

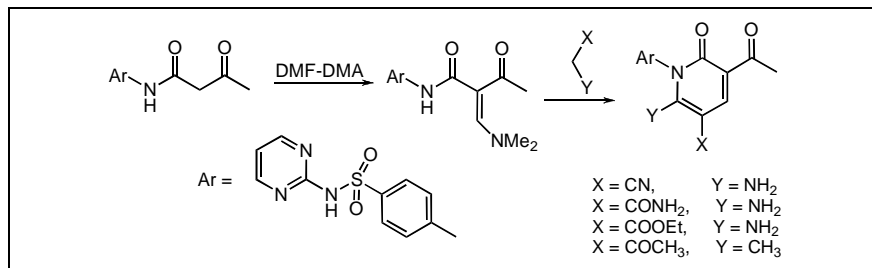
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Received June 25, 2007

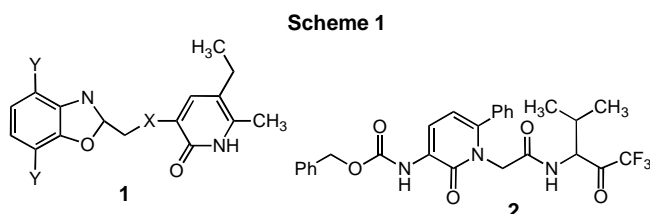


3-Oxo-*N*-{4-[(pyrimidin-2-ylamino)sulfonyl]phenyl}butanamide **3** was condensed with (DMF-DMA) in refluxing dry dioxane to yield branched structure **4** not its linear isomeric **5**. Compound **4** readily reacted with active methylene to yield compounds **8a-c**, **14**, **17** and **20** respectively. Also enaminone **4** reacted with phenyl hydrazine giving **24** and **25**. In contrast, when compound **4** reacted with hydrazine hydrate in the same experimental conditions pyrazole derivative **27** was obtained. Furthermore, condensation of anilide **3** with triethylorthoformate in refluxing acetic anhydride afforded the ethoxy methylene derivative **28**. On the other hand, compound **28** was reacted with active methylene reagents, and hydrazines to afford the products identical in all respects (mp., mixed mp., and spectral data) with those corresponding to compounds **6-27** respectively. Similarly, compound **3** was reacted with hydrazine hydrate to afford the reaction product **29**. Also, compound **3** reacted with cyanoacetamide in refluxing ethanolic piperidine solution to yield the pyridine derivative **30**. Finally, **3** reacted with hydroxylamine hydrochloride in refluxing ethanol/sodium acetate solution to yield the acyclic oxime derivative **31**.

J. Heterocyclic Chem., **45**, 1819 (2008).

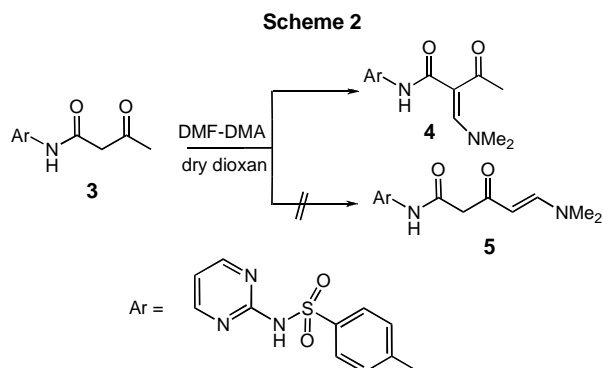
INTRODUCTION

Literature survey revealed that polyfunctionally substituted pyridones have played an important role in the development of bioactive compounds for the inhibition of enzymatic processes [1-3]. A number of representative pyridone derivative **1** are effective inhibitors of HIV reverse transcriptase. Pyridone **2** is a potent (4.5 nm), reversible nonpeptidic inhibitor of human leukocyte elastase (HLE) [4,5]. In view of our continued interest in developing efficient synthesis of polyfunctionally substituted heteroaromatics utilizing the readily obtainable starting materials [6-9], we report here the results of our investigations aiming to explore the synthetic potential of 3-Oxo-*N*-{4-[(pyrimidin-2-ylamino)sulfonyl]phenyl}butanamide **3** to synthesis of substituted pyridones from enaminone using active methylene reagents.



RESULTS AND DISCUSSION

It has been found that 3-oxo-*N*-{4-[(pyrimidin-2-ylamino)sulfonyl]phenyl}butanamide **3** was condensed with *N,N*-dimethylformamide-dimethylacetal (DMF-DMA) in refluxing dry dioxane to yield a product that may be either structure **4** or its isomeric **5**. Establishing the exact structure of the reaction product as structure **4** rather than **5** was based on elemental analysis and spectral data. ¹H nmr spectra revealed the presence of a singlet signal at $\delta = 1.2$ ppm assigned to the acetyl functional group and absence of olefinic doublet-doublet which would be observed for structure **5**.

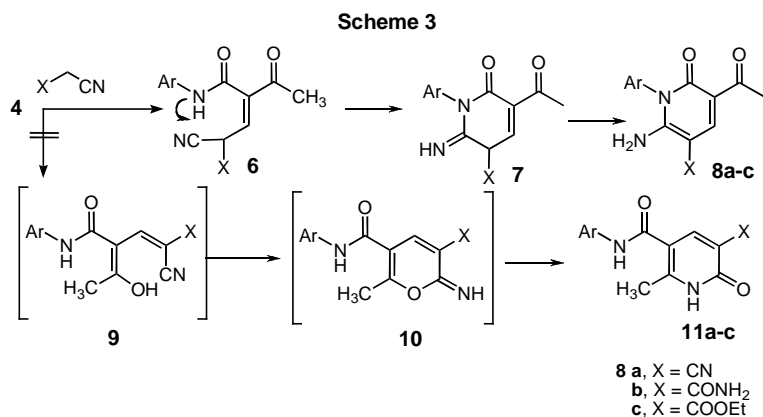


Compound **4** readily reacted with malononitrile in refluxing ethanolic piperidine solution to yield the product which may be formulated as structures **8a** or **11a**. Structure **11a** was ruled out and structure **8a** was considered to be only the reaction product based on spectroscopic data. Thus, the ^1H nmr spectrum of compound **8a** showed a singlet signal (3H) at $\delta = 3.56$ ppm assigned for acetyl protons, a broad signal at $\delta = 5.75$ ppm assigned for NH_2 protons, multiplet at $\delta = 6.51 - 7.58$ ppm assigned for CH aromatic and 2 NH, and a singlet at $\delta = 8.35$ ppm assigned for CH-pyridine. Also, its mass spectrum revealed a molecular ion peak at $m/z = 411(\text{M}^+)$ corresponding to the molecular formula $\text{C}_{18}\text{H}_{14}\text{N}_6\text{O}_4\text{S}$. Similarly, compound **4** reacted with cyanoacetamide and ethyl cyanoacetate to yield the pyridone derivatives **8b,c** rather than **11b,c** respectively.

reacted with enaminone **4** in ethanolic piperidine solution to yield compound **14**. Assignment of structure **14** for the reaction product was based on its correct elemental analysis and compatible spectroscopic data. Thus, the ^1H nmr spectrum showed, the presence of singlet signals at $\delta = 1.70, 2.05$ ppm assigned for 2 COCH_3 protons besides the expected signals. Compound **14** is assumed to be formed by condensing acetyl acetone to enaminone **4** with elimination of dimethyl amine which would afford intermediate **13** which on cyclization *via* water elimination gives **14** (Scheme 4).

Similarly, ethyl acetoacetate was reacted with enaminone **4** at the same conditions to yield compound **17** (Scheme 5).

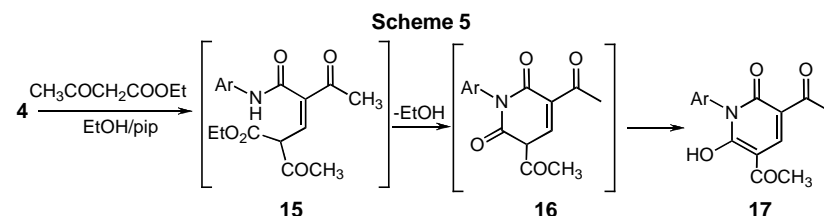
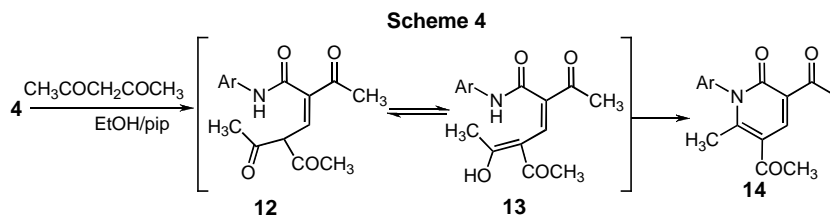
In contrast to the behavior of active methylene reagents to enaminone **4**, compound **4** readily reacted with

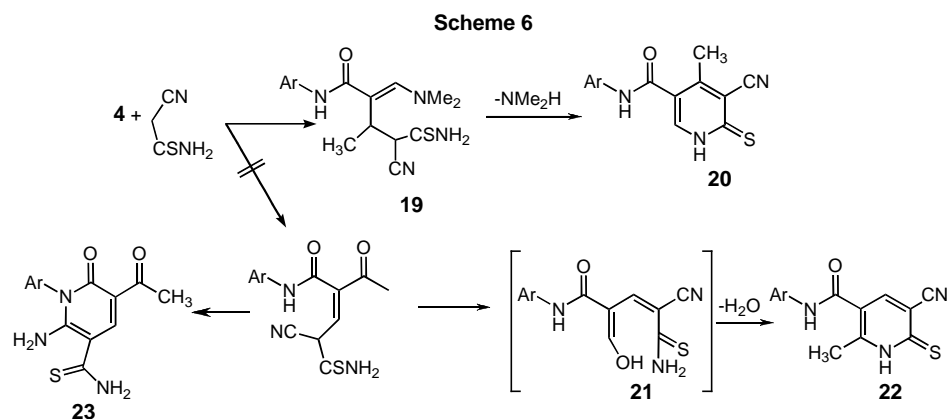


Formation of **8a-c** is believed to proceed *via* initial addition of active methylene moiety in malononitrile to afford the Michael adduct **6** *via* elimination of dimethyl amine, which cyclizes into **7** and aromatized to the pyridone derivatives **8a-c**.

Also, the behavior of enaminone **4** towards active diketone reagents was investigated. Thus, acetyl acetone

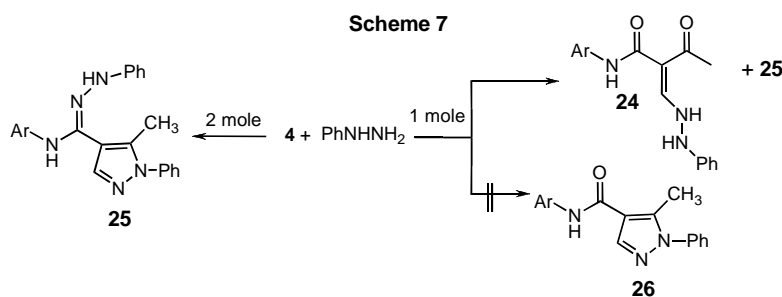
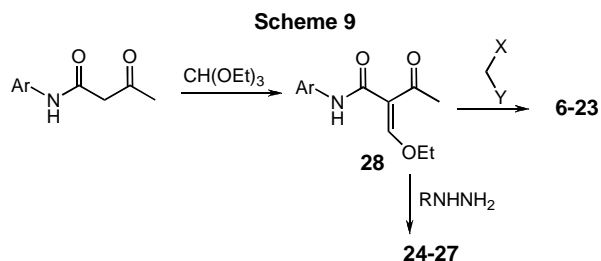
cyanthioacetamide in refluxing ethanolic piperidine solution to yield the product which may be formulated as pyridinethione **20** neither **22** nor **23**. Structure **20** was considered to be the reaction product based on its spectroscopic data and further confirmed on the bases of its chemical behavior towards different chemical reagents (Scheme 6).



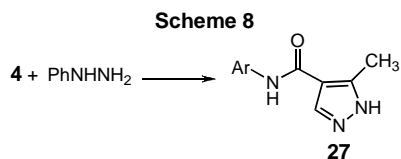


Furthermore, the behavior of enaminone **4** towards phenyl hydrazine and hydrazine hydrate was also investigated. Thus, enaminone **4** reacted with phenyl hydrazine giving products depending on the ratio between the reactants. Thus, the reaction between **4** and phenyl hydrazine in equimolar ratio yielded two products **24** and **25**. However, when the reaction is carried out using one mole of **4** with two moles of phenyl hydrazine, product **25** was isolated as the only reaction product. The exact structure of such reaction product is based on its elemental analysis and spectroscopic data. Thus, the mass spectrum of compound **24** revealed a molecular ion peak at $m/z = 452$ (M^+) corresponding to the molecular formula $\text{C}_{21}\text{H}_{20}\text{N}_6\text{O}_4\text{S}$. Compound **25** was confirmed based on its spectroscopic data (Scheme 7).

other hand, compound **28** was reacted with the active methylene reagents, and hydrazines to afford products identical in all respects (mp., mixed mp., and spectral data) with those corresponding to compounds **6-27** respectively (Scheme 9).



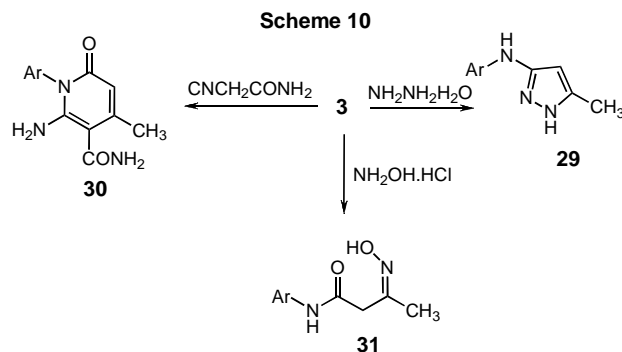
In contrast, when compound **4** reacted with hydrazine hydrate under the same experimental conditions the pyrazole derivative **27** was afforded (Scheme 8).



Also, condensation of anilide **3** with triethylorthoformate in refluxing acetic anhydride afforded the ethoxy methylene derivative **28**. Establishing of the structure **28** was based on elemental analysis and spectral data. On the

On the other hand, the reactivity of anilide **3** towards hydrazine hydrate, cyanoacetamide, and hydroxylamine hydrochloride was investigated. Thus, acetoacetanilide **3** was reacted with hydrazine hydrate to afford the reaction product **29**. Assignment of structure **29** for the reaction product was based on its correct elemental analysis and spectroscopic data. Also, anilide **3** reacted with cyanoacetamide in refluxing ethanolic pyridine solution to yield the product which may be formulated as pyridine derivative **30**. Furthermore, anilide **3** reacted with hydroxylamine hydrochloride in refluxing ethanol/sodium acetate solution to yield the acyclic oxime derivative **31**. Structure **31** was established based on its elemental analysis and spectroscopic data. Thus, its ^1H NMR

spectrum showed absorption peaks at $\delta = 2.5$ ppm (CH_3) protons, at $\delta = 3.32$ ppm assigned for (OH) proton, at $\delta = 5.97$ ppm (CH_2) protons, and at $\delta = 11.22$ ppm a broad signal assumed for (NH) proton beside the expected signals (Scheme 10).



EXPERIMENTAL

All melting points are uncorrected and were determined on a Gallenkamp apparatus; IR spectra were recorded on Shimadzu 470 spectrophotometer in potassium bromide discs; ^1H NMR spectra were recorded on a Varian EM-390 (90 MHz) spectrophotometer using TMS as internal standard, Mass spectrometer MS 30(AEL) at 70eV. Analytical data were obtained from the micro analytical data center at Cairo University.

3-Oxo-N-{4-[(pyrimidin-2-ylamino)sulfonyl]phenyl}-butanamide (3). Compound 3 was prepared as literature procedure [10].

2-Acetyl-3-(dimethylamino)-N-{4-[(pyrimidin-2-ylamino)sulfonyl]phenyl}acrylamide (4). A mixture of anilide (3) (3.34 gm, 10.0 mmoles) and DMF/DMA (Dimethylformamide/Dimethylacetal) (1.32 mL, 10.0 mmoles) in dry dioxane was heated under reflux for 3 hrs, then the solvent was evaporated under vacuum. The solid product formed was collected by filtration and crystallized from ethanol as yellow crystals; yield 42%; mp 230°; ir: 3300 (NH), 3200 (NH), 1710 (CO), 1660 (CO) cm^{-1} ; ^1H nmr (DMSO- d_6) δ : 1.2 (s, 3H, CH_3), 2.47 (s, 6H, 2 CH_3), 7-7.7 (m, 8H, aromatic protons and 1H CH), 12.2 (br, 1H, NH); MS: m/z 389 (386 M^{-3}), 389 (387 M^{-2}). *Anal.* Calcd. for $\text{C}_{17}\text{H}_{19}\text{N}_5\text{O}_4\text{S}$: C, 52.42; H, 4.93; N, 17.97; S, 8.22. Found: C, 52.47; H, 5.12; N, 18.38; S, 8.33.

General procedure for preparation of 4-(3-Acetyl-6-amino-5-substituted-2-oxo-2H-pyridin-1-yl)-N-pyrimidin-2-ylbenzene-sulfonamide (8a-c, 14, 17, 20).

Method (A). A mixture of enaminone (4) (0.01 mole) and active methylene reagents (0.01 mole) in ethanol (30 mL) containing a catalytic amount of piperidine (0.1 mL) was heated under reflux for 6 hrs. The solid product formed was collected by filtration and crystallized from the proper solvent.

Method (B). A mixture of ethoxy methylene derivative (28) (0.01 mole) and active methylene reagents (0.01 mole) in ethanol (30 mL) containing a catalytic amount of piperidine (0.1 mL) was heated under reflux for 6 hrs. The solid product formed was collected by filtration and crystallized from the proper solvent.

4-(3-Acetyl-6-amino-5-cyano-2-oxo-2H-pyridin-1-yl)-N-pyrimidin-2-ylbenzene-sulfonamide (8a). Compound 8a was obtained as colorless crystals from ethanol; yield 40%; mp 210°; ir: 3400 (NH_2), 3200 (NH), 2240 (CN), 1700 (CO), 1650 (CO) cm^{-1} ; ^1H nmr (DMSO- d_6) δ : 1.55 (s, 3H, CH_3), 3.56 (s, 1H, NH), 5.75 (s, 2H, NH_2), 6.6 (d, 2H, CH-pyrimidine- γ -protons), 6.8-7.6 (m, 5H, Ar-H), 8.4 (s, 1H, CH-C-4-pyridine ring); MS: m/z 410 (411 M^{+1}). *Anal.* Calcd. for $\text{C}_{18}\text{H}_{14}\text{N}_6\text{O}_4\text{S}$: C, 52.66; H, 3.43; N, 20.47; S, 7.80. Found: C, 52.71; H, 3.49; N, 20.52; S, 7.91.

5-Acetyl-2-amino-6-oxo-1-[4-[(pyrimidin-2-ylamino)sulfonyl]phenyl]-1,6-dihydropyridine-3-carboxamide (8b). Compound 8b was obtained as colorless crystals from ethanol; yield 35%; mp 180°; ir: 3450 (NH_2), 3200 (NH), 1700 (CO), 1650 (CO) cm^{-1} ; ^1H nmr (DMSO- d_6) δ : 1.78 (s, 3H, CH_3), 7.0-8.0 (m, 8H, Ar-H), 8.4 (s, 2H, NH_2), 10.33 (s, 1H, NH), 11.87 (s, 2H, NH_2); MS: m/z 428 (423 M^{-5}). *Anal.* Calcd. for $\text{C}_{18}\text{H}_{16}\text{N}_6\text{O}_5\text{S}$: C, 50.46; H, 3.76; N, 19.62; S, 7.48. Found: C, 50.49; H, 3.80; N, 19.68; S, 7.52.

5-Acetyl-2-amino-6-oxo-1-[4-[(pyrimidin-2-ylamino)sulfonyl]phenyl]-1,6-dihydropyridine-3-carboxylic acid ethyl ester (8c). Compound 8c was obtained as brown crystals from toluene/ethanol; yield 30%; mp 170°; ir: 3400 (NH_2), 3200 (NH), 1730 (CO), 1670 (CO) cm^{-1} ; ^1H nmr (DMSO- d_6) δ : 1.03 (t, 3H, CH_3), 1.24 (s, 3H, acetyl- CH_3), 2.52 (s, 2H, NH_2), 4.025 (q, 2H, CH_2), 7.0-8.0 (m, 7H, Ar-H), 8.4 (s, 1H, CH-C-4-pyridine ring), 10.34 (s, 1H, NH); MS: m/z 457. *Anal.* Calcd. for $\text{C}_{20}\text{H}_{19}\text{N}_5\text{O}_6\text{S}$: C, 52.51; H, 4.19; N, 15.31; S, 7.01. Found: C, 52.58; H, 4.22; N, 15.36; S, 7.10.

4-(3,5-Diacetyl-6-methyl-2-oxo-2H-pyridin-1-yl)-N-pyrimidin-2-ylbenzene-sulfonamide (14). Compound 14 was obtained as colorless crystals from methanol; yield 30%; mp 205°; ir: 3200 (NH), 1700 (CO) cm^{-1} ; ^1H nmr (DMSO- d_6) δ : 1.59 (s, 6H, 2 CH_3), 2.05 (s, 3H, CH_3), 6.4 (d, 2H, CH-pyrimidine- γ -protons); 7.4-7.9 (m, 5H, Ar-H), 8.2 (s, 1H, CH-C-4-pyridine ring), 10.11 (s, 1H, NH); MS: m/z 426. *Anal.* Calcd. for $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_5\text{S}$: C, 56.33; H, 4.25; N, 13.14; S, 7.52. Found: C, 56.39; H, 4.28; N, 13.18; S, 7.58.

4-(3,5-Diacetyl-6-hydroxy-2-oxo-2H-pyridin-1-yl)-N-pyrimidin-2-ylbenzene-sulfonamide (17). Compound 17 was obtained as yellow crystals from ethanol/acetic acid; yield 45%; mp 235°; ir: 3500 (OH), 3200 (NH), 1700 (CO), 1650 (CO) cm^{-1} ; ^1H nmr (DMSO- d_6) δ : 1.65 (s, 6H, 2 CH_3), 5.6 (s, 1H, OH), 6.6 (d, 2H, CH-pyrimidine- γ -protons), 7.4-7.8 (m, 5H, Ar-H), 8.2 (s, 1H, CH-C-4-pyridine ring), 9.63 (s, 1H, NH); MS: m/z 428. *Anal.* Calcd. for $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_6\text{S}$: C, 53.27; H, 3.76; N, 13.08; S, 7.48. Found: C, 53.31; H, 3.80; N, 13.10; S, 7.51.

5-Cyano-2-methyl-N-[4-[(pyrimidin-2-ylamino)sulfonyl]phenyl]-6-thioxo-1,6-dihydropyridine-3-carboxamide (20). Compound 20 was obtained as colorless crystals from ethanol; yield 48%; mp 248-250°; ir: 3300 (NH), 3200 (NH), 2220 (CN), 1650 (CO) cm^{-1} ; ^1H nmr (DMSO- d_6) δ : 2.06 (s, 3H, CH_3), 7.0-8.0 (m, 8H, Ar-H), 8.47 (s, 1H, NH), 10.27 (s, 1H, NH), 11.61 (s, 1H, NH); MS: m/z 426 (424 M^{-2}). *Anal.* Calcd. for $\text{C}_{18}\text{H}_{14}\text{N}_6\text{O}_3\text{S}_2$: C, 50.69; H, 3.31; N, 19.71; S, 15.04. Found: C, 50.72; H, 3.36; N, 19.76; S, 15.13.

3-Oxo-2-(N'-phenyl-hydrazinomethylene)-N-[4-[(pyrimidin-2-ylamino)sulfonyl]phenyl]-butanamide (24).

Method (A). A mixture of enaminone (4) (0.01 mole) and phenyl hydrazine (0.01 mole) in ethanol (30 mL) was heated under reflux for 8 hrs. The solid product formed during reflux (25) was collected by filtration and another product (24) was isolated after cooling the reaction mixture.

Method (B). A mixture of ethoxy methylene derivative (**28**) (0.01 mole) and phenyl hydrazine (0.01 mole) in ethanol (30 mL) was heated under reflux for 8 hrs. The solid product formed during reflux (**25**) was collected by filtration and another product (**24**) was isolated after cooling the reaction mixture. Compound **24** was obtained as pale yellow crystals from ethanol; mp 220°; ir: 3400 (NH), 3200 (NH), 1710 (CO) cm^{-1} ; MS: m/z 452. *Anal.* Calcd. for $\text{C}_{21}\text{H}_{20}\text{N}_6\text{O}_4\text{S}$: C, 55.74; H, 4.46; N, 18.57; S, 7.09. Found: C, 55.78; H, 4.50; N, 18.60; S, 7.12.

***N*-{4-[(Pyrimidin-2-ylamino)sulfonyl]phenyl}-5-methyl-*N*,1-diphenyl-1*H*-pyrazole-4-carbohydrazonamide (**25**).**

Method (A). A mixture of enaminone (**4**) (0.01 mole) and phenyl hydrazine (0.02 mole) in ethanol (30 mL) was heated under reflux for 8 hrs. The solid product formed was collected by filtration and crystallized from ethanol as pale yellow crystals; yield 30%.

Method (B). A mixture of ethoxy methylene derivative (**28**) (0.01 mole) and phenyl hydrazine (0.02 mole) in ethanol (30 mL) was heated under reflux for 8 hrs. The solid product formed was collected by filtration and crystallized from ethanol as pale yellow crystals; yield 62%; mp 260-262°; ir: 3400 (NH), 3200 (NH) cm^{-1} ; ^1H nmr (DMSO- d_6) δ : 2.5 (s, 3H, CH_3), 6.01 (s, 1H, NH), 6.55 (s, 1H, NH), 7.0-8.4 (m, 17H, Ar-H), 11.4 (s, 1H, NH); MS: m/z 524 (526 M^{+2}). *Anal.* Calcd. for $\text{C}_{27}\text{H}_{24}\text{N}_8\text{O}_2\text{S}$: C, 61.82; H, 4.61; N, 21.36; S, 6.11. Found: C, 61.86; H, 4.68; N, 21.40; S, 6.15.

3-Methyl-*N*-{4-[(pyrimidin-2-ylamino)sulfonyl]phenyl}-1*H*-pyrazole-4-carbohydrazonamide (27**).**

Method (A). A mixture of enaminone (**4**) (0.01 mole) and excess of hydrazine hydrate in ethanol (30 mL) was heated under reflux for 8 hrs. The solid product formed was collected by filtration and crystallized from 1,4-dioxane as colorless crystals.

Method (B). A mixture of ethoxy methylene derivative (**28**) (0.01 mole) and excess of hydrazine hydrate in ethanol (30 mL) was heated under reflux for 8 hrs. The solid product formed was collected by filtration and crystallized from 1,4-dioxane as colorless crystals; yield 54%; mp 255°; ir: 3400 (NH), 3200 (NH), 1660 (CO) cm^{-1} ; ^1H nmr (DMSO- d_6) δ : 2.08 (s, 3H, CH_3), 2.52 (s, 1H, NH), 6.68-7.68 (m, 9H, Ar-H and NH proton), 10.23 (s, 1H, NH), 11.4 (s, 1H, NH); MS: m/z 358. *Anal.* Calcd. for $\text{C}_{15}\text{H}_{14}\text{N}_6\text{O}_3\text{S}$: C, 50.27; H, 3.94; N, 23.45; S, 8.95. Found: C, 50.34; H, 4.12; N, 23.49; S, 8.99.

2-Acetyl-3-ethoxy-*N*-{4-[(pyrimidin-2-ylamino)sulfonyl]phenyl}acrylamide (28**).** A mixture of anilide (**3**) (0.01 mole) and triethylorthoformate (0.01 mole) in acetic anhydride (20 mL) was heated under reflux for 4 hrs, then the solvent was evaporated under vacuum. The solid product that formed was collected by filtration and crystallized from ethanol as colorless crystals; yield 55%; mp 240°; ir: 3300 (NH), 3100 (NH), 1700 (CO), 1650 (CO) cm^{-1} ; MS: m/z 390 (393 M^{+3}). *Anal.* Calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_4\text{O}_5\text{S}$: C, 52.30; H, 4.65; N, 14.35; S, 8.21. Found: C, 52.34; H, 4.67; N, 14.38; S, 8.25.

4-(5-Methyl-1*H*-pyrazol-3-ylamino)-*N*-pyrimidin-2-ylbenzene-sulfonamide (29**).** A mixture of anilide (**3**) (0.01 mole) and excess of hydrazine hydrate was fused together in sand bath

for 15 min., then pet. ether (60-80) was added. The solid product that formed was collected by filtration and crystallized from ethanol as colorless crystals; yield 40%; mp 168°; ir: 3400 (NH), 3343 (NH), 3221 (NH) cm^{-1} ; MS: m/z 330 (333 M^{+3}). *Anal.* Calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_6\text{O}_2\text{S}$: C, 50.90; H, 4.27; N, 14.44; S, 7.71. Found: C, 50.94; H, 4.29; N, 14.48; S, 7.76.

2-Amino-4-methyl-6-oxo-*N*-{4-[(pyrimidin-2-ylamino)sulfonyl]phenyl}-1,6-dihydro-pyridine-3-carboxamide (30**).** A mixture of anilide (**3**) (0.01 mole) and cyanoacetamide (0.01 mole) in ethanol (30 mL) containing a catalytic amount of piperidine (0.1 mL) was heated under reflux for 8 hrs. The solvent was evaporated under vacuum. The solid product that formed was collected by filtration and crystallized from ethanol as colorless crystals; yield 30%; mp 240°; ir: 3400 (NH_2), 3100 (NH), 1650 (CO) cm^{-1} ; ^1H nmr (DMSO- d_6) δ : 2.5 (s, 3H, CH_3), 3.18 (s, 1H, NH), 5.59 (s, 2H, NH_2), 6.47-7.54 (m, 8H, Ar-H), 8.25 (s, 2H, NH_2); MS: m/z = 400. *Anal.* Calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_6\text{O}_4\text{S}$: C, 50.99; H, 4.03; N, 20.99; S, 8.01. Found: C, 51.14; H, 4.08; N, 21.14; S, 8.06.

3-Hydroxyimino-*N*-{4-[(pyrimidin-2-ylamino)sulfonyl]phenyl}butanamide (31**).** To a mixture of anilide (**3**) (0.01 mole) and hydroxylamine hydrochloride (0.01 mole) in ethanol (20 mL), sodium acetate (0.01 mole) was added. The reaction mixture was heated under reflux for 2 hrs. The solid product formed was collected by filtration and crystallized from dioxane as colorless crystals; yield 50%; mp 250°; ir: 3500 (OH), 3400 (NH), 3200 (NH), 1650 (CO) cm^{-1} ; ^1H nmr (DMSO- d_6) δ : 2.5 (s, 3H, CH_3), 3.32 (s, 1H, OH), 5.97 (s, 2H, CH_2), 6.54-8.39 (m, 8H, Ar-H and NH proton), 11.22 (s, 1H, NH); MS: m/z 349 (345 M^+). *Anal.* Calcd. for $\text{C}_{14}\text{H}_{15}\text{N}_5\text{O}_4\text{S}$: C, 48.13; H, 4.33; N, 20.05; S, 9.18. Found: C, 48.22; H, 4.42; N, 20.08; S, 9.25.

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