dimethylformamide in the presence of catalytic amount of triethylamine to afford the corresponding pyrazolo[1,5-a]pyrimidines **15a** and **b**. Assignment of compound **15** was proved by analytical and spectral data . ^{1}H NMR spectrum of compound **15a** in DMSO–d_6 exhibited a signal at δ 2.41 ppm assignable to methylthio group. The formation of **15** was proceeded via initial alkylation[16] at N-1 to give **14** and subsequent ring closure to yield final products **15a** and **b**, Scheme (4).

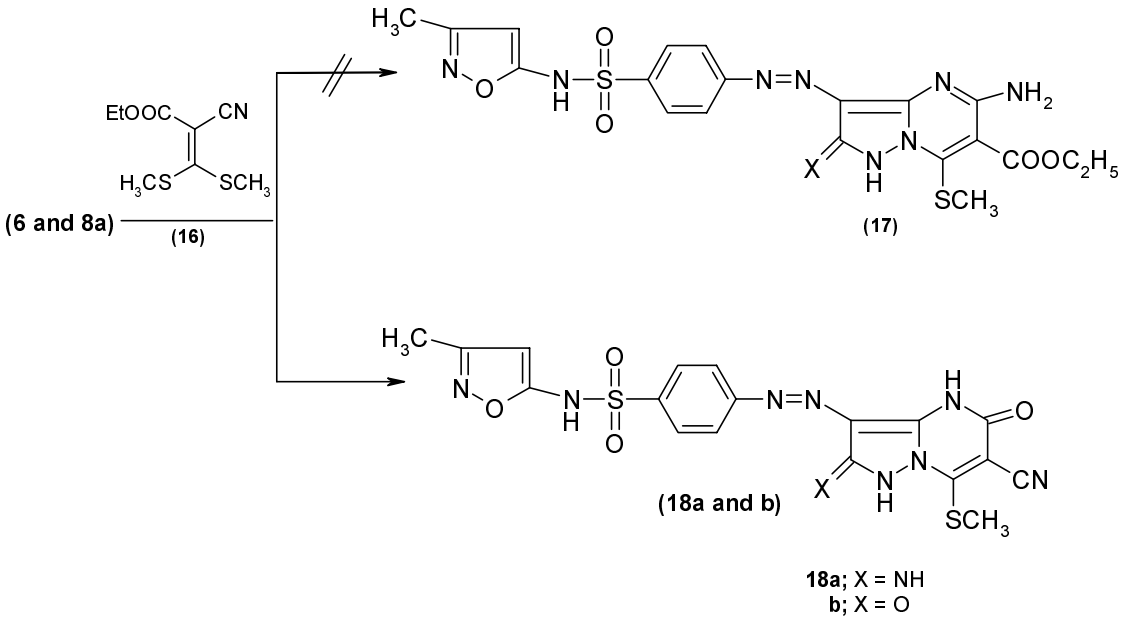
On the other hand, when aminopyrazoles **6** and **8a** were allowed to react with ethyl [bis(methylsulfanyl)methylidene]cyanoacetate **16** in dioxane containing triethyl-amine, for three products **17** and **18 a** and **b** can be formulated, Scheme (5) . on the basis of analytical and spectral data structure **17** was readily eliminated. ^{1}HNMR spectrum of

18a in DMSO–d_6 exhibited the presence of SCH_3 group and the absence of OC_2H_5 moiety.

Scheme (4)



Scheme (5)



Biological Activity

Fourteen compounds were screened in vitro for their antimicrobial activities against four strains of bacteria *Staphylococcus aureus* (NCTC-7447), *Bacillus cereus* (ATCC-14579), *Serratia marcesens* (IMRU-70), *Proteus mirabilis* (NCTC-289) and two strains of fungi *Aspergillus ochraceus Wilhelm* (AUCC-230) and penicillium chrysogenum Thom (AUCC-530) by the agar diffusion technique.[17] A 1 mg/mL solution in dimethylformamide was used. The bacteria and fungi were maintained on nutrient agar and Czapek's-Dox agar media, respectively. DMF showed no inhibition zones. The agar media were inoculated with different microorganisms culture tested. After 24h. of incubation at 30ºC for bacteria and 48 h of incubation at 28ºC for fungi, the diameter of inhibition zone (mm) was measured (Table 1). Ampicillin in a concentration 25 μg m^{-1} and Mycostatine (30 μg m^{-1}) used as a references for antibacterial and antifungal activities, respectively. The minimal inhibitory concentration (MIC) of some of the tested compounds was measured by a twofold serial dilution method.[18] The most of the synthesized compounds exhibited various antimicrobial activity towards all the microorganisms used.

Table(1): Antimicrobial activity of some synthesized compounds and inhibition zones

Compd. No.	Gram positive bacteria		Gram negative bacteria		Fungi	
	Staphyloccus aureus (NCTC 7447)	*Bacillus cereus* (ATCC-14579)	*Serratia marcesens* (IMRU-70)	*Proteus mirabilis* (NCTC-289)	*Aspergillus ochraceus Wilhelm* (AUCC-230)	*Penicillium chrysogenum Thom* (AUCC-530)
2a	++	++	++	++	+	+
2c	++	++	+++	++	++	+
3	++	+	+	++	+	+
5	+	++	++	+	+	+
6	++	++	+	++	+	+
7b	+	++	++	+	+	++
8a	++	++	++	+	+	++
8b	+++	+	++	++	+	++
9a	++	++	++	++	+	++
10	++	++	++	++	+	++
11	+++	+	++	++	+	++
12	+++	+	++	++	++	++
15a	+++	+++	++	++	+	+
18a	+++	+++	++	++	+	+
Standard	++++	++++	++++	++++	++++	++++

\+ : Less active (0.2-0.5 cm); ++ : Moderately active (0.6-1.4 cm); +++ : Highly active (1.5-3.0 cm); ++++ : Very highly active (over 3.0 cm)

Experimental

All melting points are uncorrected. IR spectra were recorded on a Shimadzu – 440 infrared spectrophotometer (ν; cm^{-1}) using the KBr technique (Shimadzu, Japan). ^{1}H-NMR spectra were measured on a Varian EM 360–90 MHz spectrophotometer (Varian, UK), (δ, ppm) using TMS as an internal standard. The mass spectra were performed by a Shimadzu GC–MS–QP 100 Ex (Shimadzu, Japan). Elemental analyses were carried out by the Microanalytical Research Center, Faculty of Science, Cairo university. The characteristics data for the prepared compounds are given in Table (2).

Formation of hydrazones (2a-e). Sulfonamide (0.01 mole) was dissolved in a mixture of concentrated HCI (7 mL) and water (5 mL) and cooled to 5- 10°C in ice bath. To a stirred mixture a cold aqueous solution of sodium nitrite (0.01 mole 5mL) was then added. The diazonium salt so obtained was filtered into a cold mixture of sodium acetate (3 gm) and active methylene compound (0.01 mole) in ethanol (30 mL). The resulting solid was washed with water (100 mL) and recrystallized from proper solvent to give **2a-e**, **Table (2).** IR **(2a)**: 3250, 3100 (NH), 2950 (CH-aliph.), 2200 (CN), 1710 (CO). IR **(2b)**: 3450, 3250 (NH), 2900 (CH-aliph.), 2200 (CN).^{1}H-NMR (**2b;** DMSO–d_6): 2.31 (s, 3H, CH_3), 6.15 (s,1H, isoxazole–H), 7.61-7.92 (m,5H, Ar–H+SO_2NH)11.46 (s, 1H. NH; exchangeable). IR **(2d)**: 3450, 3250 (NH), 2200 (CN), 1700 (CO). ^{1}HNMR (**2d**; DMSO–d_6); 1.29 (t, 3H, CH_3), 2.30 (s, 3H. CH_3), 4.32 (q,2H,OCH_2), 6.14 (s, 1H, isoxazole–H), 7.90 (m, 4H, Ar–H), 8.51 (broad, 1H, NH; exchangeable), 12.40 (s, 1H, NH; exchangeable).

1-Benzoyl–3,5-diamino-4-[4-(N-acetyl sulfamoyl)]phenylazopyrazole](3).

A solution of hydrazone **2a** (0.01 mole) and benzoyl hydrazine (0.01 mole) in dioxane (20 mL) was refluxed for 24 h, then allowed to cool and poured into cold water (50 mL). The solid product was collected and recrystallized from proper solvent to give **3**, **Table (2)**. IR: 3420, 3380 (NH_2), 1705, 1640 (CO), 1600 (N= N). ^{1}H-NMR (DMSO–d_6): 1.96 (s,3H, $COCH_3$),7.51- 8.01(m, 11H, Ar–H + NH_2), 8.60 (s, 2H, NH_2; exchangeable), 12.20 (s, 1H, NH; exchangeable).

3,5–Diamino–4–(4-sulfonylhydrazide)phenylazo-pyrazole(5). A mixture of hydrazone **2a** (0.01 mole) and hydrazine hydrate (0.012 mole) in ethanol (40 mL) was heated under reflux for 2 hr. The solid product which produce on heating was collected and recrystallized from proper solvent to give **5**, **Table (2)**. IR 3480, 3200 (NH_2), 1600 (N=N). ^{1}H-NMR (DMSO–d_6): 6.00 – 6.50 (broad, 4H , $2NH_2$; exchangeable), 7.31 (s, 2H, NH_2; exchangeable), 7.81(m, 5H, Ar–H+NH), 10.90 (s,1H, NH; exchangeable).

3,5– diamino–4-[4 -N-(3-methylisoxazolyl)sulfamoyl]phenylazo-pyrazole (6).

A mixture of hydrazone **2b** (0.01 mole) and hydrazine hydrate (0.012 mole) in ethanol (40 mL) was heated under reflux for 5 min, the solid product which formed on heating was collected and recrystallized from proper solvent to give **6**, **Table (2)**. IR 3400, 3230 (NH_2), 1610 (N=N).

3,5-diamino-1-phenyl-4-[4-(N–substituted)sulfamoyl]phenylazo-pyrazoles (7a,b) .

A mixture of hydrazone **2a** or **2b** (0.01 mole) and phenyl hydrazine (0.01 mole) in ethanol (30 mL) was refluxed for 24 hr. and then allowed to cool. The solid product was collected and recrystallized from proper solvent to give **7**, **Table (2)**. IR **(7b)**: 3475, 3369, 3272 (NH,NH_2), 2940 (CH-aliph), 1600 (N=N). ^{1}HNMR (**7b**; DMSO-d_6): 2.31 (s, 3H, CH_3), 6.19 (s, 1H, isoxazole–H), 7.34, 7.37 (2s, 4H, $2NH_2$; exchangeable), 7.52–7.95 (m, 9H, Ar–H), 11.40 (s, 1H,NH; exchangeable).

3-Amino-4–[4-(N-substituted)sulfamoyl]phenylazo-pyrazol-5-ones(8a,b). A mixture of hydrazone **2d** or **2e** (0.01 mole) and hydrazine hydrate (0.012 mole) in ethanol (40 mL) was refluxed for 24 hr, then allowed to cool and poured into cold water (50 mL) and acidified with HCl. The solid product was collected and recrystallized from proper solvent to give **8**, **Table (2)**. IR **(8a)**: 3450, 3400 (NH_2), 1680 (CO),1600 (N=N). ^{1}HNMR (**8a**;DMSO–d_6): 2.30 (s, 3H, CH_3), 5.99 (s, 2H, NH_2; exchangeable), 6.17(s,1H, isoxazole-H), 7.70–7.87 (m, 5H, Ar–H + NH), 10.80 (s, 2H, 2NH, exchangeable).

5-Amino-1-thiocarbamoyl-3-[imino(oxo)]-4-[4-N-(3-methylisoxazolyl)sulfamoyl-phenylazo-pyrazoles (9a, b). A mixture of hydrazone **2b** or **2d** (0.01 mole), thiosemicarbazide (0.01 mole) and triethylamine (0.5 mL) in dioxane (30 mL) was heated under reflux for 12 hr. The solid product which produced on heating was collected and recrystallized from proper solvent to give **9**, **Table (2)**. IR **(9a)**: 3400, 3220 (NH_2), 1600 (N=N). ^{1}HNMR (**9a**; DMSO–d_6): 2.31 (s, 3H, CH_3), 6.19 (s, 1H, isoxazole–H), 7.87- 8.00 (m, 6H, Ar–H + NH_2), 8.20 (s, 1H, SO_2NH; exchangeable), 9.80, 11.60 (2s, 4H, $2NH_2$; exchangeable). MS **(9a)**: 421 (M+; 22%), 397 (47%), 339 (31%), 312 (36%), 257 (base peak; 100%), 227 (60%), 209 (39%) and 164 (39.6%).

2-Amino-3-[4-(N-3-methylisoxazolyl)sulfamoyl]phenylazo-6,7-dihydro-7-thioxo-pyrazolo[1,5-a][1,3,5]triazine (10). A mixture of pyrazole **9a** (0.01 mole) and triethyl orthoformate (10 mL) was refluxed for 10 hr at 100^{o}C. The excess of reagent was removed and to the cold mixture was added ether. The obtained solid was filtered, dried and recrystallized from proper solvent to give **10**, **Table (2)**.IR :3430, 3370,3320,(NH,NH_2) and 1610 (N=N).^{1}HNMR (DMSO-d_6): 2.29 (s, 3H, CH_3), 6.20 (s, 1H, isoxazole-H), 7.91-7.95 (m, 6H , Ar – H+ NH), 8.40, 11.60 (2s, 2H , 2NH; exchangeable), 8.21 (s, 1H, triazine- H).

2-Amino-5-methyl-3-[4-(N-3-methylisoxazolyl)sulfamoyl]phenylazo-6,7-dihydro-7- thioxo-pyrazolo[1,5-a][1,3,5]triazine (11). Compound **9a** (0.01 mole) was refluxed in acetic anhydride (10 mL) for 3 hr, then allowed to cool. The solid product was collected and recrystallized from proper solvent to give **11**, **Table (2)**. IR: 3432, 3309, 3141 (NH, NH_2), 2985 (CH - aliph), 1604 (N= N). ^{1}HNMR (DMSO–d_6): 2.19, 2.26 (2s, 6H, $2CH_3$), 6.14 (s, 1H, isoxazole-H), 7.40–7.91 (m, 6H, Ar–H + NH), 9.80, 11.20 (2s, 2H, 2NH; exchangeable) .

2- Amino-5-phenyl-3-[4-N-(3–methylisoxazolyl)sulfamoyl]phenylazo- 6,7 dihydro-7-thioxo-pyrazolo[1,5-a][1,3,5]triazine(12). A mixture of **9a** (0.01 mole) and benzoyl chloride (0.01 mole) in pyridine (15 mL) was refluxed for 12 hr and then allowed to

cool. The solid product was collected and recrystallized from proper solvent to give **12**, **Table (2)**. IR: 3410, 3320 (NH_2), 1600 (N=N).

5-Amino-7-methylsulfanyl-3-[4-N-(3-methylisoxazolyl)sulfamoyl]phenylazo-2-imino(or oxo)- 1,2- dihydro-pyrazolo[1,5–a]pyrimidin-6- carbonitriles (15a ,b).

To a suspension of **6** or **8 a** (0.01 mole) and [bis(methylsulfanyl) methylidene]-malononitrile **13** (0.01 mole) in dimethylformamide (20 mL), (0.5mL) of triethylamine was added. The mixture was refluxed for 3 h. and then allowed to cool. The precipitated material was isolated by suction and recrystallized from proper solvent to give **15**, **Table (2)**: IR **(15a)**: 3400, 3200 (NH_2), 2200 (CN), 1600 (N=N). ^{1}HNMR **(15a)** (DMSO-d*6*): 2.31 (s, 3H, CH_3), 2.41 (s, 3H, SCH_3), 3.71 (broad, 2H ,NH_2), 6.19 (s, 1H, isoaxzole-H), 7.81–8.00 (m, 6H, Ar–H+NH_2), 11.80 (broad, 1H. NH; exchangeable). MS **(15a)**: 487 (M^+, 26%), 484 (36%), 464 (base peak ; 100%), 411 (29%), 386 (50.7%), 377 (52%), 364 (40%) and, 350 (55%). IR **(15b)**: 3450, 3300 (NH_2), 2200 (CN), 1670 (CO), 1600 (N=N).

7-Methylsulfanyl-3-[4-N-(3-methylisoxazolyl)sulfamoyl]phenylazo-2-imino(or oxo) -1,2,4,5-tetrahydro-5-oxo-pyrazolo[1,5-a]pyrimidin-6-carbonitriles(18a,b).

To a mixture of the compound **6** or **8a** (0.01 mole) and ethyl [bis (methylsulfanyl) methylidene] cyanoacetate **16** (0.01 mole) in dioxane (20 mL), three drops of triethylamine were added. The resulting mixture was refluxed for 4 hr and then allowed to cool at room temperature and diluted with water (30 mL). The solid product so formed was collected by filtration and recrystallized from proper solvent to give **18**, **Table (2)**. IR **(18a)**: 3320, 3150 (NH_2), 2950 (CH–aliph), 2210 (CN), 1660 (CO). ^{1}HNMR (**18a**; DMSO –d_6): 2.31 (s.3 H , CH_3), 2.61 (s, 3H , SCH_3), 4.01 (broad, 2H, NH_2), 6.91 (s, 1H, isoxazole–H), 7.90–7.98 (m, 5H, Ar–H+NH), 11.51 (s, 1H, NH; exchangeable). MS **(18a)**: 485 (M^+ ; 30%). IR **(18b)**: 3400, 3200 (NH_2), 2200 (CN), 1650 (broad CO).

Table (2) : Characteristics data for the prepared compounds

Compd. No.	M. p [C°]	Yield %	Solv. Cryst.	Mol. Formula (Mole. Wt)	Elemental analysis Calcd./Found C	H	N
2a	183-4	82	Ethanol	$C_{11}H_9N_5O_3S$ (291)	45.36 45.30	3.11 3.10	24.05 24.00
2b	225-6	85	Ethanol	$C_{13}H_{10}N_6O_3S$ (330)	47.27 47.20	3.05 3.00	25.45 25.30
2c	170-1	75	Ethanol	$C_{14}H_{12}N_6O_3S$ (344)	48.84 48.70	3.51 3.50	24.42 24.50
2d	220-2	90	Ethanol	$C_{15}H_{15}N_5O_5S$ (377)	47.75 47.60	4.00 3.90	18.57 18.50
2e	150-2	87	Ethanol	$C_{16}H_{17}N_5O_5S$ (391)	49.11 49.10	4.38 4.20	17.90 17.80
3	185-6	80	Ethanol	$C_{18}H_{17}N_7O_4S$ (427)	50.59 50.50	4.00 3.90	22.94 22.90
5	250-2	74	Dioxane	$C_9H_{12}N_8O_2S$ (296)	36.49 36.50	4.08 4.10	37.81 37.80
6	220-1	84	Dioxane	$C_{13}H_{14}N_8O_3S$ (362)	43.09 43.10	3.89 3.80	30.92 30.90
7a	255-6	80	Ethanol	$C_{17}H_{17}N_7O_3S$ (399)	51.13 51.20	4.29 4.10	24.56 24.50
7b	100-2	76	Ethanol	$C_{19}H_{18}N_8O_3S$ (438)	52.06 52.10	4.14 4.20	25.57 25.60
8a	240-1	75	Ethanol	$C_{13}H_{13}N_7O_4S$ (363)	42.98 42.90	3.61 3.40	26.99 26.80
8b	243-4	77	Ethanol	$C_{14}H_{15}N_7O_4S$ (377)	44.56 44.60	4.01 3.90	25.99 25.90
9a	180-2	92	Dioxane	$C_{14}H_{15}N_9O_3S_2$ (421)	39.91 39.80	3.59 3.50	29.91 29.90
9b	150-2	87	Benzene	$C_{14}H_{14}N_8O_4S_2$ (422)	39.81 39.80	3.34 3.30	26.52 26.50
10	110-3	60	Ethanol	$C_{15}H_{13}N_9O_3S_2$ (431)	41.76 41.70	3.04 3.10	29.22 29.20
11	198-9	65	DMF	$C_{16}H_{15}N_9O_3S_2$ (445)	43.15 43.20	3.39 3.40	28.30 28.30
12	>300	67	Ethanol	$C_{21}H_{17}N_9O_3S_2$ (507)	49.71 49.60	3.38 3.30	24.84 24.70
15a	210-1	64	Ethanol	$C_{18}H_{16}N_{10}O_3S_2$ (484)	44.63 44.60	3.33 3.30	28.91 28.80
15b	190-1	76	Ethanol	$C_{18}H_{15}N_9O_4S_2$ (485)	44.54 44.50	3.11 3.10	25.96 25.90
18a	180-2	74	Ethanol	$C_{18}H_{15}N_9O_4S_2$ (485)	44.54 44.60	3.11 3.10	25.96 25.90
18b	210-2	73	Ethanol	$C_{18}H_{14}N_8O_5S_2$ (486)	44.45 44.30	2.90 2.70	23.03 23.10

References

1. A. K. Gadad, C. S. Mahajanshetti, S. Nimbalkar, A. Raichurkar, *Eur. J. Med. Chem.* **2000**, *35*, 853.

2. T. H. Maren , *Ann . Rev. Pharmaco. Toxic.* **1976**, *16*, 309.
3. C. T. Surpuran, A. Scozzafava, B .C. Jurca, M. A. Liies, *Eur. J. Med. Chem.,* **1998**, *33* , 83.
4. J. J. Li, Q. D, Anderson, E. G. Burton, J. N. Cogburn , J. T. Collins, D. J. Garland, S. A. Gregory, H. C. Huang, P. C. Isakson, C. M. Koboldt, E. W. Logusch, M. B. Norton, W. E. Perkins, E. J. Reinhard, K. Seibert, A. W. Veenhuizen, Y . Zang, D. B. Reitz, *J. Med. Chem.* **1995**, *38*, 4570.
5. S. M. Sondhi, M. Johar, N. Singhal, S. G. Dastidar, R. Shukla, R. Raghubir, *Monatshefte Für Chemie* **2000**, *131*, 511.
6. G. Turan– Zitouni, P. Chevallet, F. S. Kilic, K. Erol, *Eur. J. Med . Chem* **2000**, *35*, 635.
7. S. G. Kücükgüzel, S. Rollas, H. Erdeniz. M. Kiraz. A. C. Ekinci, A. Vidin, *Eur. J. Med. Chem.* **2000,** *35*, 761.
8. M. H Elnagdi, N. Al-awdi, A. W. Erian , *"Comprehensive Heterocyclic Chemistry"* 2nd ed; A. R. Katritzki, C. W. Rees, **1996**, Vol. 7, Elsevier Ltd , Oxford , UK , P 431.
9. M. H. Elnagdi, M. R. H . Elmoghayar, G. H. Elgemeie , *Adv . Heterocylic Chem* **1987**, *41*, 320.
10. D. Caetwright, J .D. Collins, U. Smith, L. Philip. *(Imperical Chem. industries Ltd.) S. African*, 7901, 138 ; *Chem. Abstr* . **1981,** *94*, 1751736 **.**
11. M. S. A. El-Gaby, *Phosphorus, Sulfur and Silicon* **2000**, *156*, 157.
12. M. S. A. El-Gaby, A. A. Atalla, A. M. Gaber, K. A. Abd Al-Wahab, *IL Farmaco* **2000**, *55*, 596.
13. M. S. A. El-Gaby, A. Z. Sayed, F .A. Abu–Shanab, A. M. Hussein, *Phosphorus, Sulfur and Silicon* **2000,** *164*, 1.
14. M. H. Elnagdi, E. M. Kandel, H. A. Elfaham, *J . Heterocycl . Chem.* **1980**, *17*, 73.
15. M. Yokoyama, H. Togo, S. Konda, *Sulf . Reports* **1990**, *10*, 23.
16. M. A. Zahran, A. M. Sh. El- Sharief, M. S. A. El-Gaby, Y. A. Ammar, U. H. El-Said, *IL Farmaco* **2001**, *56*, 277.
17. L. P. Carrod and F. D. Grady, *Antibiotic and Chemotherapy*, 3rd ed., Churchill livingestoner Edinburgh, **1972,** 477.
18. Pcourvalin, interpretive reading antimicrobial susceptibility tests, *Am. Soc., Microbial. News* **1992**, *85*, 368-375.

Povzetek

Vrsto sulfa zdravil smo pustili reagirati s spojinami z aktivirano metilensko skupino in pripravili hidrazone **2a-e** in preverili njihovo reaktivnost s hidrazini. Opisali smo tudi druge pretvorbe. Nekatere pripravljene spojine so bile testirane in vitro za morebitno antimikrobno delovanje.