A novel route to synthesis of substituted pyrazoles, oxoalkanonitrile and glyoxalonitrile containing sulfa drug moieties

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Estudios con arilhidrazono-3-oxopropanales: Una nueva ruta de síntesis de pirazoles substituidos, oxoalcanonitrilo y glioxalonitrilo que contienen fragmentos farmacológicos sulfa

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Recibido: 20 de enero de 2008; aceptado: 11 de marzo de 2008

RESUMEN

El acoplamiento de las enaminonas 1 con sales de diazonio da los hidrazonopropanales 3a-h. El compuesto 3 reacciona con ω-bromoacetofenona o α-cloroacetanilida rindiendo 5 y 8. Estos compuestos se ciclan suavemente, dando 6 y 9 respectivamente. Por reacción con fenilhidrazina se obtienen las difenilhidrazonas 10, que ciclan a los arilazopirazoles 11 en piridina a reflujo. Sin embargo, la reacción de 3c-f con hidrato de hidrazina rinde los pirazoles 12. La reacción de 3 con hidrocloruro de fenilhidrazina da 11. Finalmente, la reacción de 3c con hidrocloruro de hidroxilamina rinde la aldoxima 14, que por calefacción en piridina a reflujo da 15 en lugar de 16.

Palabras clave: **Arilhidrazono-3-oxopropanales. Pirazoles. Oxoalcanonitrilo. Glioxalonitrilo.**

SUMMARY

Coupling of enaminones 1 with diazonium salts gave the hydrazonopropanals 3a-h. Compound 3 react with ω-bromoacetophenone or α-chloroacetanilide to yield 5 and 8. These compounds were cyclized smoothly into 6 and 9 respectively. Reactions of 3 with phenylhydrazine gave diphenylhydrazones 10 which cyclized into arylazopyrazoles 11 in refluxing pyridine. However reaction of 3c-f with hydrazine hydrate afforded pyrazoles 12. Reactions of 3 with phenylhydrazine hydrochloride afforded 11. Finally, reactions of 3c with hydroxylamine hydrochloride afforded the aldoxime 14 that on refluxing in pyridine gave 15 not 16.

Key words: **Arylhydrazono-3-oxopropanals. Pyrazoles. Oxoalkanonitrile. Glyoxalonitrile.**

RESUM

L'acoblament de les enaminones 1 amb sals de diazoni dóna els hidrazonopropanals 3a-h. El compost 3 reacciona amb ω-bromoacetofenona o α-cloroacetanilida rendint 5 i 8. Aquests compostos es ciclitzen suaument donant 6 i 9 respectivament. Per reacció amb fenilhidrazina s'obtenen les difenilhidrazones 10, que ciclitzen als arilazopirazoles 11 en piridina a reflux. Això però, la reacció de 3c-f amb hidrat d'hidrazina rendeix els pirazoles 12. La reacció de 3 amb hidroclorur de fenilhidrazina dóna 11. Finalment, la reacció de 3c amb hidroclorur d'hidroxilamina rendeix l'aldoxima 14, que per calefacció en piridina a reflux dóna 15 enlloc de 16.

Mots clau: **Arilhidrazono-3-oxopropanals. Pirazoles. Oxoalcanonitril. Glioxalonitril.**

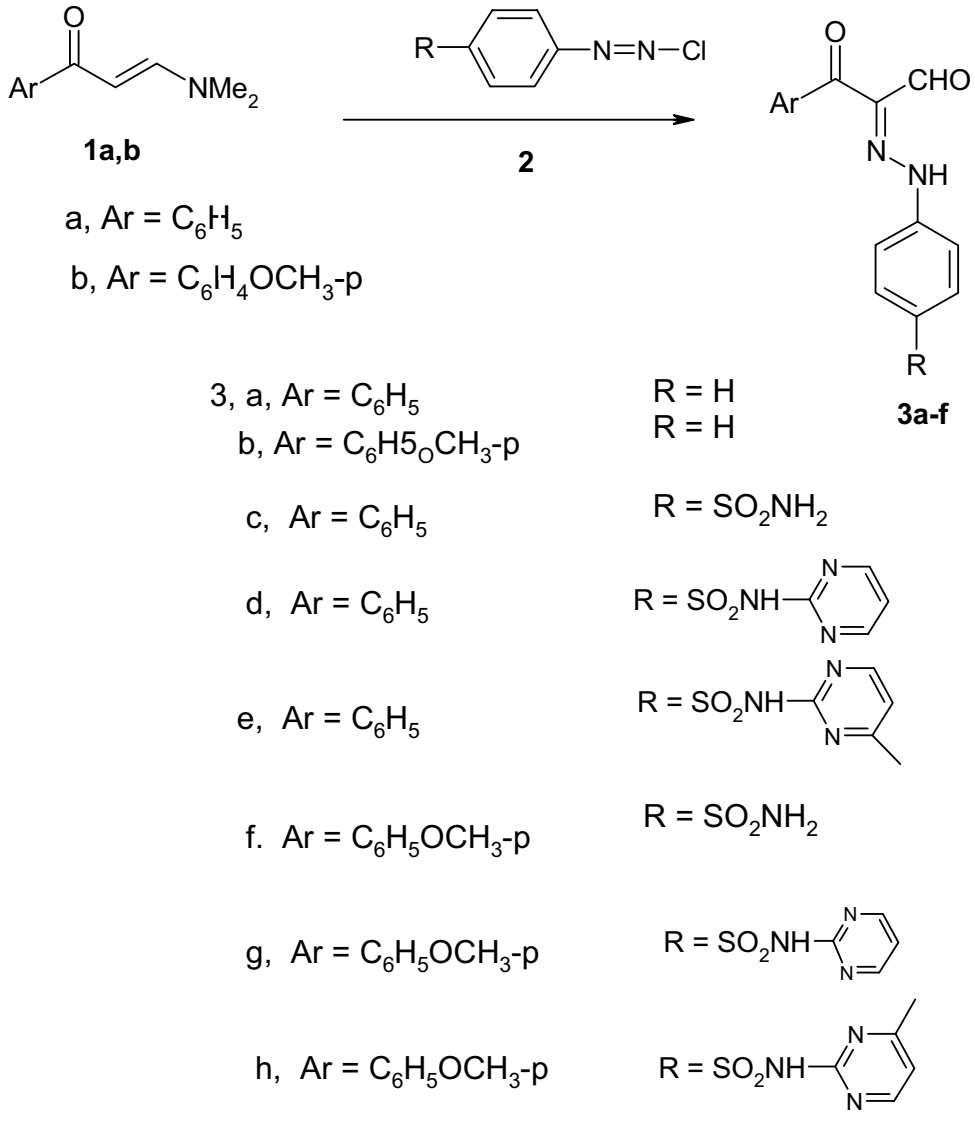
INTRODUCTION

The chemistry of 1.2.3-trione-2-arylhydrazones has been investigated[1-3]. There are little attention has been aimed on the chemistry of compounds related to 2-arylhydrazono-3-oxopropanals[4, 5]. In previous work we reported the synthesis of **1** and used as precursors for preparation of some heterocyclic rings[6]. In continuation of our previous interest in the synthesis of variety of heterocycles from the readily obtainable inexpensive starting materials[7-11]. In view of the continued interest in the chemistry of these compounds we report here the utility of 2-arylhydazono-3-oxopropanals **3** readily obtained via coupling enaminone **1** with substituted diazonium salts (sulphonamides) to synthesized many of new heterocyclic compounds. Thus, enaminones **1a,b** coupled readily with diazonium salts of sulphonamides **2** to give hydrazonopropanals **3a-g** (Scheme 1).

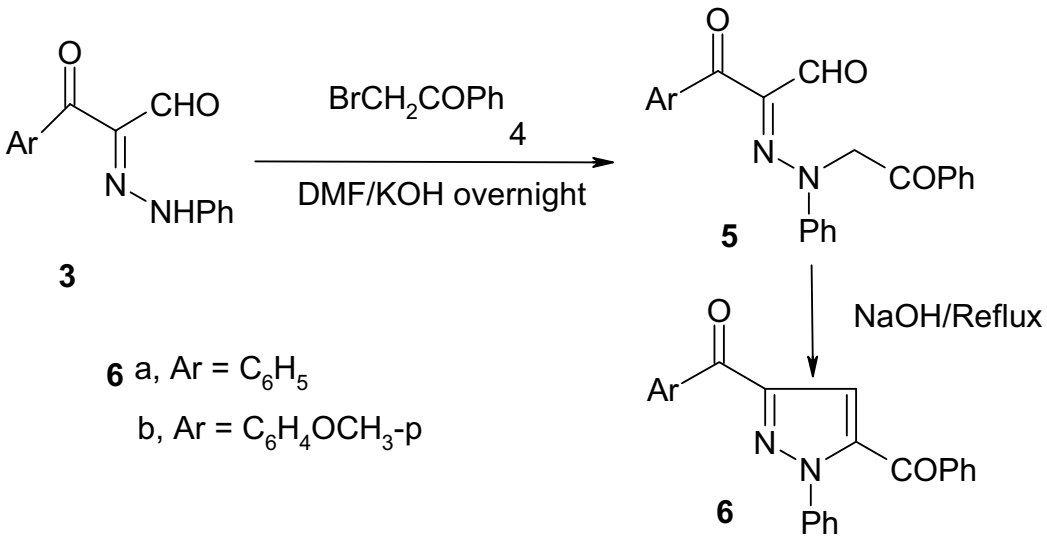
Reacting **3a,b** with α-haloketone, namely ω-bromoacetophenone in ethanolic potassium hydroxide has resulted in the formation of functionally substituted **5a,b**. These cyclised smoothly on reflux in DMF containing potassium hydroxide to yield the diarylpyrazole derivatives **6a,b**. To our knowledge this first report about synthesis of pyrazoles in this way (Scheme 2).

Similarly, compound **3a,d** reacted with α-chloroactanilide to yield **8** which cyclized by DMF in the presence of sodium hydroxide to yield the pyrazoles **9**. Compounds **9** were established based on its spectral data and elemental analysis. For example the ^{1}H NMR for compound **9a** revealed singlet signal at δ 8.84 ppm assigned for the pyrazole-CH, δ 15.23 ppm assigned for NH group. Moreover, the mass spectrum for the compound **9a** gave molecular ion peak at m/z = 447 (M^{+1}) (Scheme 3).

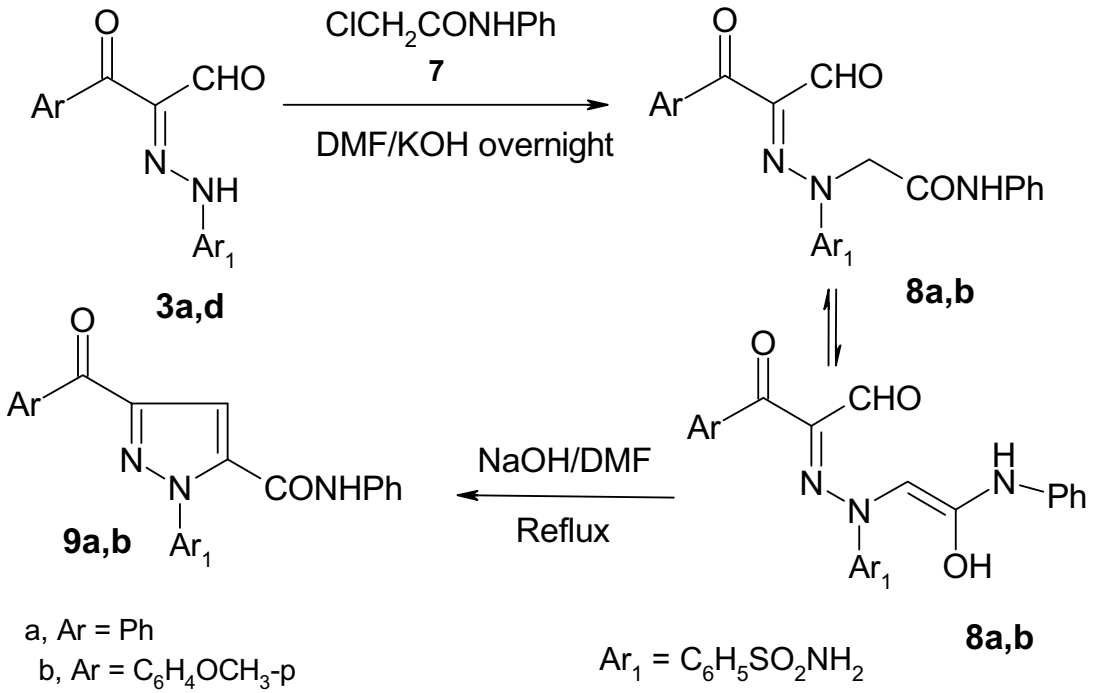
Compound **3** reacted with phenylhydrazine to yield diphenylhydrazones **10** which cyclised into arylazopyrazoles **11** in refluxing pyridine. However, reactions of **4c,d** with hydrazine hydrate in refluxing ethanol afforded the pyrazole **12a,b**. Compounds **12** were confirmed by spectral data (^{1}H NMR and MS), So, the ^{1}H NMR for compound **12a** as example revealed singlet signal at δ 9.26 ppm assigned for pyrazol-H and singlet signal at δ 13.94 ppm assigned to NH group. Also, the mass spectrum of compound **12a** was compatible with the molecular ion peak m/z = 327 (M^+).



Scheme 1.

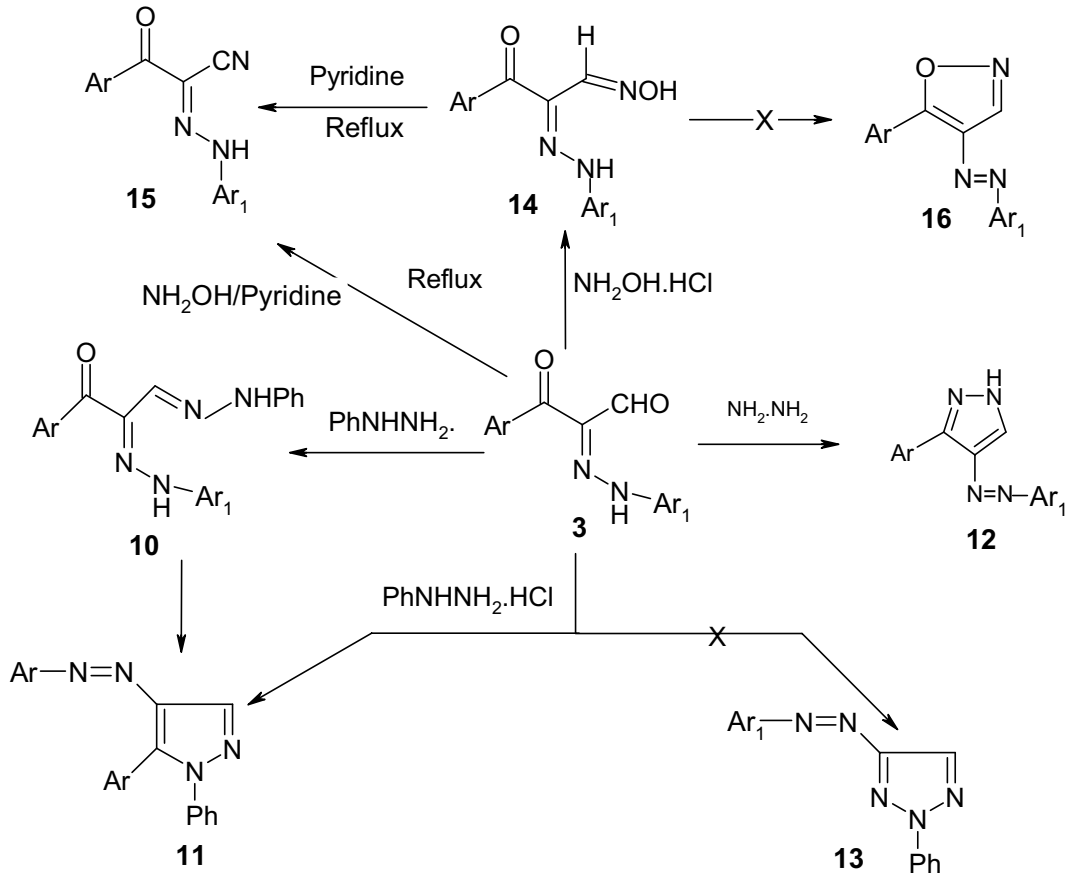


Scheme 2.



Scheme 3.

Attempts to prepare the triazole derivative **13** by reaction of **3c** with phenylhydazine hydrochloride as literature failed.[12] But under the reaction conditions we obtained product identical in all respects (mp., mixed mp. and spectral data) with those corresponding to compounds **11a,b**. Finally, reactions of **3c** with hydroxylamine hydrochloride in aqueous ethanolic sodium carbonate afforded the aldoxime **14**. Although aldoximes are expected to cyclize readily into isoxazoles in basic medium, initial attempted cyclization of aldoxime **14** in refluxing pyridine failed and has resulted in the formation of the 3-oxoalkanonitrile **15**. The formation of **15** from **14** is believed to occur via initial protonation of the oxime oxygen followed by water elimination and proton loss facilitated by the solvent. Alternatively, compound **15** has been directly obtained from the reaction of **14** with the reagent system hydroxylamine hydrochloride in refluxing pyridine.[13-15]



	Ar	Ar1
10a	C_6H_5	$C_6H_4SO_2NH_2$
b	C_6H_5	$C_6H_4SO_2NH$-pyrimidin-2yl
c	$C_6H_4OCH_3$-p	$C_6H_4SO_2NH_2$
d	$C_6H_4OCH_3$-p	$C_6H_4SO_2NH$-pyrimidin-2-yl

11-15a, Ar = C_6H_5, Ar1 = $C_6H_4SO_2NH_2$
b, Ar = $C_6H_4OCH_3$-p, Ar1 = $C_6H_4SO_2NH_2$

Scheme 4.

EXPERIMENTAL

All melting points are uncorrected and were determined on a Gellankap apparatus; IR (KBr) spectra were recorded on Schimadzu 470 spectrophotometer in potassium bromide discs; ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz) spectrophotometer using TMS as an internal standard; Mass spectrometer MS 30 (AEL) at 70ev; Analytical data were obtained from the microanalytical data center at Cairo university.

General procedure for the preparation compounds (3a-b):

Compound **3a,b** were prepared as liturature.[14]

General procedure for the preparation of compounds (3c-h):

A cold solution of aryldizonium salt (10 mmol) was prepared by adding a solution of sodium nitrite (1.5 gm in 10 ml H_2O) to cold solution of arylamine hydrochloride (10 ml in 5 ml concentrated HCl) with stirring in ice bath. The resulting solution of aryldiazonium salt was then added to cold solution of enaminone **1a** or **1b** (10 mmol) in ethanol (50 ml) containing sodium hydroxide (6.0 gm) and the mixture was stirred at 0ºC for 1 hour. The solid product, so formed, was collected by filtration and crystallized from the proper solvent.

4-[N`-(1-Formyl-2-oxo-2-phenylethylidene)-hydrazino]-benzenesulfonamide (3c):

It was obtained as green crystals from DMF/dioxan; yield 73%; mp. 335ºC; IR (KBr) ν cm^{-1} 1743-1651 (2CO); 3450-3210 (NH and NH_2); ^{1}H NMR (DMSO-d_6) δ = 7.41-7.89 (m, 11H, Ar-H and NH_2); 10.00 (s, 1H, CHO); 14.11 (s, 1H, NH); Ms: m/z = 331 (M^+); Found C, 54.37; H, 3.95; N, 12.68, S, 9.68; Calcd for $C_{15}H_{13}N_3O_4S$ (331.35): C, 54.37; H, 3.95, N, 12.68; S, 9.68.

4-[N`-(1-Formyl-2-oxo-2-phenylethylidene)-hydrazino]-N-pyrimidin-2-yl-benzenesulfonamide (3d):

It was obtained as yellow crystals from DMF/dioxan; yield 73%; mp. 299ºC.; IR (KBr) ν cm^{-1} 1714-1650 (2CO); 3450-3210 (NH, NH_2); Found C, 55.80; H, 3.75; N, 17.23; S, 7.91; Calcd for $C_{19}H_{15}N_5O_4S$ (331.35): C, 55.47; H, 3.69; N, 17.11; S, 7.83.

4-[N`-(1-Formyl-2-oxo-2-phenylethylidene)-hydrazino]-N-(4-methyl-pyrimidin-2-yl-)benzenesulfonamide (3e):

It was obtained as brown crystals from DMF/dioxan; yield 70%; mp. 277-279 ºC; IR (KBr) ν cm^{-1} 1710-1651 (2CO); 3450-3210 (NH and NH_2); Found: C, 56.84; H, 4.15; N, 16.62; S, 7.61; Calcd for $C_{20}H_{17}N_5O_4S$ (423.45): C, 56.73; H, 4.05; N, 16.54; S, 7.57.

4-[N`-[1-Formyl-2-(4-methoxyphenyl)-2-oxo-ethylidene]-hydrazino}-bensenesulfonamide (3f):

It was obtained as orange crystals from DMF/ethanol(1:3); yield 75%; mp. 311ºC; IR (KBr) ν cm^{-1} 1710-1653 (2CO); 3450-3210 (NH and NH_2); ^{1}H NMR (DMSO-d_6) δ = 3.88 (s, 3H, OCH_3); 6.92-8.50 (m, 10H, Ar-H and NH_2); 11.00 (s, 1H, CHO); 13.25 (s, 1H, NH); Found C, 53.26; H, 4.27; N, 11.78; S, 8.99; Calcd for $C_{16}H_{15}N_3O_5S$ (361.38): C, 53.18; H, 4.18; N, 11.63; S, 8.87.

4-{N`-[1-Formyl-2-(4-methoxy-phenyl)-2-oxo-ethylidene]-hydrazino}-N-pyrimidin-2-yl-benzenesulfonamide (3g):

It was obtained as red crystals from DMF/ethanol (1:3); yield 71%; mp. 332-334 ºC; IR (KBr) ν cm^{-1} 1714-1650 (2CO); 3450-3210 (NH and NH_2); Found C, 54.78; H, 3.92; N, 16.05; S, 7.47; Calcd for $C_{20}H_{17}N_5O_5S$ (439.45): C, 54.66; H, 3.86; N, 15.94; S, 7.30.

4-{N`-[1-Formyl-2-(4-methoxy-phenyl)-2-oxo-ethylidene]-hydrazino}-N-(4-methylpyrimidin-2-yl-)benzenesulfonamide (3h):

It was obtained as green crystals from DMF/EtOH; yield 73%; mp. >360 ºC; IR (KBr) ν cm^{-1} 1714-1652 (2CO); 3448-3215 (2NH); ^{1}H NMR (DMSO-d_6) δ = 2.48 (s, 3H, CH_3); 3.84 (s, 3H, OCH_3); 7.06-7.96 (m, 10H, Ar-H and NH_2); 9.96 (s, 1H, CHO); 11.77 (s, 1H, SO_2NH), 13.99 (s, 1H, NH); Found C, 55.73; H, 4.37; N, 15.51; S, 7.19; Calcd for $C_{21}H_{19}N_5O_5S$ (453.48): C, 55.62; H, 4.22; N, 15.44; S, 7.07.

Preparation of compounds (5a,b and 8a,b):

General procedure:

To a solution of compound 3 (10 mmol) in DMF (10 ml) containing potassium hydroxide (10 mmol) ω-bromoacetophenone or chloroacetanilide (0.01 mol) were added. The reaction mixture was left overnight and poured into cold water. The solid precipitate was filtered off and crystallized from ethanol.

3-Oxo-2-[(2-oxo-2-phenyl-ethyl)- phenylhydrazono]-3-phenyl-propionaldehyde(5a):

It was obtained as green crystals from ethanol; yield 58%; mp. 128 ºC; IR (KBr) ν cm^{-1} 1724 (CO); 1674 (CO); 1650 (CO); Found C, 74.69; H, 5.05; N, 7.67; Calcd for $C_{23}H_{18}N_2O_3$ (370.41): C, 74.58; H, 4.90; N, 7.56.

3-(4-Methoxy-phenyl)-3-oxo-2-[(2-oxo-2-phenylethyl)-phenyl-hydrazono]-propionaldehyde(5b):

It was obtained as orange crystals from ethanol; yield 65%; mp. 133 ºC; IR (KBr) ν cm^{-1} 1710 (CO); 1674 (CO); 1650 (CO); Found: C, 72.05; H, 5.18; N, 7.18; Calcd for $C_{24}H_{20}N_2O_4$ (400.44): C, 71.99; H, 5.03; N, 7.00.

General preparation of (6a,b and 9a,b):

Each of compound 5 or 8 (10 mmol) was refluxed in NaOH DMF solution for 4 hours, then left to cool at room temperature. The mixture was poured into water, the solid product obtained was filtered off and crystallized from the proper solvent.

(5-Benzoyl-1-phenyl-1H-pyrazol-3-yl)-phenyl-methanone (6a):

It was obtained as green crystals from ethanol; yield 58%; mp. 163 ºC; IR (KBr) ν cm^{-1} 1766 (CO); 1743 (CO); Found C, 78.44; H, 5.60; N, 7.99; Calcd for $C_{23}H_{16}N_2O_2$ (352.40): C, 78.39; H, 4.58; N, 7.95.

5-Benzoyl-1-phenyl-1H-pyrazol-3-yl)-(4-methoxyphenyl)-methanone(6b):

It was obtained as brown crystals from ethanol; yield 58%; mp. 198 ºC; IR (KBr) ν cm^{-1} 1766 (CO); 1743 (CO); ^{1}H NMR (DMSO-d_6) δ =3.92 (s, 3H, OCH_3); 7.45-8.11 (m, 15H, Ar-H and pyrazole-CH); Found C, 75.47; H, 4.88; N, 7.45; Calcd for $C_{24}H_{18}N_2O_3$ (382.42): C, 75.38; H, 4.74; N, 7.33.

2-[-N`-(1-Formyl-2-oxo-2-phenylethylidene)-N-(4-sulfamoylphenyl)-hydrazino]-N-phenylacetamide (8a):

It was obtained from ethanol as red crystals; yield 44%; mp. 111 ºC. IR (KBr) ν cm^{-1} 1724 (CO); 1674 (CO); 1645 (CO); Found C, 59.49; H, 4.44; N, 12.17; S, 6.95; Calcd for $C_{23}H_{20}N_4O_5S$ (464.50): C, 59.47; H, 4.34; N, 12.06; S, 6.90.

2-[-N`-(1-Formyl-2-(4-methoxy-phenyl)-2-oxo-ethylidene]-N-(4-sulfamoylphenyl)-hydrazino]-N-phenylacetamide (8b):

It was obtained as red crystals from ethanol; yield 44%: mp. 127 ºC; IR (KBr) ν cm^{-1} 1724 (CO); 1674 (CO); 1645 (CO); ^{1}H NMR (DMSO-d_6) δ = 3.87 (s, 3H, OCH_3); 7.06-7.96 (m, 14H, Ar-H and NH_2); 9.53 (s, 1H, CH); 9.96 (s, 1H, CHO); 11.82 (s, 1H, NH); 14.18 (s, 1H, OH); Found C, 58.31; H, 4.52; N, 11.38; S, 6.05; Calcd for $C_{24}H_{22}N_4O_6S$ (494.53): C, 58.29; H, 4.48; N, 11.33; S. 6.48.

5-Benzoyl-2-(4-sulfamoylphenyl)-2H-pyrazole-3-carboxylic acid phenylamide (9a):

It was obtained as red crystals from ethanol in 44% yield; mp. 187 ºC; IR (KBr) ν cm^{-1} 1697-1635 (2CO); 3159-3475 (NH and NH_2); ^{1}H NMR (DMSO-d_6) δ = 7.13-7.89 (m, 16H, Ar-H and NH_2); 8.84 (s, 1H, pyrazol-CH); 15.23 (s, 1H, NH), Ms: m/z = 447 (M^{+1}); Found C, 61.97; H, 4.16; N, 12.65; S, 7.27; Calcd for $C_{23}H_{18}N_4O_4S$ (446.49): C, 61.87; H, 4.06; N, 12.55; S, 7.18.

5-(4-Methoxybenzoyl)-2-(4-sulfamoylphenyl)-2H-pyrazole-3-carboxylic acid phenylamide (9b):

It was obtained as red crystals from ethanol in 39% yield; mp. 167 ºC: IR (KBr) ν cm^{-1} 1712-1635 (2CO); 3363-3240 (NH and NH_2); Found C, 60.56; H, 4.35; N, 11.87; S, 6.88; Calcd for $C_{24}H_{20}N_4O_5S$ (476.51): C, 60.49; H, 4.23; N, 11.76, S, 6.73.

General preparation of compounds (10a-d):

A mixture of compounds 3c-f (10 mmol) and phenylhydrazine (1.08g, 10 mmol) was refluxed in ethanol (10 ml) for 1hour. The solvent was removed under vacuo and the residue cooled to deposit the solid, which was crystallized from ethanol.

4-{N`-[2-Oxo-2-phenyl-(1-phenylhydrazonomethyl)-ethylidene]-hydrazino}-benzenesulfonamide (10a):

It was obtained as red crystals from ethanol; yield 58%; mp. 201 ºC; IR (KBr) ν cm^{-1} 3425-3255 (NH and NH_2); 1650 (CO); ^{1}H NMR (DMSO-d_6) δ = 6.93-7.93 (m, 16H, Ar-H and NH_2); 8.35 (s, 1H, CH); 11.01 (s, 1H, NH); 13.31 (s, 1H, NH); Found C, 59.94; H, 4.65; N, 16.73; S, 7.71; Calcd for $C_{21}H_{19}N_5O_3S$ (421.48): C, 59.84; H, 4.54; N, 16.62; S, 7.61.

4-{N`-[2-Oxo-2-phenyl-1-(phenyl-hydrazonomethyl)-ethylidene]-hydrazino}-N-pyrimidin-2-yl-benzenesulfonamide (10b):

It was obtained as red crystals from ethanol; yield 57%; mp. 278-300 ºC; IR (KBr) ν cm^{-1} 3455-3233 (NH and NH_2); 1665 (CO); Calcd for $C_{25}H_{21}N_7O_3S$ (499.56): C, 60.11; H, 4.24; N, 19.63; S, 6.42; Found C, 60.36; H, 4.38; N, 19.77; S, 6.53.

4-{N`-[2-(4-Methoxyphenyl)-2-oxo-1-(phenyl-hydrazonmethyl)-ethylidene]-hydrazino}-benzenesulfonamide (10c):

It was obtained yellow crystals from ethanol; yield 59%; mp. 200-202 ºC; IR (KBr) ν cm^{-1} 3425-3211(NH and NH_2); 1654 (CO); ^{1}H NMR (DMSO-d_6) δ = 3.88 (s, 3H, OCH_3); 6.90-7.99 (m,15H, Ar-H and NH_2); 8.51 (s, 1H, CH); 11.00 (s, 1H, NH); 13.25 (s, 1H, NH); Found C, 58.64; H, 4.71; N, 15.63; S, 7.25; Calcd for $C_{22}H_{21}N_5O_4S$ (451.51): C, 58.53; H, 4.69; N, 15.51; S, 7.10.

4-{N`-[2-(4-Methoxy-phenyl)-2-oxo-1-(phenyl-hydrazonomethyl)-ethylidene]-hydrazino}-N-pyrimidin-2-yl-benzenesulfonamide (10d):

It was obtained as brown crystals from ethanol; yield 58%; mp. 211-213 ºC; IR (KBr) ν cm^{-1} 3335-3212 (NH and NH_2); 1654 (CO); Found C, 59.02; H, 4.46; N, 18.64; S, 6.15; Calcd for $C_{26}H_{23}N_7O_4S$ (529.58): C, 58.97; H, 4.38; N, 18.51; S, 6.05.

General preparation of compounds (11a,b):

A solution of each compounds **10a** or **10b** (10 mmol) in pyridine (10 mmol) was refluxed for 3 hours. The resultant solution was poured in water and acidified with dilute HCl. The solid product obtained was filtered off and crystallized from ethanol.

4-(1,5-Diphenyl-1H-pyrazol-4-ylazo)benzenesulfonamide(11a):

It was obtained as red crystals from ethanol; yield 58%; mp. 198 ºC; IR (KBr) ν cm^{-1} 3475-3406 (NH_2); ^{1}H NMR (DMSO-d_6) δ = 7.34-7.73 (m, 16H, Ar-H and NH_2); 8.20 (s, 1H, pyrazole-CH); Ms: m/z = 403 (M^+); Found C, 62.68; H, 4.37; N, 17.37; S, 8.06; Calcd for $C_{21}H_{17}N_5O_2S$ (403.47): C, 62.52; H, 4.25; N, 17.36; S, 7.95.

4-[5-(4-Methoxyphenyl)-1-phenyl-1H-pyrazol-4-ylazo] benzenesulfonamide(11b):

It was obtained as red crystals from ethanol; yield 58%; mp. 205-207 ºC; IR (KBr) ν cm^{-1} 3425-3255 (NH_2); Found C, 61.02; H, 4.53; N, 16.25; S, 7.57; Calcd for $C_{22}H_{19}N_5O_3S$ (433.49): C, 60.96; H, 4.42; N, 16.16; S, 7.40.

General preparation of compounds (12a-b):

A solution of each compound **3c,d** (10 mmol) and hydrazine hydrate (10 mmol) was refluxed in ethanol (10 ml) for 1hour. The solvent was removed under vacuo and the residue cooled at room temperature. The solid product obtained was filtered off and crystallized from ethanol.

4-(5-Phenyl-1H-pyrazol-4-ylazo)benzensulfonamide (12a):

It was obtained as green crystals from ethanol; yield 53%; mp. 222-224 ºC; IR (KBr) ν cm^{-1} 3332-3240 (NH and NH_2); ^{1}H NMR (DMSO-d_6) δ = 7.27-7.97 (m, 11H, Ar-H and NH_2); 9.26 (s, 1H, pyrazole-CH); 13.94 (s, 1H, NH); Ms: m/z = 327 (M^+); Found C, 55.16; H, 4.14; N, 21.45; S, 9.82; Calcd for $C_{15}H_{13}N_5O_2S$: (327.37): C, 55.04; H, 4.00; N, 21.39; S, 9.79.

4-[5-(4-Methoxyphenyl)-1H-pyrazol-4-ylazo]benzensulfonamide (12b):

It was obtained as brown crystals from ethanol; yield 57%; mp. 218 ºC; IR (KBr) ν cm^{-1} 3433-3254 (NH and NH_2); Found C, 53.85; H, 4.34; N, 19.73; S, 9.01; Calcd for $C_{16}H_{15}N_5O_3S$: (357.39): C, 53.77; H, 4.23; N, 19.60; S, 8.97.

4-{N`-[1-(Hydroxyiminomethyl)-2-oxo-2-phenylethylidene]-hydazino}-benzenesulfonamide (14):

A warm solution of hydroxylamine hydrochloride (10 mmol) and sodium carbonate (10 mmol) in 10 ml water were added to a stirred solution of arylhydrazonopropanl **3c** (10 mmol) in ethanol (4 ml). The reaction mixture was stirred at room temperature for 1 hour. The oxime soon separated as semi-solid crystals that were solidified by cooling in cruched ice. The solid product so formed was collected by filtration and recrystallized from ethanol; yield 73 %; mp. 304-306 ºC; IR (KBr) ν cm^{-1} 3350-3150 (NH_2); 1674 (CO); Found C, 52.19; H 4.15, N 16.23, S, 9.34; Calcd for $C_{15}H_{14}N_4O_4S$: (346.37): C, 52.02; H, 4.07; N, 16.18; S, 9.26.

4-[N`-(1-Cyano-2-oxo-2-phenylethylidene)-hydrazino]-benzenesulfonamide (15):

Method (A)

A solution of compound **3** (10 mmol) was refluxed in pyridine for 1hour, then left to cool at r. t. The target nitriles separated as yellow crystals that were collected by filtration and crystallized from ethanol/dioxan (1:3); yield 73%; mp. 315 ºC; IR (KBr) ν cm^{-1} 3016-3385 (NH_2-NH); 2218 (CN); 1674 (CO); MS: m/z = 328 (M^+); Found C, 54.92; H, 3.73; N, 17.17; S, 9.85; Calcd for $C_{15}H_{12}N_4O_3S$ (328.35): C, 54.87; H, 3.68; N, 17.06; S, 9.77.

Method (b)

A solution of compound **3c** (10 mmol) and hydroxylamine (10 mmol) was refluxed in pyridine for 3 hours, then let the mixture solution to cool and acidified by dilute HCl. The solid product so formed was collected by filtration and recrystallized from ethanol.

TABLE I

No of compounds	A	B	C	D
4a	++++	++++	++++	+++
4b	++++	++	++++	+++
4d	++++	+++	++++	+++
4f	+++	+++	++++	+++
6a	+	++	++	+
9a	+++	++	+++	++++
9b	+++	++++	++	++++
11a	++++	+++	++	++++
11b	++	++	+++	++++
12a	+	++	++	+++
12b	+++	++	++++	+++

Where:
A = Staphylococcus aurous B = Streptococcus mitor
C = Esherichia coli D = Nisseria sica
--- = Negative + = Poor + + = Fair
+++ = Good + + + + = Very good

BIOLOGICAL ACTIVITIES

Most of the synthesized compounds have been tested against four different kinds of bacteria. The result of antimicrobial studies presented in Table 1. It has been found that the prepared compound show antimicrobial activity against *Staphylococcus aurous*, *Streptococcus mitor*, *Esherichia coli* and *Nisseria sica*.

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