Heteroatom Chemistry
Volume 15, Number 1, 2004

N-[4-(Dicyanomethylazo)phenyl]-2-saccharin-2-ylacetamide in the Synthesis of Pyridazine and Pyrimidine Derivatives

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Received 23 April 2003

ABSTRACT: *N-[4-(Dicyanomethylazo)phenyl]-2-saccharin-2-ylacetamide* (**2**) *proved to be a convenient precursor for the synthesis of a variety of pyridazine and pyrimidine derivatives* **4a,b,6**, *and* **7**. *Also a series of substituted pyrimidines* **10–16** *were prepared from the reaction of N-[4-(2-amino-1-cyano-2-substitutedvinylazo)phenyl]-2-(saccharin-2-yl)acetamide* **9a,b** *with different reagents via initial addition to either the cyano or amino group, followed by cyclization. Some of the synthesized heterocycles were screened for their biological activity.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 15:2–8, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10194

INTRODUCTION

Our interest in the syntheses of heterocyclic systems involving saccharinyl moiety is due to its significant biological and pharmacological activities [1,2]. In continuing search for heterocycles of biological activity [3,4], we thought it worthwile to synthesize pyridazine [5–7] and pyrimidine [8–10] derivatives of the saccharinyl moiety with the objective of obtaining new biologically active compounds.

RESULTS AND DISCUSSION

The starting compound *N*-[4-(dicyanomethylazo)-phenyl]-2-(saccharin-2-yl)acetamide (**2**) was prepared by diazotizing the amino group of saccharinylacetamide derivative and coupling the product with malononitrile in ethanolic sodium acetate solution at 0–5°C. Compound **2** reacted with ethyl cyanoacetate or ethyl acetoacetate in refluxing ethanol containing catalytic amounts of triethylamine to yield the pyridazine derivatives **4a,b** via the intermediate **3**. The reaction of **2** with malononitrile in refluxing ethanol/Et_3N solution afforded the pyridopyridazine derivative **6** [11] via intermediate **5**. As an extension, the behavior of **2** toward some nitrogen nucleophiles was investigated. Thus, the reaction of **2** with equimolar amounts of urea and thiourea in refluxing ethanolic sodium ethoxide solution afforded the pyrimidine derivatives **7a,b** (Scheme 1).

Treatment of **2** with piperidine or morpholine (**8a,b**) in refluxing ethanol yielded as 1:1 adducts the acyclic enaminonitriles **9a,b**.

The reaction of **9a,b** with urea and thiourea gave pyrimidine derivatives **10a–d**. Similarly, condensation of **9a,b** with formamide afforded *N*-[4-(4-amino-6-(piperidin-1-yl/morpholin-4-yl)pyrimidin-5-ylazo)phenyl]-2-saccharin-2-ylacetamide (**11a,b**) (Scheme 2).

The enaminonitrile moiety proved to be a highly reactive intermediate [12–14] for the synthesis of biologically active compounds. We extended our investigation on the reactivity toward isothiocyanates which was reported to afford a variety of products [15,16] depending on the reaction conditions. Thus the reaction of **9a,b** with phenyl isothiocyanate in refluxing dioxane or on fusion at 110–120°C afforded the pyrimidine derivatives **13a,b** via the formation of the disubstituted thiourea **12a,b**. On the other hand,

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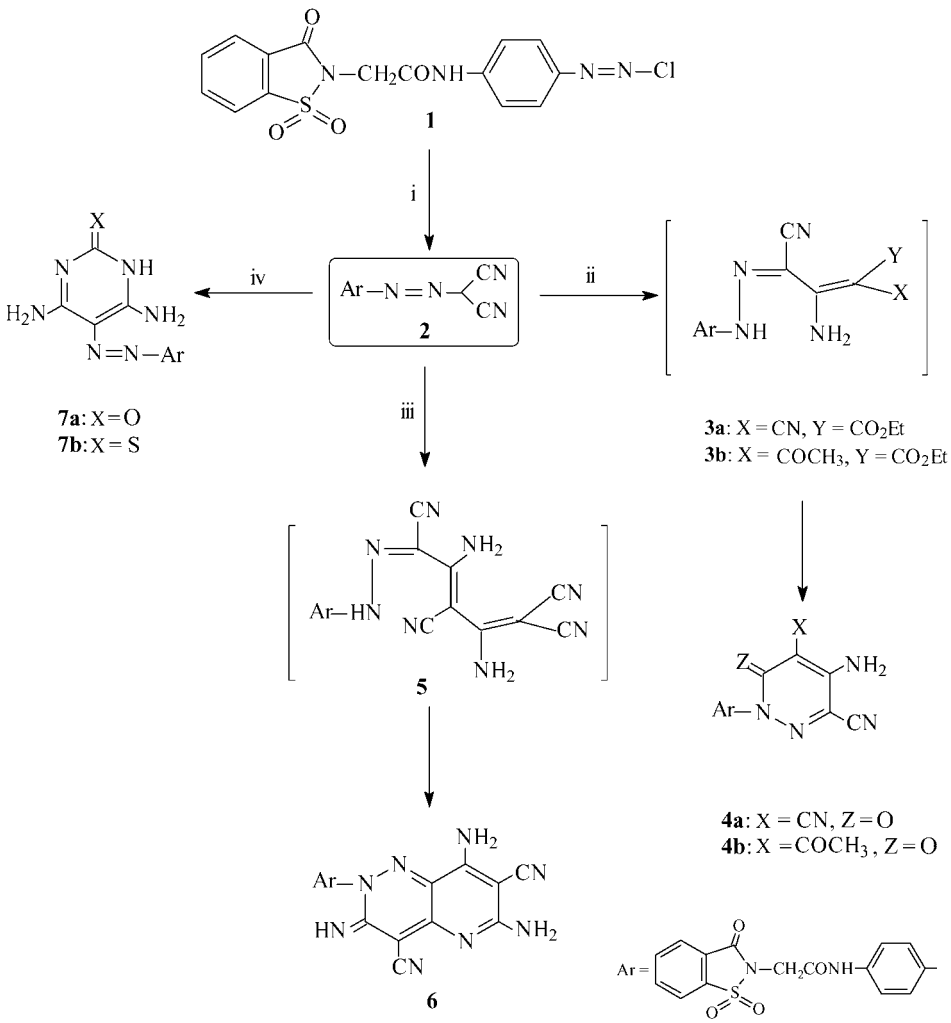


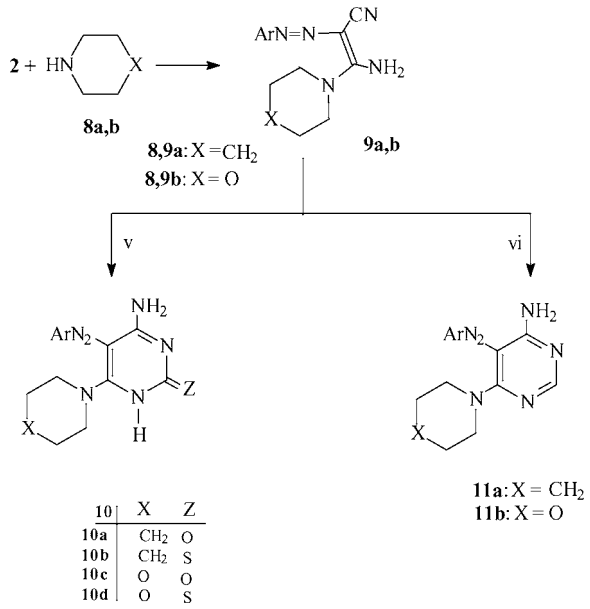
SCHEME 1 Reagents and conditions: (i) $CH_2(CN)_2$, EtOH, AcONa; (ii) XCH_2Y, EtOH, Et_3N; (iii) $2CH_2(CN)_2$, EtOH, Et_3N; (iv) H_2NCXNH_2, EtONa.

the reaction of **9a,b** with phenyl isothiocyanate in DMF containing powdered sodium hydroxide yielded the 2-thioxo-1,2,3,4-tetrahydropyrimidines **14a,b**. The structure of compounds **14a,b** were established chemically by independent synthesis via base-catalyzed cyclization of thiourea derivatives **12a,b** in DMF containing powder sodium hydroxide.

Our interest in this study was focused on the behavior of enaminonitrile toward carbon disulfide at different reaction conditions, aiming hopefully to establish a synthetic approach to some more nitrogen heterocycles. Thus **9a,b** reacted with carbon disulfide in pyridine at room temperature and afforded 1,3-thiazines **15a,b**, which upon treatment with aniline in refluxing ethanol afforded **14a,b**. In the reaction of **9a,b** with carbon disulfide under reflux dithioxopyrimidines **16a,b** were formed (Scheme 3). The structures of the above compounds were confirmed from their physical, analytical, and spectral data (cf. Experimental).

Biological Activity

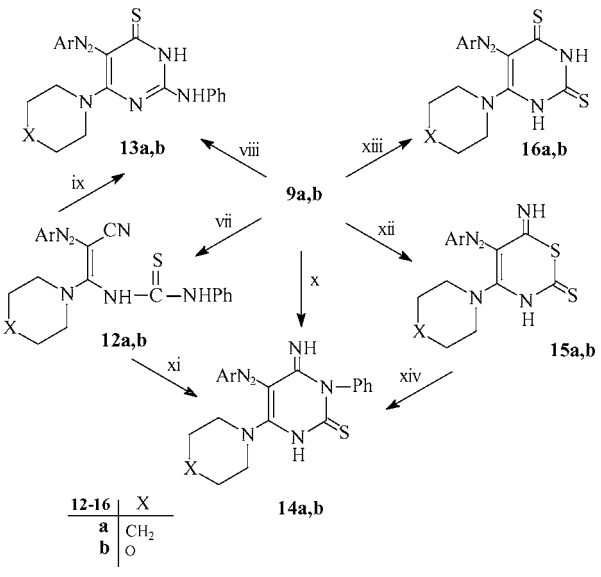
The antibacterial activity of some synthesized compounds was tested in vitro using the hole plate and filter paper method [17] against various pathogenic bacteria. The tested compounds were dissolved in 10% acetone (v/v). The concentrations were chosen as 500, 250, and 125 μg/ml. The results are summarized in Table 1. Compounds **4a** and **6** showed a moderate activity against different strains of bacteria. On the other hand, the other compounds **7b, 10a, 11b, 13a, 14b, 15a**, and **16b** showed promising activity toward bacteria. These data indicate that the introduction of saccharinyl moiety to pyridazine and pyrimidine derivatives enhances their antibacterial activity.



SCHEME 2 Reagents and conditions: (v) $H_2N–CZ–NH_2$, fusion; (vi) $HCONH_2$.

EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. IR spectra in KBr were recorded on a Shimadzu 470 spectrophotometer. ^1H NMR spectra were recorded on a Varian Gemini, 200 MHz instrument using TMS as internal reference (chemical shifts are expressed as δ, ppm) and the mass spectra were obtained on a Shimadzu GCMS QP 1000 Ex mass spectrometer (70 eV EI mode).



SCHEME 3 Reagents and conditions: (vii) PhNCS, dioxane, reflux 6 h; (viii) PhNCS, fusion at 120°C 7 h; (ix) dioxane, reflux 6 h; (x) PhNCS, DMF, NaOH, stirring at r.t. 4 h; (xi) DMF, NaOH stirring 2 h; (xii) CS_2, dry pyridine, stirring at r.t. 24 h; (xiii) CS_2, dry pyridine, reflux 1 h; (xiv) $PhNH_2$, stirring at 100°C 3 h.

*N-[4-Dicyanomethylazo)phenyl]-2-saccharin-2-ylacetamide (**2**)*

A cold solution of aryldiazonium chloride **1** (30 mmol) [prepared from 0.1 mol of *N*-(4-aminophenyl)-2-saccharinylacetamide and appropriate quantities of hydrochloric acid and sodium nitrite] was added to a solution of malononitrile (10 mmol) in ethanol (40 ml) containing sodium acetate (1.6 g). The reaction mixture was stirred at 0°C for 2 h and at room temperature for 1 h, and then left overnight in the refrigerator. The solid product so formed was collected by filtration and crystallized from ethanol to give **2**. Yield, 76%, mp 195–197°C; IR: ν = 3350 (NH), 2221 (CN), 1695 (imidic CO), 1665 (amidic CO), 1530 (N=N), 1350, 1150 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$): δ = 4.36 (s, 2H, CH_2), 6.98 (s, 1H, CH), 7.31–8.20 (m, 8H, Ar—H), 9.96 (s, 1H, NH, exchangeable); MS: *m/z* (%) 408 (61.2). Anal. Calcd for $C_{18}H_{12}N_6O_4S$ (408.39): C, 52.94; H, 2.96; N, 20.58; S, 7.85%. Found: C, 52.82; H, 2.83; N, 20.69; S, 7.96%.

Preparation of Pyridazine Derivatives **4a,b**

Equimolar amounts of **2** (10 mmol) and ethyl cyanoacetate or ethyl acetoacetate in ethanol (30 ml) containing a catalytic amount of Et_3N (3 drops) were heated under reflux for 2 h. The solid product so obtained was collected by filtration and crystallized to give **4a,b**.

*N-[4-(4-Amino-3,5-dicyano-6-oxo-6H-pyridazin-1-yl)phenyl]-2-saccharin-2-ylacetamide (**4a**)*. Yield, 54%, mp 283–235°C (dioxane); IR: ν = 3380–3290 (NH_2), 3180 (NH), 2220, 2215 (2CN), 1675, 1670 cm^{-1} (2CO); ^1H NMR ($CDCl_3$): δ = 4.34 (s, 2H, CH_2), 6.25 (s, 2H, NH_2), 7.32–8.41 (m, 8H, Ar—H), 9.89 (s, 1H, NH, exchangeable). Anal. Calcd for $C_{21}H_{13}N_7O_5S$ (475.44): C, 53.05; H, 2.76; N, 20.62%. Found: C, 53.19; H, 2.89; N, 20.50%.

*N-[4-(5-Acetyl-4-amino-3-cyano-6-oxo-6H-pyridazin-1-yl)phenyl]-2-saccharin-2-ylacetamide (**4b**)*. Yield, 58%, mp 271–273°C (dioxane); IR: ν = 3400–3295 (NH_2), 3190 (NH), 2221 (CN), 1695, 1680, 1675 cm^{-1} (3CO); ^1H NMR ($CDCl_3$): δ = 3.21 (s, 3H, CH_3), 4.35 (s, 2H, CH_2), 6.33 (s, 2H, NH_2), 7.22–8.31 (m, 8H, Ar—H), 9.90 (s, 1H, NH, exchangeable). Anal.

TABLE 1 Antibacterial Activity of Tested Compounds

	Bacillus subtilis		Bacillus cereus		Salmonella typhimurium		Escherichia coli	
	A	*MIC*	*A*	*MIC*	*A*	*MIC*	*A*	*MIC*
4a	+	125	++	250	+	125	++	500
6	++	250	++	250	+	125	+	125
7b	+++	125	++	250	+++	250	++	250
10a	++	250	+	250	+++	125	++	250
11b	+	125	++	125	++	250	++	125
13a	+++	500	++	250	++	125	++	250
14b	+++	250	+	125	++	250	++	125
15a	++	500	++	250	++	125	++	250
16b	++	250	++	500	+++	250	++	250

A, antimicrobial activity of tested compounds; MIC, minimum inhibitory concentration; +, >5 mm slightly active; ++, >7 mm moderately active; and +++, >9 mm highly active.

Calcd for $C_{22}H_{16}N_6O_6S$ (492.47): C, 53.66; H, 3.27; N, 17.07%. Found: C, 53.78; H, 3.39; N, 17.19%.

*N-[4-(6,8-Diamino-4,7-dicyano-3-imino-3H-pyrido[3,2-c]pyridazin-2-yl)phenyl]-2-saccharin-2-ylacetamide (***6***)*

A mixture of **2** (10 mmol) and malononitrile (20 mmol) in ethanol (30 ml) containing a catalytic amount of Et_3N (3 drops) was heated under reflux for 2 h. The solid product so obtained was collected by filtration and crystallized to give **6**. Yield, 57%, mp 253–255°C (DMF); IR: ν = 3410–3200 (multiple bands, NH_2, NH), 2224, 2220 (2CN), 1670 cm^{-1} (amidic CO); ^1H NMR ($CDCl_3$): δ = 4.33 (s, 2H, CH_2), 6.26, 6.32 (2s, $2NH_2$), 7.23–8.32 (m, 8H, Ar—H), 9.51, 9.91 (2s, 2H, 2NH, exchangeable). Anal. Calcd for $C_{24}H_{16}N_{10}O_4S$ (540.51): C, 53.33; H, 2.98; N, 25.91%. Found: C, 53.21; H, 2.83; N, 25.80%.

Preparation of Pyrimidine Derivatives **7a,b**

To a solution of **2** (10 mmol) in ethanolic sodium ethoxide solution (10 mmol) in absolute ethanol (30 ml), urea or thiourea (10 mmol) was added. The reaction mixture was boiled under reflux for 3 h. The mixture was then cooled, poured onto cold water, and neutralized with dilute HCl. The solid product was collected by filtration and crystallized to give **7a,b**.

*N-[4-(4,6-Diamino-2-oxo-1,2-dihydropyrimidin-5-ylazo)phenyl]-2-saccharin-2-ylacetamide (***7a***).* Yield, 57%, mp 221–223°C (ethanol); IR: ν = 3490–3260 (multiple bands, OH, NH_2), 3220–3190 (NH), 1680, 1675 (amidic CO), 1535 cm^{-1} (N=N); MS: *m/z* (%) 468 (91.2). Anal. Calcd. for $C_{19}H_{16}N_8O_5S$ (468.45): C, 48.71; H, 3.44; N, 23.92%. Found: C, 48.86; H, 3.32; N, 23.81%.

*N-[4-(4,6-Diamino-2-thioxo-1,2-dihydropyrimidin-5-ylazo)phenyl]-2-saccharin-2-ylacetamide (***7b***).* Yield, 55%, mp 210–212°C (ethanol); IR: ν = 3350–3340 (NH_2), 3210–3180 (NH), 2100 (SH), 1675 (amidic CO), 1533 (N=N), 1240 cm^{-1} (CS); ^1H NMR (DMSO): δ = 4.39 (s, 2H, CH_2), 5.99 (s, 4H, $2NH_2$), 7.21–8.11 (m, 8H, Ar—H), 9.91, 9.99 (2s, 2H, 2NH, exchangeable). Anal. Calcd for $C_{19}H_{16}N_8O_4S_2$ (484.51): C, 47.10; H, 3.33; N, 23.13; S, 13.24%. Found: C, 47.21; H, 3.43; N, 23.26; S, 13.13%.

Preparation of Enaminonitriles **9a,b**

Equimolar amounts (30 mmol) of **2** and piperidine (**8a**) or morpholine (**8b**) in absolute ethanol (50 ml) were refluxed for 3 h. The solid product so formed on cooling was collected by filtration and crystallized to give colorless crystals of **9a,b**.

*N-[4-(2-Amino-1-cyano-2-piperidin-1-ylvinylazo)-phenyl]-2-saccharin-2-ylacetamide (***9a***).* Yield, 71%, mp 241–243°C (DMF/H_2O); IR: ν = 3410–3345 (NH_2), 2215 (CN), 1670 (amidic CO), 1536 cm^{-1} (N=N); ^1H NMR (DCl_3): δ = 1.54 (m, 6H, $(CH_2)_3$), 3.42 (m, 4H, CH_2NCH_2), 4.38 (s, 2H, CH_2), 6.31 (s, 2H, NH_2), 7.34–8.12 (m, 8H, Ar—H), 9.20 (s, 1H, NH, exchangeable). Anal. Calcd for $C_{23}H_{23}N_7O_4S$ (493.54): C, 55.97; H, 4.70; N, 19.87%. Found: C, 55.83; H, 4.83; N, 19.74%.

*N-[4-(2-Amino-1-cyano-2-morpholin-4-ylvinylazo)phenyl]-2-saccharin-2-ylacetamide (***9b***).* Yield, 69%, mp 251–253°C (DMF/H_2O); IR: ν = 3400–3350 (NH_2), 3200 (NH), 2220 (CN), 1668 (amidic CO), 1530 cm^{-1} (N=N); ^1H NMR ($CDCl_3$): δ = 3.42 (m, 4H, CH_2NCH_2), 3.63 (m, 4H, CH_2OCH_2), 4.37 (s, 2H, CH_2), 6.36 (s, 2H, NH_2), 7.24–8.33 (8H, Ar—H), 9.93 (s, 1H, NH, exchangeable). Anal. Calcd for

$C_{22}H_{21}N_7O_5S$ (495.51): C, 53.33; H, 4.27; N, 19.79; S, 6.47%. Found: C, 53.41; H, 4.36; N, 19.62; S, 6.56%.

Preparation of Pyrimidine Derivatives **10a–d**

A mixture of **9a** or **9b** (10 mmol) in either urea or thiourea (20 mmol) was heated on an oil-bath at 120–130°C for 1 h with constant stirring. The temperature was then raised to 230°C and finally the mixture was heated at 230°C for 1 h. The molten product was dissolved in a hot dilute solution of NaOH. The boiling filtrate acidified with glacial acetic acid and the solid product, so formed, was collected by filtration and crystallized to give **10a–d**.

*N-[4-(4-Amino-2-oxo-6-piperidin-1-yl-1,2-dihydropyrimidin-5-ylazo)phenyl]-2-saccharin-2-ylacetamide (***10a***).* Yield, 65%, mp 270–272°C (DMF–ethanol, 1:2); IR: ν = 3390–3320 (NH_2), 3250–3190 (NH), 1665 cm^{-1} (amidic CO); ^1H NMR (DMSO): δ = 1.63 (m, 6H, $(CH_2)_3$), 3.81 (m, 4H, CH_2NCH_2), 4.34 (s, 2H, CH_2), 6.30 (s, 2H, NH_2), 7.1–8.32 (m, 8H, Ar—H), 9.91, 9.99 (2s, 2H, 2NH, exchangeable). Anal. Calcd for $C_{24}H_{24}N_8O_5S$ (536.56): C, 53.72; H, 4.51; N, 20.88%. Found: C, 53.84; H, 4.67; N, 20.70%.

*N-[4-(4-Amino-6-piperidin-1-yl-2-thioxo-1,2-dihydropyrimidin-5-ylazo)phenyl]-2-saccharin-2-ylacetamide (***10b***).* Yield, 63%, mp 243–245°C (DMF–ethanol, 1:2); IR: ν = 3400–3335 (NH_2), 3185–3120 (NH), 1660 (amidic CO), 1230 cm^{-1} (CS); MS: *m/z* (%) 552 (78.2). Anal. Calcd for $C_{24}H_{24}N_8O_4S_2$ (552.63): C, 52.16; H, 4.38; N, 20.28%. Found: C, 52.22; H, 4.27; N, 20.39%.

*N-[4-(4-Amino-6-morpholin-4-yl-2-oxo-1,2-dihydropyrimidin-5-ylazo)phenyl]-2-saccharin-2-ylacetamide (***10c***).* Yield, 60%, mp 226–228°C (butanol); IR: ν = 3395–3290 (NH_2), 3200–3160 (NH), 1670 cm^{-1} (amidic CO); ^1H NMR (DMSO): δ = 3.66 (m, 4H, CH_2NCH_2), 7.23–8.41 (m, 8H, Ar—H), 9.94, 9.99 (2s, 2H, 2NH, exchangeable). Anal. Calcd for $C_{23}H_{22}N_8O_6S$ (538.54): C, 51.30; H, 4.12; N, 20.81%. Found: C, 51.39; H, 4.25; N, 20.70%.

*N-[4-(4-Amino-6-morpholin-4-yl-2-thioxo-1,2-dihydropyrimidin-5-ylazo)phenyl]-2-saccharin-2-ylacetamide (***10d***).* Yield, 63%, mp 236–238°C (butanol); IR: ν = 3400–3320 (NH_2), 3195–3140 (NH), 1675 (amidic CO), 1240 cm^{-1} (CS); ^1H NMR (DMSO): δ = 3.48 (m, 4H, CH_2NCH_2), 3.71 (m, CH_2OCH_2), 4.33 (s, 2H, CH_2) 6.42 (s, 2H, NH_2), 7.35–8.42 (m, 8H, Ar—H), 9.87, 9.96 (2s, 2H, 2NH, exchangeable). Anal. Calcd for $C_{23}H_{22}N_8O_5S_2$ (554.60): C, 49.81; H, 4.00; N, 20.20%. Found: C, 49.93; H, 4.12; N, 20.32%.

Preparation of Pyrimidine Derivatives **11a,b**

A mixture of **9a** or **9b** (10 mmol) and formamide (30 mmol) was heated under reflux for 7 h. After cooling, the reaction mixture was poured into ice. The resulting solid was washed with water and crystallized to furnish **11a,b**.

*N-[4-(4-Amino-6-piperidin-1-ylpyrimidin-5-ylazo)-phenyl]-2-saccharin-2-ylacetamide (***11a***).* Yield, 59%, mp 271–273°C (acetic acid); IR: ν = 3400–3310 (NH_2), 3190 (NH), 1665 cm^{-1} (amidic CO); ^1H NMR ($CDCl_3$): δ = 1.49 (m, 6H, $(CH_2)_3$), 3.53 (m, 4H, CH_2NCH_2), 4.38 (s, 2H, CH_2), 6.41 (s, 2H, NH_2), 7.21–8.39 (m, 8H, Ar—H), 8.51 (s, 1H, pyrimidine-H_2), 9.92 (s, 1H, NH, exchangeable). Anal. Calcd for $C_{24}H_{24}N_8O_4S$ (520.56): C, 55.37; H, 4.65; N, 21.53%. Found: C, 55.49; H, 4.53; N, 21.65%.

*N-[4-(4-Amino-6-morpholin-4-ylpyrimidin-5-ylazo)phenyl]-2-saccharin-2-ylacetamide (***11b***).* Yield, 62%, mp 280–282°C (acetic acid), IR: ν = 3410–3320 (NH_2), 3200 (NH), 1668 cm^{-1} (amidic CO); ^1H NMR ($CDCl_3$): δ = 3.52 (m, 4H, CH_2NCH_2), 3.61 (m, 4H, CH_2OCH_2), 4.41 (s, 2H, CH_2), 6.37 (s, 2H, NH_2), 7.22–8.31 (m, 8H, Ar—H), 8.52 (s, 1H, pyrimidine-H_2), 9.96 (s, 1H, NH, exchangeable with D_2O). Anal. Calcd for $C_{23}H_{22}N_8O_5S$ (522.54): C, 52.87; H, 4.24; N, 21.44%. Found: C, 52.72; H, 4.35; N, 21.56%.

Preparation of Thiourea **12a,b**

A mixture of **9a** or **9b** (10 mmol) and phenyl isothiocyanate in dioxane (30 ml) was heated under reflux for 6 h. The solvent was distilled off. The solid product obtained on cooling was crystallized to give **12a,b**.

*N-{4-[1-Cyano-2-(3-phenylthioureido)-2-piperidin-1-ylvinylazo]phenyl}-2-saccharin-2-ylacetamide (***12a***).* Yield, 76%, mp 166–168°C (ethanol); IR: ν = 3290–3180 (NH), 2223 (CN), 1680 (amidic CO), 1245 cm^{-1} (CS); ^1H NMR ($CDCl_3$): δ = 1.61 (m, 6H, $(CH_2)_3$), 3.72 (m, 4H, CH_2NCH_2), 4.29 (s, 2H, CH_2), 7.15–8.24 (m, 13H, Ar—H), 10.1, 10.3, 10.5 (3s, 3H, 3NH, exchangeable). Anal. Calcd for $C_{30}H_{28}N_8O_4S_2$ (628.73): C, 57.31; H, 4.49; N, 17.82%. Found: C, 57.44; H, 4.34; N, 17.94%.

*N-{4-[1-Cyano-2-morpholin-4-yl-2-(3-phenylthioureido)vinylazo]phenyl}-2-saccharin-2-ylacetamide (***12b***).* Yield, 78%, mp 186–188°C (ethanol); IR:

ν = 3280–3190 (NH), 2226 (CN), 1682 (amidic CO), 1249 cm^{-1} (CS); MS: *m/z* (%) 630 (83.1). Anal. Calcd for $C_{29}H_{26}N_8O_5S_2$ (630.70): C, 55.23; H, 4.16; N, 17.77%. Found: C, 55.35; H, 4.28; N, 17.61%.

Preparation of Pyrimidine Derivatives **13a,b**

Method A. A solution of **12a** or **12b** (5 mmol) in dioxane (25 ml) was heated under reflux for 6 h. On cooling the reaction mixture, the separated solid was filtered off and crystallized to give **13a,b**.

Method B. A mixture of equimolar amounts of **9a** or **9b** and phenyl isothiocyanate (10 mmol) was fused in an oil-bath at 110–120°C for 7 h. The reaction mixture was cooled, treated with ethyl acetate, and filtered. The solid product was crystallized to give **13a,b**.

*N-[4-(2-Phenylamino-4-piperidin-1-yl-6-thioxo-1,6-dihydropyrimidin-5-ylazo)phenyl]-2-saccharin-2-ylacetamide (***13a***).* Yield, 68%, mp 271–273°C (benzene); IR: ν = 3200–3160 (NH), 1675 (amidic CO), 1248 cm^{-1} (CS); MS: *m/z* (%) 628 (75.31). Anal. Calcd for $C_{30}H_{28}N_8O_4S_2$ (628.73): C, 57.31; H, 4.49; N, 17.82%. Found: C, 57.43; H, 4.38; N, 17.95%.

*N-[4-(4-Morpholin-4-yl-2-phenylamino-6-thioxo-1,6-dihydropyrimidin-5-ylazo)phenyl]-2-saccharin-2-ylacetamide (***13b***).* Yield, 61%, mp 230–232°C (benzene); IR: ν = 3210–3170 (NH), 1672 (amidic CO), 1248 cm^{-1} (CS); ^{1}H NMR (DMSO): δ = 3.60 (m, 4H, CH_2NCH_2), 3.63 (m, 4H, CH_2OCH_2), 4.19 (s, 2H, CH_2), 7.22–8.34 (m, 13H, Ar—H), 9.69, 10.2, 10.32 (3s, 3H, 3NH, exchangeable). Anal. Calcd for $C_{29}H_{26}N_8O_5S_2$ (630.70): C, 55.23; H, 4.16; N, 17.77%. Found: C, 55.12; H, 4.28; N, 17.62%.

Preparation of Pyridimine Derivatives **14a,b**

Method A. Phenyl isothiocyanate (10 mmol) was added to a stirred mixture of **9a** or **9b** (10 mmol) and powdered sodium hydroxide (0.8 g) in DMF (25 ml). After stirring for 4 h, the reaction mixture was poured into dilute acetic acid (5%, 25 ml). The precipitated product was filtered and crystallized to give **14a,b**.

Method B. The disubstituted thiourea **12a** or **12b** (6 mmol) was stirred in DMF (20 ml) containing powdered sodium hydroxide (0.5 g). After stirring for 2 h, the reaction mixture was poured into dilute acetic acid (5%, 15 ml). The precipitated product was filtered and crystallized to give **14a,b**.

Method C. A mixture of **15a** or **15b** (5 mmol) and aniline (5 mmol) in ethanol (20 ml) was refluxed for 3 h and then allowed to cool. The solid product was collected by filtration and crystallized to give **14a,b**.

*N-[4-(4-Imino-3-phenyl-6-piperidin-1-yl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-ylazo)phenyl]-2-saccharin-2-ylacetamide (***14a***).* Yield, 58%, mp 200–202°C (butanol); IR: ν = 3360–3200 (NH), 1672 (amidic CO), 1241 cm^{-1} (CS); ^{1}H NMR (DMSO): δ = 1.63 (m, 6H, $(CH_2)_3$), 3.69 (m, 4H, CH_2NCH_2), 4.24 (s, 2H, CH_2), 7.11–8.32 (m, 13H, Ar—H), 9.66, 9.89, 10.1 (5s, 3H, 3NH, exchangeable). Anal. Calcd for $C_{30}H_{28}N_8O_4S_2$ (628.73): C, 57.31; H, 4.49; N, 17.82%. Found: C, 57.43; H, 4.37; N, 17.71%.

*N-[4-(4-Imino-6-morpholin-4yl-3-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-ylazo)phenyl]-2-saccharin-2-ylacetamide (***14b***).* Yield, 64%, mp 222–224°C (butanol); IR: ν = 3320–3185 (NH), 1670 (amidic CO), 1240 cm^{-1} (CS), MS: *m/z* (%) 630 (76.33). Anal. Calcd for $C_{29}H_{26}N_8O_5S_2$ (630.70): C, 55.23; H, 4.16; N, 17.77%. Found: C, 55.36; H, 4.28; N, 17.63%.

Preparation of 1,3-Thiazine Derivatives **15a,b**

A mixture of **9a** or **9b** (8 mmol), carbon disulfide (6 ml), and dry pyridine (10 ml) was stirred at room temperature for 24 h. The reaction mixture was poured onto ice water and diluted with HCl. The solid product was filtered, washed with water, and crystallized to give **15a,b**.

*N-[4-(6-Imino-4-piperidin-1-yl-2-thioxo-3,6-dihydro-2H-[1,3]thiazin-5-ylazo)phenyl]-2-saccharin-2-ylacetamide (***15a***).* Yield, 80%, mp 266–268°C (DMF–methanol, 1:2); IR: ν = 3320–3190 (NH), 1678 (amidic CO), 1250 cm^{-1} (CS); MS: *m/z* (%) 569 (72.13). Anal. Calcd for $C_{24}H_{23}N_7O_4S_3$ (569.68): C, 50.60; H, 4.07; N, 17.21%. Found: C, 50.72; H, 4.16; N, 17.34%.

*N-[4-(6-Imino-4-morpholin-4-yl-2-thioxo-3,6-dihydro-2H-[1,3]thiazin-5-ylazo)phenyl]-2-saccharin-2-ylacetamide (***15b***).* Yield, 82%, mp 242–244°C (DMF–methanol, 1:2); IR: ν = 3340–3200 (NH), 1680 (amidic CO), 1247 cm^{-1} (CS); ^{1}H NMR (DMSO): δ = 3.58 (m, 4H, CH_2NCH_2), 3.61 (m, 4H, CH_2OCH_2), 4.22 (s, 2H, CH_2), 7.12–8.14 (m, 8H, Ar—H), 9.89, 10.2, 10.52 (3s, 3H, 3NH, exchangeable). Anal. Calcd for $C_{23}H_{21}N_7O_5S_3$ (571.66): C, 48.32; H, 3.70; N, 17.15%. Found: C, 48.20; H, 3.83; N, 17.26%.

Preparation of Pyrimidine Derivatives **16a,b**

Method A. A mixture of **9a** or **9b** (8 mmol), carbon disulfide (6 ml), and dry pyridine (20 ml) was refluxed for 1 h and then allowed to stand at room temperature for 12 h. The reaction mixture was poured onto ice/water neutralized with dilute HCl. The solid product was filtered, washed with water, and crystallized to give **16a,b**.

Method B. A mixture of **9a** or **9b** (8 mmol), carbon disulfide (6 ml), and powdered KOH (0.4 g) in DMF (20 ml) was kept at room temperature overnight. Then the reaction mixture was heated under reflux for 2 h, cooled, and poured onto ice. The aqueous suspension was acidified with acetic acid (10%, 10 ml) and the separated product was filtered, washed with water, and crystallized to give **16a,b**.

*N-[4-(6-Piperidin-1-yl-2,4-dithioxo-1,2,3,4-tetrahydropyrimidin-5-ylazo)phenyl]-2-saccharin-2-ylacetamide (***16a***).* Yield, 84%, mp 281–283°C (butanol); IR: $\nu = 3210$–3150 (NH), 1671 (amidic CO), 1246 cm^{-1} (CS); ^1H NMR (DMSO): $\delta = 1.64$ (m, 6H, $(CH_2)_3$), 3.74 (m, 4H, CH_2NCH_2), 4.26 (s, 2H, CH_2), 7.16–8.23 (m, 8H, Ar—H), 10.1, 10.26, 10.48 (3s, 3H, 3NH, exchangeable). Anal. Calcd for $C_{24}H_{23}N_7O_4S_3$ (569.68): C, 50.60; H, 4.07; N, 17.21%. Found: C, 50.73; H, 4.18; N, 17.34%.

*N-[4-(6-Morpholin-4-yl-2,4-dithioxo-1,2,3,4-tetrahydropyrimidin-5-ylazo)phenyl]-2-saccharin-2-ylacetamide (***16b***).* Yield, 87%, mp 251–253°C (butanol); IR: $\nu = 3250$–3190 (NH), 1673 (amidic CO), 1246 cm^{-1} (CS); MS: *m/z* (%) 571 (31.32). Anal. Calcd for $C_{23}H_{21}N_7O_5S_3$ (571.66): C, 48.32; H, 3.70; N, 17.15%. Found: C, 48.45; H, 3.83; N, 17.26%.

ACKNOWLEDGMENT

The author is grateful to Dr. M. M. Amer, Botany Department, Faculty of Science, Benha University, for biological screening.

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