A Novel Synthesis of Some 1,4-Phenylene-bis-heterocyclic Carboxamide Derivatives

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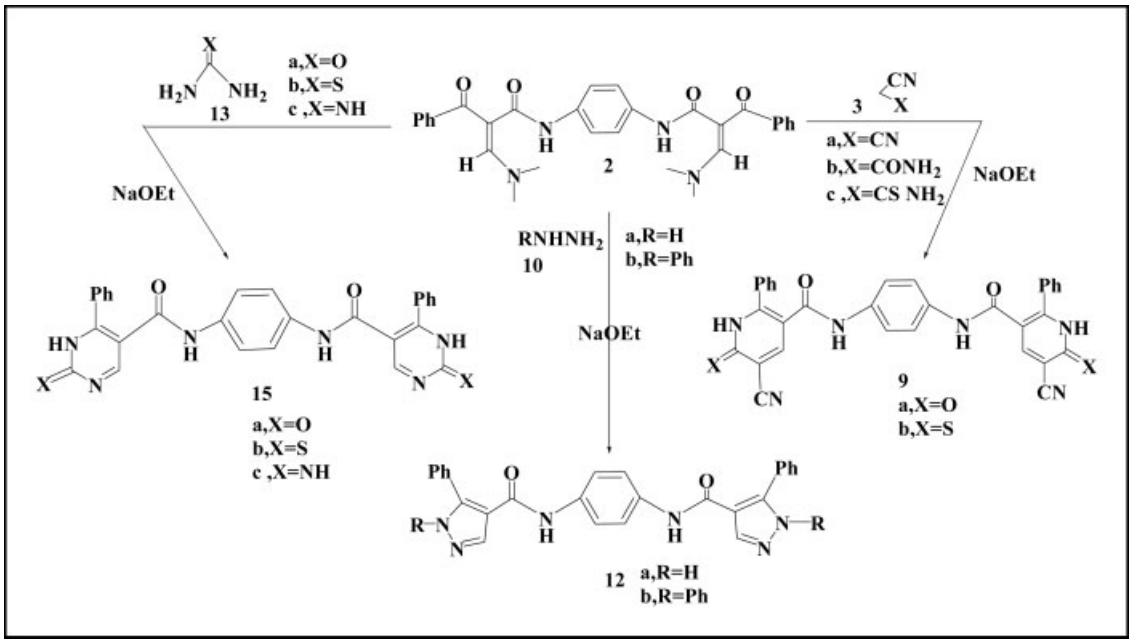

N,N′-(1,4-phenylene)bis(3-oxo-3-phenylpropanamide) **1** reacts with DMFDMA in refluxing toluene to afford *N,N′*-(1,4-phenylene)bis(2-benzoyl-3-(dimethylamino)acrylamide) **2**. Compound **2** reacts with a twofold excess of the active methylene reagents **3a-c** to afford the pent-2-enediamide derivatives **7** and **8a,b**, respectively. Compounds **7** and **8a** could be cyclized to afford the same compound *N,N′*-(1,4-phenylene)bis(5-cyano-6-oxo-2-phenyl-1,6-dihydropyridine-3-carboxamide) **9a** while **8b** was cyclized to afford the 6-thioxo analogue **9b**. Compound **2** reacts with hydrazine derivatives **10a,b** in refluxing ethanol/piperidine to afford the hydrazinylacrylamide derivatives **11a,b**, which have been cyclized to the corresponding *N,N′*-(1,4-phenylene)bis(1*H*-pyrazole-4-carboxamide) derivatives **12a,b**, respectively. Compound **2** reacts also with urea derivatives **13a-c** in refluxing ethanol/piperidine to afford the *N,N′*-(1,4-phenylene)bis(2-benzoyl-3-substituted-acrylamide) derivatives **14a-c**, which could be cyclized into *N,N′*-(1,4-phenylene)bis(6-phenyl-1,2-dihydropyrimidine-5-carboxamide)-2-oxo; 2-thioxo or 2-imino derivatives **15a-c**, respectively.

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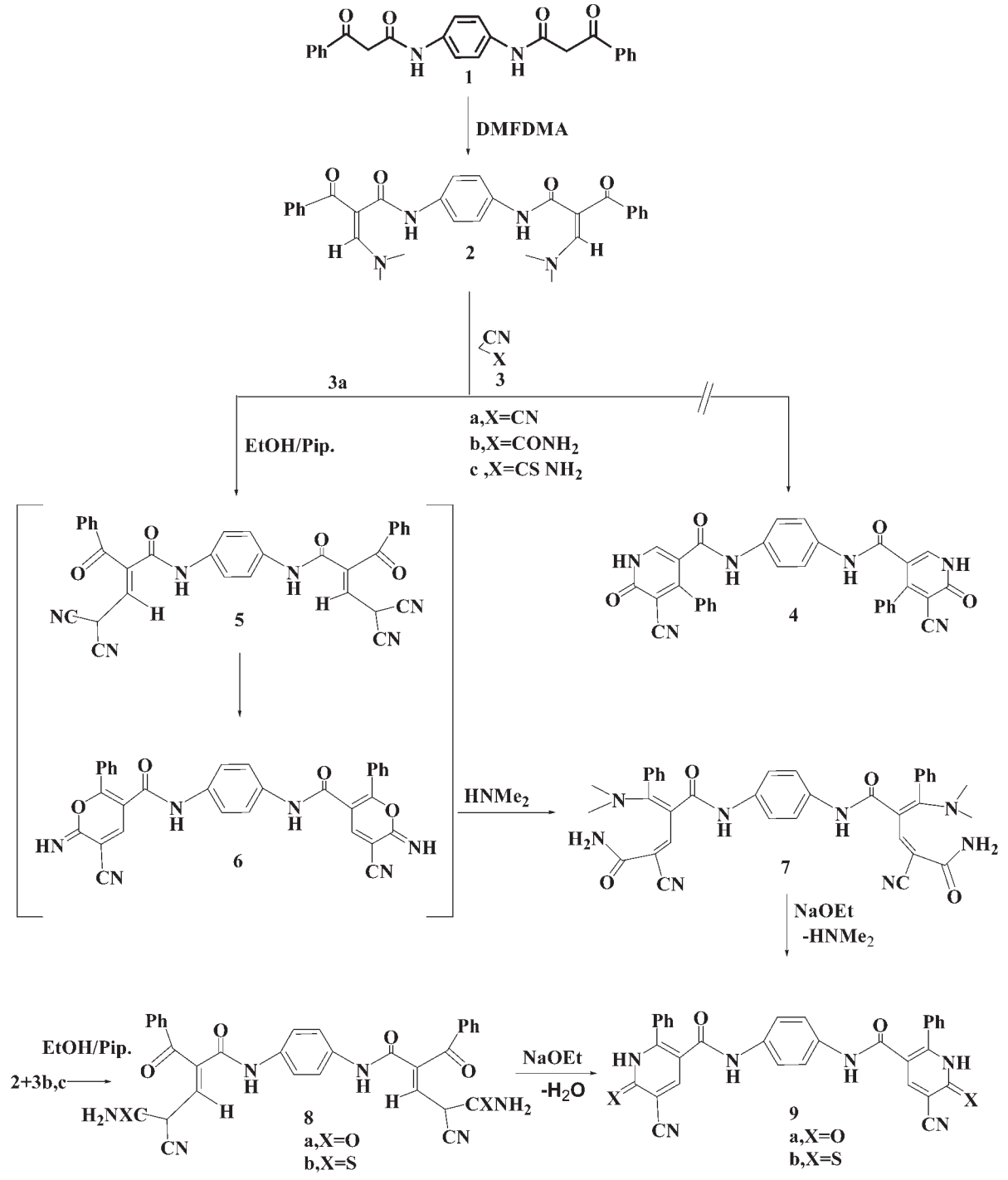
INTRODUCTION

Pyridines and pyridones represent an important class of organic compounds due to their pharmaceutical applications [2–4]. Furthermore functionalized pyrazoles have received much attention due to their diverse biological activities as immunosuppressant agents, selective COX-2 inhibitors, and antitumor agents [5]. Pyrimidine derivatives also exhibit HMG-CoA reductase inhibitory effect and antitumor activity [6]. The majority of attention has been so far paid to the development of syntheses of only one functionally substituted unit of these nuclei [7,8]. To our knowledge there is only one report describing the synthesis of compounds containing two 4*H*-benzopyran units [9], but those containing two pyridone units, two pyrazole units or two pyrimidine units, are hitherto not investigated. The reaction of enaminones with active methylene reagents [10], amines [11], or hydrazines [12] represents one of the strategies for the preparation of 2-1*H*-pyridones, pyrroles, and pyridazines, respectively. In the last two decades, we have been involved in a program aiming at the synthesis of functionally substituted heterocyclic compounds from

Scheme 1. Preparation of compounds **2**, **7**, **8**, and **9**.

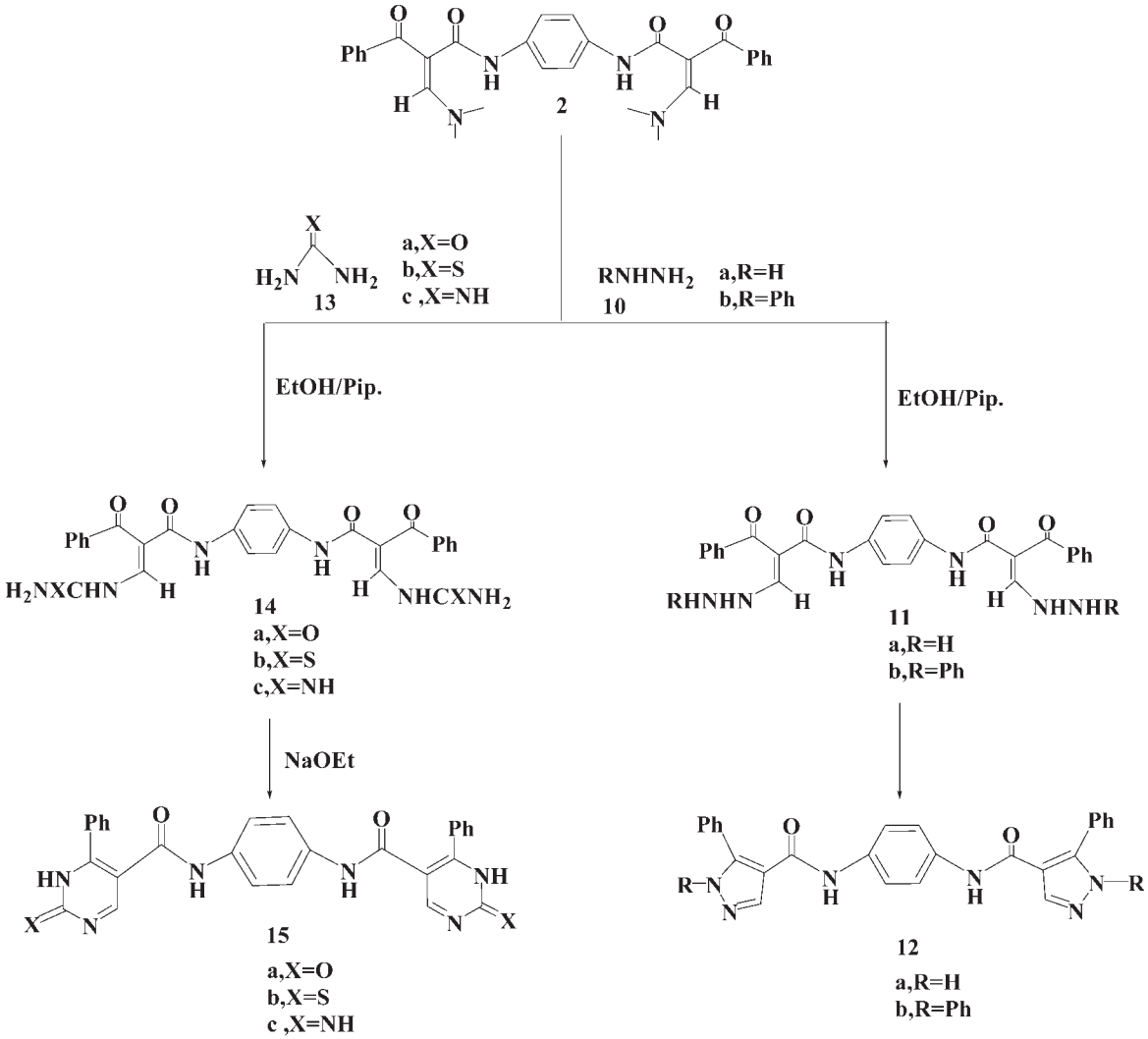


cheap laboratory available starting materials to be tested as biodegradable agrochemicals [13–15]. Some functional compounds bearing two or more of the aforementioned units are required for biological activity studies. 1,4-Phenylenediamine seemed a suitable candidate to fulfill this objective.

RESULTS AND DISCUSSION

1,4-Phenylenediamine smoothly undergoes the condensation reaction with twofold excess of ethyl benzoylacetate in refluxing dimethylformamide (DMF) to afford quantitatively *N,N′*-(1,4-phenylene)bis(3-oxo-3-phenylpropanamide) **1**.

Scheme 2. Preparation of compounds **11**, **12**, **14**, **15**.



Compound **1** reacts with dimethylformamide dimethylacetal (DMFDMA) in refluxing toluene to afford *N,N′*-(1,4-phenylene)bis(2-benzoyl-3-(dimethylamino)acrylamide) **2** in quantitative yield (*cf.* Scheme 1).

Compound **2** reacts with a twofold excess of malononitrile **3a** to afford a product of molecular mass m/z = 642. This molecular mass is applicable to the molecular formula $C_{36}H_{34}N_8O_4$. *N,N′*-(1,4-phenylene)bis(2-cyano-4-((dimethylamino)(phenyl)methylene)pent-2-enediamide) **7** (Scheme 1) was assigned to this product based on analytical and spectral data (*cf.* Experimental part). In this reaction it is apparent that malononitrile moieties readily substitute the dimethylamino groups in **2** with elimination of dimethylamine to give the intermediate **5** rather than the initial condensation of **3a** with the carbonyl groups of **2** and cyclization after the claimed hydrolysis of two cyano groups (one on each side) to amide groups to give **4** [16,17]. The intermediate **5** undergoes cyclization to the bis-iminopyran derivative **6**, which is re attacked by dimethylamine to afford the isolable product **7**. Recently, we could prove via an X-ray crystallographic study that **3a** substitutes NMe_2 followed by cyclization into iminopyran and ring opening by the attack of dimethylamine [10].

Refluxing compound **7** in ethanol/sodium ethoxide furnished its cyclization to the desired *N,N′*-(1,4-phenylene)bis(5-cyano-6-oxo-2-phenyl-1,6-dihydropyridine-3-carboxamide) **9a** via re-elimination of dimethylamine. The IR spectrum of this product showed absorption bands at υ_{max} at 3451–3141 cm^{-1} for the NH protons, 2213 cm^{-1} for the CN groups, 1687 and 1659 cm^{-1} for the carbonyl groups. The mass spectrum showed the molecular ion peak at m/z = 552 [M^+]. ^1H NMR spectrum showed signals at δ_H = 7.15–7.68 (m, 14H, Ar-Hs), 7.70 (s, 2H, 2NH), 7.99 (s, 2H, Pyridone 4-Hs), 10.07 (s, 2H, 2NH). Thus structure **9a** was established

for this product on the basis of the spectral and element analysis data, which are in complete agreement with this structure.

Compound **2** also reacts with cyanoacetamide **3b** in refluxing ethanol with few drops of piperidine as catalyst to afford the product **8a** via substitution of NMe_2 in **2** by cyanoacetamide. Refluxing compound **8a** in ethanol/sodium ethoxide furnished its cyclization to afford the same product **9a** via loss of water. This finding is in complete agreement with our reported behavior of **3b** with enaminones that had been rationalized in our previous article [10].

Following the same mechanistic pathway during its reaction with **3b**, compound **2** reacts with cyanothioacetamide **3c** in refluxing ethanol/piperidine to afford a yellow crystalline product, which showed the presence of sulfur in the element test. The IR spectrum showed carbonyl absorption bands at υ_{max} = 1658 & 1680 cm^{-1} and the mass spectrum showed the molecular ion peak at m/z = 620 [M^+]. Based on these data as well as the ^1H NMR and elemental analytical data structure **8b** was assigned to this product. Refluxing compound **8b** in ethanol/sodium ethoxide led to its cyclization via loss of water to afford the *N,N′*-(1,4-phenylene)bis(5-cyano-2-phenyl-6-thioxo-1,6-dihydropyridine-3-carboxamide) compound **9b** (*cf*. Scheme 1 and Experimental part).

Compound **2** reacts also with hydrazine hydrate **10a** and with phenyl hydrazine **10b** in refluxing ethanol/piperidine to afford the hydrazinylacrylamide derivatives **11a** and **11b**, respectively (Scheme 2), in which the hydrazino moiety (—-NHNHR) of **10a** or **10b** substitutes the -NMe_2 of **2** on both sides. These could be readily cyclized in refluxing ethanol/sodium ethoxide to give *N,N′*-(1,4-phenylene)bis(5-phenyl-1*H*-pyrazole-4-carboxamide) **12a** and *N,N′*-(1,4-phenylene)bis(1,5-diphenyl-1*H*-pyrazole-4-carboxamide) **12b**. Analytical and spectral data are in complete agreement with structures **11a,b** and **12a,b** (*cf*. experimental).

Similarly, compound **2** reacts with urea **13a**, thiourea **13b**, and guanidine **13c** in refluxing ethanol/piperidine to afford yellow products with molecular masses 540, 672, and 538, respectively. It is apparent also in this case that the dimethylamino groups of **2** were substituted by the —$NHCXNH_2$ of the respective urea derivative with elimination of dimethylamine to afford compounds **14a**, **14b**, and **14c**, respectively.

Compounds **14a-c** could also be cyclized upon their reflux in ethanol/sodium ethoxide solution to afford the desired *N,N′*-(1,4-phenylene)bis(2-oxo-6-phenyl-1,2-dihydropyrimidine-5-carboxamide) **15a** *N,N′*-(1,4-phenylene)bis(6-phenyl-2-thioxo-1,2-dihydropyrimidine-5-carboxamide) **15b** and *N,N′*-(1,4-phenylene)bis (2-imino-6-phenyl-1,2-dihydropyrimidine-5-carboxamide) **15c**, respectively.

CONCLUSION

We could obtain some novel *p*-phenylene-bis-heterocyclic carboxamides from readily available cheap starting materials that could be useful for biological evaluation studies.

EXPERIMENTAL

Melting points were measured on an Electrothermal (9100) apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin Elmer 1430 spectrophotometer. The ^1H NMR and ^{13}C NMR spectra were taken on a Varian Gemini 300 MHz spectrometer in DMSO-d_6 using TMS as internal standard and chemical shifts are expressed in δ ppm values. Mass spectra were taken on a Shimadzu GCMS-GB 1000 PX (70 ev). Elemental analyses were carried out at the Micro-analytical Center at Cairo University.

***N,N′*-(1,4-phenylene)bis(3-oxo-3-phenylpropanamide) 1.** A mixture of *p*-phenylenediamine (10 mmol) and ethyl benzoylacetate (20 mmol) in DMF (15 mL) was refluxed for 3 h and then left to cool to room temperature. The reaction mixture was then poured onto ice-cold water and the precipitated solid was filtered off and recrystallized from ethanol to afford **1** as yellow crystalline solid; yield (3.84 g; 96%); mp 237–238°C (EtOH/DMF). υ_{max} = 3470, 3377, 3271 (NH), 1687(CO), 1641 (amide CO); δ_H. MS: m/z = 400 (M^+). δ_H = 3.54 (s, 4H, $2CH_2$), 7.29–7.85 (m, 14H, arom. H), 9.95 (s, 2H, 2NH).

Anal. Calcd for $C_{24}H_{20}N_2O_4$ (400.43): C, 71.99; H, 5.03; N, 7.00. Found: C, 72.08; H, 5.13; N, 7.28.

***N,N′*-(1,4-phenylene)bis(2-benzoyl-3-(dimethylamino)acrylamide) 2.** To compound **1** (4 g; 10 mmol) in 20 mL of dry toluene was added (2.4 g; 20 mmol) of DMFDMA and the reaction mixture was refluxed for 4 h, whereby the reactants dissolve completely to a clear solution and then a precipitate reappeared. The flask was left to cool to room temperature and the solid product was collected by filtration and recrystallized from ethanol to give compound **2** as yellow crystalline solid; yield (4.85 g; 95%); mp 209–210°C (EtOH/DMF). υ_{max} = 3400, 3265, 3131 (NH), 1655(CO), 1642 (amide CO); δ_H = 3.33 (s, 12H, $4CH_3$), 7.14–8.00 (m, 14H, arom.), 7.44 (s, 2H, olefinic protons), 10.07 (s, 2H D_2O exch., 2NH). MS: m/z = 510 (M^+).

Anal. Calcd for $C_{30}H_{30}N_4O_4$ (510.58): C, 70.57; H, 5.92; N, 10.97. Found: C, 70.62; H, 5.98; N, 11.17.

***N,N′*-(1,4-phenylene)bis(2-cyano-4-((dimethylamino)(phenyl)methylene)pent-2-enediamide)7.** To a mixture of the enaminone **2** (5.1 g; 10 mmol) and malononitrile **3a** (1.32 g; 20 mmol) in ethanol (25 mL) was added few drops of piperidine as catalyst. The reaction mixture was refluxed for 2 h and then left to cool to room temperature. The solid product thus precipitated that was collected by filtration and crystallized from acetic acid to afford compound **7** as yellow crystalline product: yield (5 g, 78%); mp 246–247°C (AcOH); υ_{max} = 3451, 3333, 3141 (NH & NH_2), 2213 (CN), 1687 (CO), and 1659 (CO) cm^{-1}; MS: m/z = 642 [M^+]; δ_H = 2.85 (s, 12H, 4 × CH_3), 7.15–7.68 (m, 14H, Ar-Hs), , 6.78 (s, 4H, $2NH_2$), 7.70 (s, 2H, 2NH), 7.98 (s, 2H, 3-Hs).

Anal. Calcd *for* $C_{36}H_{34}N_8O_4$: (642.71): C, 67.28; H, 5.33; N, 17.43. Found: C, 67.35; H, 5.38; N, 17.35.

The reaction of the enaminone 2 with the acetamides 3b,c. To a mixture of the enaminone **2** (5.1 g; 10 mmol) and cyanoacetamide **3b** (1.64 g; 20 mmol) or cyanothioacetamide **3c** (2.0 g, 20 mmol) in ethanol (25 mL) was added few drops of piperidine as catalyst. The reaction mixture was refluxed in each case for 2 h and then left to cool at room temperature. The solid products thus precipitated were collected by filtration and crystallized from acetic acid to afford compound **8a** and **8b**.

***N,N′*-(1,4-phenylene)bis(2-benzoyl-4-cyanopent-2-enediamide) 8a.** Yellow crystalline product: yield (4.47 g, 76%); mp 234–235°C (AcOH); υ_{max} = 3452, 3330, 3142 (NH & NH_2), 2215 (CN), 1686 (CO), and 1656 (CO), 1640 (CO) cm^{-1}; MS: m/z = 588 [M^+]; δ_H = 3.34 (d, 2H, 2Hs; j = 12.62 Hz), 7.15–7.68 (m, 14H, Ar-Hs), 7.72 (s, 2H, 2NH), 7.98 (d, 2H, 3-Hs; j = 12.62 Hz), 10.05 (s, 4H, $2NH_2$).

Anal. Calcd *for* $C_{32}H_{24}N_6O_6$: (588.57): C, 65.30; H, 4.11; N, 14.28. Found: C, 65.32; H, 4.15; N, 14.38.

***N,N′*-(1,4-phenylene)bis(5-amino-2-benzoyl-4-cyano-5-thioxopent-2-enamide) 8b.** Yellow crystalline product: yield (4.28 g, 69%); mp 213–215°C (AcOH); υ_{max} = 3454, 3332, 3140 (NH & NH_2), 2219 (CN), 1679 (CO), and 1656 (CO) cm^{-1}; MS: m/z = 621 [M^+ + 1]; δ_H = 3.32 (d, 2H, 2Hs; j = 12.6 Hz), 7.14–7.67 (m, 14H, Ar-Hs), 7.73 (s, 2H, 2NH), 7.92 (d, 2H, 3-Hs; j = 12.6 Hz), 10.04 (s, 4H, $2NH_2$).

Anal. Calcd for $C_{32}H_{24}N_6O_4S_2$: (620.70): C, 61.92; H, 3.90; N, 13.54; S, 10.33. Found: C, 61.98; H, 3.85; N, 13.74; S, 10.50.

Cyclization of 7 and 8a,b. To the solution of each compounds **7**, **8a**, and **8b** (10 mmol) in 20 mL of ethanol was added few drops of sodium ethoxide (freshly prepared by dissolving 0.1 g of sodium metal in 10 mL of absolute ethanol). The reaction mixture was refluxed for 1 h in each case then left to cool overnight. The contents of the flask was poured on ice cold water and acidified with few drops of HCl till just neutral. The precipitated solids were collected by filtration and recrystallized to give.

***N,N′*-(1,4-phenylene)bis(5-cyano-6-oxo-2-phenyl-1,6-dihydropyridine-3-carboxamide) 9a.** Pale yellow crystals, yield (3.7 g, 67 % from **7**; mp 282–283°C (AcOH) and 3.86 g; 70% from **8a**; mp 284–285°C (AcOH); υ_{max} = 3451, 3333, 3141 (NH), 2213 (CN), 1687 (CO), and 1659 (CO) cm^{-1}; MS: m/z = 552 [M^+]; δ_H = 7.15–7.68 (m, 14H, Ar-Hs), 7.70 (s, 2H, 2NH), 7.99 (s, 2H, Pyridone 4-Hs), 10.07 (s, 2H, 2NH).

Anal. Calcd for $C_{32}H_{20}N_6O_4$: (552.54): C, 69.56; H, 3.65; N, 15.21. Found: C, 69.55; H, 3.68; N, 15.28.

***N,N′*-(1,4-phenylene)bis(5-cyano-2-phenyl-6-thioxo-1,6-dihydropyridine-3-carboxamide) 9b.** Yellow crystalline product, yield (4.2 g; 72 %), mp. 291–292°C (AcOH); υ_{max} = 3345, 3228 (NH), 2215 (CN), and 1658 cm^{-1} (CO); MS: m/z = 585 [M^+ + 1]; δ_H = 7.15–7.68 (m, 16H, Ar.), 8.25 (br.s., 2H, 2NH), 10.12 (br.s., 2H, 2NH). δ_C = 104.9 (s), 116.2 (s), 118.05 (s), 119.58 (d), 127.34 (d), 127.67 (d), 128.34 (d), 133.14 (s), 136.85 (s), 154.39 (s), 160.17 (d), 166.5 (s), 175, 52 (s).

Anal. Calcd for $C_{32}H_{20}N_6O_2S_2$: (584.67): C, 65.74; H, 3.45; N, 14.37; S, 10.97. Found: C, 65.78; H, 3.55; N, 14.45; S, 10.58.

The reaction of the enaminone 2 with hydrazine hydrate and phenyl hydrazine 10a,b. To a mixture of the enaminone **2** (5.1 g; 10 mmol) and hydrazine hydrate **10a** or phenyl hydrazine **10b** (20 mmol) in ethanol (25 mL) was added few drops of piperidine as catalyst. The reaction mixture was refluxed for 3 h, where a solid precipitate was formed during the reflux. The flask was left to cool to room temperature and the product was collected by filtration in each case and washed thoroughly with cold ethanol and recrystallized from DMF/ethanol to afford **11a,b**, respectively.

***N,N′*-(1,4-phenylene)bis(2-benzoyl-3-hydrazinylacrylamide) 11a.** Pale yellow crystals, Yield (2.7 g; 56%), mp. 235–236°C (EtOH/DMF); υ_{max} = 3343, 3235, 2156 (NH & NH_2), 1687 and 1655 cm^{-1} (2CO); MS: m/z = 484 [M^+]; δ_H = 4.45 (br. s, 4H, $2NH_2$), 7.04–7.68 (m, 14H, Ar.Hs), 7.76 (s, 2H, olefin Hs), 8.15 (s, 2H, 2NH), 9.55 (br.s., 2H, 2NH).

Anal. Calcd for $C_{26}H_{24}N_6O_4$: (484.51): C, 64.45; H, 4.99; N, 17.35. Found: C, 64.48; H, 5.09; N, 17.47.

***N,N′*-(1,4-phenylene)bis(2-benzoyl-3-(2-phenylhydrazinyl) acrylamide) 11b.** Yellow crystals, Yield (3.8 g; 60%), mp. 243–245°C (EtOH/DMF); υ_{max} = 3344, 3226 (NH), 1685, and 1654 (2CO) cm^{-1}; MS: m/z = 636 [M^+]; δ_H = 5.56 (s, 2H, 2NH), 7.14–7.72 (m, 24H, Ar. Hs), 7.74 (s, 2H, olefin Hs), 8.25 (s, 2H, 2NH), 9.77 (br.s., 2H, NH).

Anal. Calcd for $C_{38}H_{32}N_6O_4$: (636.70): C, 71.68; H, 5.07; N, 13.20. Found: C, 71.75; H, 5.27; N, 13.38.

Cyclization of 11a,b. To a solution of each of compounds **11a** and **11b** (10 mmol) in 20 mL of ethanol was added few drops of sodium ethoxide (freshly prepared by dissolving 0.1 g of sodium metal in 10 mL of absolute ethanol). The reaction mixture was refluxed for 1 h in each case then left to cool overnight. The reaction mixture was poured on ice cold water and neutralized with few drops of HCl. The precipitated solids were collected by filtration and recrystallized to give **12a,b**, respectively.

***N,N′*-(1,4-phenylene)bis(5-phenyl-1H-pyrazole-4-carboxamide) 12a.** Pale yellow crystals, Yield (2.6 g; 58%), mp. 295–296°C (EtOH/DMF); υ_{max} = 3343, 3235 (NH), and 1655 cm^{-1} (CO); MS: m/z = 448 [M^+]; δ_H = 7.06–7.65 (m, 16H, Ar.Hs), 8.15 (s, 2H, 2NH), 9.25 (br.s., 2H, 2NH).

Anal. Calcd for $C_{26}H_{20}N_6O_2$: (448.48): C, 69.63; H, 4.49; N, 18.74. Found: C, 69.52; H, 4.58; N, 18.96.

***N,N′*-(1,4-phenylene)bis(1,5-diphenyl-1H-pyrazole-4-carboxamide) 12b.** Yellow crystals, Yield (3.78 g; 63%), mp. 300–302°C (EtOH/DMF); υ_{max} = 3344, 3226 (NH), and 1657 (CO) cm^{-1}; MS: m/z = 600 [M^+]; δ_H = 7.21–8.34 (m, 26H, Ar. Hs), 9.77 (br.s., 2H, NH). δ_C = 118.81 (s), 119.55 (d), 120.67 (d), 127.75 (d), 127.3 (d), 128.55 (d), 129.05 (d), 129.22 (d), 133.08 (s), 136.53 (s), 138.94 (s), 139.52 (d), 140.01 (s), 193.19 (s).

Anal. Calcd for $C_{38}H_{28}N_6O_2$: (600.67): C, 75.98; H, 4.70; N, 13.99. Found: C, 76.08; H, 4.76; N, 13.85.

The reaction of the enaminone 2 with urea derivatives 13a-c. To a mixture of the enaminone **2** (5.1 g; 10 mmol) and urea **13a**, thiourea **13b**, or guanidine hydrochloride **13c** (20 mmol) in ethanol (25 mL) was added few drops of triethylamine as catalyst in case of **13a,b** and two mole equivalents in case of **13c**. The reaction mixture was refluxed in each case for 3 h and then left to cool overnight. The contents of the flask was poured on ice-cold water and neutralized by HCl. The precipitated products were collected by filtration in each case and recrystallized from DMF/ethanol to afford **14a**, **14b**, and **14c**, respectively.

***N,N′*-(1,4-phenylene)bis(2-benzoyl-3-ureidoacrylamide) 14a.** Yellow crystals, Yield (3.51 g; 65%), mp. 213–215°C (EtOH/DMF); υ_{max} = 3342, 3226, 3167 (NH & NH_2), 1678, 1662, and 1658 (3CO) cm^{-1}; MS: *m*/*z* = 540 [M^+]; δ_H = 5.51 (s, 4H, $2NH_2$), 7.08–7.65 (m, 14H, Ar. Hs), 7.92 (s, 2H, 2NH), 8.45 (s, 2H, olefin Hs), 10.17 (s, 2H, 2NH).

Anal. Calcd. for $C_{28}H_{24}N_6O_6$: (540.53): C, 62.22; H, 4.48; N, 15.55. Found: C, 62.28; H, 4.56; N, 15.75.

***N,N′*-(1,4-phenylene)bis(2-benzoyl-3-thioureidoacrylamide) 14b.** Yellow crystalline product, Yield (3.8 g; 67%), mp. 219–220°C (EtOH/DMF); υ_{max} = 3340, 3225, 3165 (NH & NH_2), 1676, 1660, and 1655 (3CO) cm^{-1}; MS: *m*/*z* = 572 [M^+]; δ_H = 5.52 (s, 4H, $2NH_2$), 7.08–7.66 (m, 14H, Ar. Hs), 7.75 (s, 2H, olefin Hs), 7.93 (s, 2H, 2NH), 10.15 (s, 2H, 2NH).

Anal. Calcd. for $C_{28}H_{24}N_6O_4S_2$: (572.66): C, 58.73; H, 4.22; N, 14.68; S, 11.20. Found: C, 58.78; H, 4.26; N, 14.78; S, 11.00.

***N,N′*-(1,4-phenylene)bis(2-benzoyl-3-guanidinoacrylamide) 14c.** Yellow powder, Yield (3.6 g; 68%), mp. 222–224°C (EtOH/DMF); υ_{max} = 3338, 3222, 3170 (NH & NH_2), 1678, and 1658 (2CO) cm^{-1}; MS: *m*/*z* = 538 [M^+]; δ_H = 5.51 (s, 4H, $2NH_2$), 7.05–7.68 (m, 16H, Ar. + olefin Hs), 7.92 (s, 2H, 2NH), 8.15 (s, 2H, 2NH), 10.17 (s, 2H, 2NH).

Anal. Calcd. for $C_{28}H_{26}N_8O_4$: (538.56): C, 62.44; H, 4.87; N, 20.81. Found: C, 62.32; H, 4.58; N, 20.70.

Cyclization of compounds 14a-c. To a solution of each of compounds **14a, 14b**, or **14c** (10 mmol) in 20 mL of ethanol was added few drops of sodium ethoxide and the reaction mixture was refluxed for 1 h in each case then left to stand overnight. The reaction mixture was poured on ice cold water and neutralized with few drops of HCl. The precipitated solids were collected by filtration and recrystallized to give **15a-c**, respectively.

***N,N′*-(1,4-phenylene)bis(2-oxo-6-phenyl-1,2-dihydropyrimidine-5-carboxamide) 15a.** Yellow crystals, Yield (3.27 g; 65%), mp. 286–287°C (EtOH/DMF); υ_{max} = 3342, 3226 (NH), 1662, and 1658 (2CO) cm^{-1}; MS: *m*/*z* = 504 [M^+]; δ_H = 7.12–7.85 (m, 16H, Ar. Hs), 7.92 (s, 2H, 2NH), 10.17 (s, 2H, 2NH).

Anal. Calcd. for $C_{28}H_{20}N_6O_4$: (504.50): C, 66.66; H, 4.00; N, 16.66. Found: C, 66.70; H, 4.05; N, 16.48.

***N,N′*-(1,4-phenylene)bis(6-phenyl-2-thioxo-1,2-dihydropyrimidine-5-carboxamide) 15b.** Yellow crystals, Yield (3.59 g; 67%), mp. 290–291°C (EtOH/DMF); υ_{max} = 3345, 3228 (NH), and 1655 (CO) cm^{-1}; MS: *m*/*z* = 535 [$M^+ - 1$]; δ_H = 7.14–7.88 (m, 16H, Ar. Hs), 7.90 (s, 2H, 2NH), 10.17 (s, 2H, 2NH).

Anal. Calcd. for $C_{28}H_{20}N_6O_2S_2$: (536.63): C, 62.67; H, 3.76; N, 15.66; S, 11.95. Found: C, 62.80; H, 3.72; N, 15.45; S, 12.25.

***N,N′*-(1,4-phenylene)bis(2-imino-6-phenyl-1,2-dihydropyrimidine-5-carboxamide) 15c.** Yellowish orange crystals, Yield (3.16 g; 63%), mp. 280–282°C (EtOH/DMF); υ_{max} = 3343, 3232 (NH), and 1656 (CO) cm^{-1}; MS: *m*/*z* = 502 [M^+]; δ_H = 6.45 (s, 2H, 2NH), 7.14–7.88 (m, 16H, Ar), 7.94 (s, 2H, 2NH), 10.17 (s, 2H, 2NH).

Anal. Calcd. for $C_{28}H_{22}N_8O_2$: (502.53): C, 66.92; H, 4.41; N, 22.30. Found: C, 67.12; H, 4.47; N, 22.50.

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REFERENCES AND NOTES

[1] This work is abstracted in part from the Ph.D. thesis of Mrs. Nehal A. Sobhy.

[2] Meyer, H.; Sitt, R.; Thomas, G.; KaurseH.; Ger. Offen. 3015 219; Chem Abstr 1982, 96, 6604d.

[3] Deshang, P.; Cipolina, J. A.; Lowmoster, N. K. J Org Chem 1988, 53, 1356.

[4] Worbel, J.; Li, Z.; Dietrich, A.; McCaleb, M.; Mihan, B.; Serdy, J.; Sullivan, D. J Med Chem 1998, 41, 1084.

[5] (a) Wang, A. X.; Qinghua, X.; Lane, B.; Mollison, K. W.; Hsieh, G. C.; Marsh, K.; Sheets, M. P.; Luly, J. R.; Coghlan, M. J. Bioorg Med Chem Lett 1998, 8, 2787; (b) Kim, H. H.; Park, T. G.; Moon, T. C.; Chang, H. W.; Jahng, Y. Arch Pharm Res 1999, 22, 372; (c) Park, H.-J.; Lee, K.; Park, S.-J.; Ahn, B.; Lee, J.-C.; Yeong, H.; Lee, C. K.-I. Bioorg Med Chem Lett 2005, 15, 3307.

[6] (a) Watanabe, M.; Koike, H.; Ishiba, T.; Okada, T.; Hirai, S. S. K. Bioorg Med Chem Lett 1997, 5, 437; (b) Quintero, A.; Pelcastre, A.; Solano, J. D. J Pharm Pharmaceut Sci 1999, 2, 108.

[7] Torres, M.; Gil, S.; Parra, M. Curr Org Chem 2005, 9, 1757.

[8] Yermolayev, S. A.; Gorobets, N. Yu.; Lukinova, E. V.; Shishkin, O. V.; Shishkina, S. V.; Desenko, S. M. Tetrahedron 2008, 64, 4649.

[9] Fing, Y.-J.; Miao, C.-B.; Gao, Y.; Tu, S.-J.; Fang, F.; Shi, D.-Q. Chin J Chem 2004, 22, 622.

[10] Abdelrazek, F. M.; Elsayed, A. N. J Heterocycl Chem, 2009, 46, 949.

[11] Abdelrazek, F. M.; Metwally, N. H. Synth Commun, to appear.

[12] Abdelrazek, F. M.; Elsayed, A.N. Afinidad, to appear.

[13] Abdelrazek, F. M.; Metz, P.; Metwally, N. H.; El-Mahrouky, S. F. Arch Pharm Chem Life Sci (Weinheim) 2006, 339, 456.

[14] Abdelrazek, F. M.; Metz, P.; Kataeva, O.; Jaeger, A.; El-Mahrouky, S. F. Arch Pharm Chem Life Sci (Weinheim) 2007, 340, 543.

[15] Abdallah, T. A.; Metwally, N. H.; Abdelrazek, F. M. Afinidad 2008, 65, 393.

[16] Al-Omran, F.; Al-Awadhi, N.; Abdelkhalik, M. M.; Kaul, K.; Abu El-Khair, A.; ElnagdiM. H. J Chem Res (S) 1997, 84; (M) 1997, 601

[17] Al-Omran, F.; Abu El-Khair, A.; Elnagdi, M. H. J Chem Res (S) 1998, 798.