Behavior of 2-cyano-3-(dimethylamino)-N-(4-phenylthiazol-2-yl)-acrylamide towards some nitrogen nucleophiles

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Abstract
The versatile, hitherto unreported 2-cyano-3-(dimethylamino)-N-(4-phenylthiazol-2-yl)-acrylamide 2 was synthesized and allowed to react with hydroxylamine, hydrazine and guanidine to afford regioselectively the isoxazole 4, pyrazole 6 and pyrimidine 8 derivatives, respectively. The reaction of 2 with thiourea and / or ethyl glycinate in a basic medium afforded the regioisomeric pyrimidinethione 9 and 3,5-dioxo-1,4-diazepine-6-carbonitrile 14. Compound 2 reacts also with 2-amino-4-phenylthiazole, 2-amino-4-methylpyridine, 2-aminotetrazole, 2-aminobenzothiazole and 2-aminobenzimidazole to give the corresponding bridgehead nitrogen heterocycles namely thiazolo[3,2-a]pyrimidine 18, tetrazolo[1,5-a]pyrimidine 19, pyrimido [2,1-b]benzothiazole 21, and pyrido[1,2-a]benzimidazole 23. The mechanistic aspects for the formation of the newly synthesized compounds is discussed.

Keywords: Thiazoles, enaminonitriles, N-nucleophiles, heterocycles

Introduction

Enaminonitriles are versatile reagents and their chemistry has recently received a considerable attention as precursors to, otherwise not readily obtainable heteroaromatics.1-10 Several novel syntheses of azoles, azines, and azoloazines utilizing enaminonitriles as starting components have been reported by Elnagdi and coworkers.11-14 On the other hand, the considerable biological and medicinal activities of thiazoles and those linked to different heterocycles through a carboxamide linkage initiated a considerable recent interest in the development of syntheses of these molecules.15-19 These compounds were found to be associated with a wide range of chemotherapeutic activities.20 In continuation of our interest in the synthesis of heterocycles containing a thiazole moiety,21-28, we report herein the results of our study of the reactions of an enaminonitrile 2 with several nitrogen nucleophiles. The aim of the present paper is to present an
efficient synthesis of novel 2-heteroaryl-thiazoles, which have not been reported hitherto. The results of screening of their biological activity will be reported in due course.

Results and Discussion

The starting material, 2-cyano-N-(4-phenylthiazol-2-yl)acetamide 1 was prepared in a quantitative yield using a modified literature procedure by heating 2-amino-4-phenylthiazole in dry toluene with 1-cyanoacetyl-3,5-dimethylpyrazole as cyanoacetylation agent. Treatment of 1 with dimethylformamide-dimethylacetal (DMF-DMA) in refluxing toluene afforded the corresponding enaminonitrile 2. The structure of 2 has been assigned as a reaction product on the basis of analytical and spectral data. The IR spectrum displayed absorption bands at 3230 cm\(^{-1}\) due to NH function, at 2196 cm\(^{-1}\) due to conjugated C≡N function, at 1668 cm\(^{-1}\) due to amidic C=O function. The \(^1H\)-NMR spectrum (DMSO-\(d_6\)) exhibited two sharp singlet signals at \(\delta\) 3.27 ppm and 3.33 ppm assignable to \(N,N\)-dimethylamino protons, another two singlet signals at \(\delta\) 7.57 and 8.07 ppm specific for thiazole-H5 proton and methine proton, respectively, a multiplet signal at \(\delta\) 7.20-7.95 ppm region owing to aromatic protons, and a broad singlet signal at \(\delta\) 11.44 ppm due to NH proton. The mass spectrum showed a molecular ion peak at \(m/z\) = 298, corresponding to a molecular formula C\(_{15}\)H\(_{14}\)N\(_4\)OS.

The behavior of the enaminonitrile 2 towards some \(N\)-nucleophiles to attain polyfunctionally substituted azoles, azines, and related fused systems linked to a thiazole moiety through a carboxamide linkage of potential pharmaceutical interest, has been investigated.

Treatment of 2 with hydroxylamine hydrochloride in refluxing ethanol - dimethylformamide (1:1) mixture in the presence of anhydrous potassium carbonate afforded an orange product which was identified as 5-amino-N-(4-phenylthiazole-2-yl)-isoxazole-4-carboxamide 4. The spectral data of the isolated product was in complete agreement with structure 4. The IR spectrum revealed the lack of an absorption band corresponding to a conjugated C≡N function and showed absorption bands at 3405, 3345, 3234, and 1666 cm\(^{-1}\) corresponding to NH\(_2\), NH, and amidic C=O functions, respectively. The \(^1H\) NMR spectrum (DMSO-\(d_6\)) showed two broad singlet signals at \(\delta\) 5.86 and 11.44 ppm and two sharp singlet signals at \(\delta\) 7.56 and 8.88 ppm characteristic of NH\(_2\), NH, thiazole-H5, and isoxazole-H3 protons respectively, beside a multiplet signal at \(\delta\) 7.28-8.00 ppm region distinctive for aromatic protons. The mass spectrum showed a molecular ion peak at \(m/z\) = 286, corresponding to molecular formula C\(_{13}\)H\(_{10}\)N\(_5\)O\(_2\)S.

The 5-aminopyrazole 6 was achieved as a sole product by heating the enaminonitrile 2 with hydrazine hydrate in ethanol. Inspection of \(^1H\)-NMR spectrum enabled establishing structure 6 for this pyrazole derivative since the pyrazole H-3 appeared as a singlet at \(\delta\) 8.23 ppm. We could not trace in the \(^1H\)-NMR spectrum any signals for the tautomeric 3-aminopyrazole as this could reveal pyrazole-H5 as a doublet. The mass spectrum of 6 showed a molecular ion peak (M\(^+\)) at \(m/z\) = 285 corresponding to a molecular formula C\(_{13}\)H\(_{11}\)N\(_5\)OS.

Similarly, the enaminonitrile 2 reacted with guanidine in a mixture of ethanol and dimethylformamide (2:1) containing anhydrous potassium carbonate under reflux to yield in good yield, a product that was identified as 2,4-diamino-N-(benzothiazol-2-yl)pyrimidine-5-
carboxamide 8. The structure of compound 8 was assigned on the basis of the elemental analysis and spectral data. The IR spectrum showed absorption bands at 3382–3122 cm\(^{-1}\), corresponding to two NH\(_2\) and NH functions, and at 1664 cm\(^{-1}\) due to amidic C=O function. The \(^1\)H-NMR spectrum (DMSO–d\(_6\)) revealed two broad singlet signals at \(\delta 6.53\) and 8.67 ppm assignable to two NH\(_2\) protons, a singlet signal at \(\delta 8.79\) ppm characteristic to pyrimidine-H6 proton, an aromatic multiplet at \(\delta 7.31–7.96\) ppm, and another broad singlet signal at \(\delta 11.51\) ppm due to NH proton. The mass spectrum showed a molecular ion peak (M\(^+\)) at \(m/z = 312\), corresponding to a molecular formula C\(_{14}\)H\(_{12}\)N\(_6\)O\(_2\).

Formation of compounds 4, 6 and 8 is assumed to take place via a Michael type addition of the amino group of the hydroxylamine, hydrazine and guanidine to the activated double in compound 2 to form the non-isolable intermediates 3, 5 and 7 which readily undergo intramolecular cyclization followed by loss of dimethylamine molecule to form the target compounds (Scheme 1).

**Scheme 1.** Synthesis of isoxazole 4, pyrazole 6 and pyrimidine 8 derivatives.

The site selectivity in cycloaddition of some nitrogen ambident nucleophiles with the enaminonitrile 2 was also studied. Thus, reaction of 2 with thiourea in refluxing ethanol containing a catalytic amount of piperidine afforded a single product (as examined by TLC) for which three isomeric cycloadducts 9, 10 and 11 seemed possible (Scheme 2). However, the pyrimidinethione 9 was assigned for the reaction product on the basis of its elemental analysis and spectral data. The IR spectrum lacked an absorption band due to a nitrile function and revealed absorption bands at 3395-3162, 1670, 1635, and 1279 cm\(^{-1}\) characteristic to three NH,
two amidic C=O, and C=S functions, respectively. The $^1$H-NMR spectrum (DMSO–d$_6$) exhibited no signal due to NH$_2$ protons which was attributed to either structures 10 or 11 and displayed a doublet signal at δ 8.22 ppm with coupling constant ($J = 6.8$ Hz) assignable to pyrimidine-H6 proton, three broad singlet signals at δ 8.98, 11.02 and 11.74 ppm, specific for three NH protons, in addition to an aromatic multiplet in the region δ 7.21–7.96 ppm. Moreover, its $^{13}$C-NMR spectrum revealed 12 carbon types, the most important signals being displayed at δ 175.7, 166.7, and 165.5 characteristics for C=S, acyclic amide, and cyclic amide carbonyl carbons, respectively. The mass spectrum showed a molecular ion peak (M$^+$) at $m/z = 330$ which is in an agreement with the molecular formula C$_{14}$H$_{10}$N$_4$O$_2$S$_2$.

![Scheme 2. Synthesis of pyrimidinethione 9 and 3,5-dioxo-1,4-diazepine-6-carbonitrile 14.](image)

It is interesting in this connection that the reaction of 2 with ethyl glycinate hydrochloride in a boiling mixture of ethanol and dimethylformamide containing triethylamine as a catalyst does not afford the pyrrole derivative 13, as could have been expected in analogy to the formation of 9. Actually, the product of this reaction was identified on the basis of its spectral data as 3,5-
dioxo-4-(4-phenylthiazol-2-yl)-2,3,4,5-tetrahydro-1H-1,4-diazepine-6-carbonitrile 14. The IR spectrum has no absorption band characteristic to an ester group and it revealed the presence of C=\(\text{N}\) stretching band at 2205 cm\(^{-1}\) and two amidic C=O stretching bands at 1672 and 1665 cm\(^{-1}\). Its mass spectrum showed the molecular ion at \(m/z = 310\). Two peaks at \(m/z = 151 (37.5\%)\) and 150 (100%, base peak) identify the 1,4-diazepine unit. The \(^1\)H-NMR spectrum of 14 supported its structure, as it revealed the 1,4-diazepine ring protons as two doublet signals at \(\delta 3.45\) and 8.63 ppm assignable to 2-CH\(_2\) and 7-H protons, respectively, and a broad singlet signal at 8.31 ppm exchangeable with D\(_2\)O characteristic of NH proton, beside the other expected signals. Its \(^1^3\)C-NMR spectrum revealed 13 carbon types, the construction of diazepine ring system 14 makes its two amidic carbonyl carbons resonate downfield at 164.9 and 160.9, the other significant signals being displayed at 115.6 and 48.2 corresponding to nitrile carbon and methylene carbon, respectively. The formation of 14 rather than 13 may be attributed to the intermediacy of the non-isolable transamination adduct 12, which underwent cyclization \(\text{via}\) loss of ethanol and dimethylamine molecules.

In view of the growing biological importance of fused thiazoles, particularly thiazolo[3,2-a]pyrimidines,\(^{32-33}\) it was of interest to synthesize 5-oxo-3-phenyl-N-(4-phenylthiazol-2-yl)-5H-thiazolo[3,2-a]pyrimidine-6-carboxamide. This bicyclic system is considered as a thia-analogue of the natural purine bases, adenine and guanine. Thus, treatment of 2 with 2-amino-4-phenylthiazole in boiling glacial acetic acid furnished a single product for which two possible isomeric structures 16 and 18 were considered (Scheme 3). Unfortunately, both elemental analysis and spectral data of the isolated product were in assignment with the two theoretically possible structures 16 and 18. The IR spectrum showed the lack of absorption bands corresponding to conjugated C=\(\text{N}\) and NH\(_2\) functions and presence of bands at 3385 cm\(^{-1}\) due to NH function, 1680 and 1652 cm\(^{-1}\) due to two amidic C=O functions. Its \(^1\)H-NMR spectrum exhibited two singlet signals at \(\delta 6.13\) and 7.52 ppm specific for fused thiazole-H5 proton and thiazole-H5 proton, respectively, a singlet signal at \(\delta 8.38\) due to pyrimidine-H6 in addition to an aromatic multiplet at \(\delta 7.29-7.97\) ppm region and a broad singlet signal at \(\delta 12.74\) ppm exchangeable with D\(_2\)O due to NH proton. The mass spectrum showed a molecular ion peak at \(m/z = 340\) corresponding to a molecular formula C\(_{22}\)H\(_{14}\)N\(_4\)O\(_2\)S.

The differentiation between structures 16 and 18 has been achieved by their alternate synthesis through the isolation of the intermediacy 17 rather than 15 \(\text{via}\) conducting the reaction in boiling ethanol followed by cyclization to 18 by boiling in glacial acetic acid. The intermediacy of 17 was confirmed by both elemental analysis and spectral data. The \(^1\)H-NMR spectrum displayed no singlet signal for the imino proton and revealed a doublet signal at \(\delta 8.22\) ppm due to =CH-NH proton, and two broad singlet signals at \(\delta 11.16\) and 12.80 assignable to two NH protons. The mass spectrum showed a molecular ion peak at \(m/z = 429\), corresponding to a molecular formula C\(_{22}\)H\(_{15}\)N\(_5\)OS\(_2\).

The direct formation of 18 from 2 and 2-amino-4-phenylthiazole indicates that the initially formed substitution product namely 2-cyano-N-(4-phenylthiazol-2-yl)-3-[(4-phenylthiazol-2-yl)amino]acrylamide 16 underwent \textit{in situ} deaminative cyclization under the employed reaction
conditions to give 5-oxo-3-phenyl-N-(4-phenylthiazol-2-yl)-5H-thiazolo[3,2-a]pyrimidine-6-carboxamide 18 as the end product.

The foregoing results prompted us to investigate the applicability and synthetic potency of 2 to develop a facile and convenient route to bridgehead nitrogen heterocyclic systems namely tetrazolo[1,5-a]pyrimidine, pyrido[1,2-a]pyrimidine, pyrimido[1,2-a]benzimidazole and pyrimido[2,1-b]benzothiazole of an expected pharmaceutical interest.


Thus, reaction of 2 with 2-hetaryl amines namely, 5-aminotetrazole and 2-amino-4-methylpyridine in refluxing glacial acetic acid afforded solely 7-oxo-N-(4-phenylthiazol-2-yl)-4,7-dihydrotetrazolo[1,5-a]pyrimidine-6-carboxamide 19 and 8-methyl-4-oxo-N-(4-phenylthiazol-2-yl)-4H-pyrido[1,2-a]pyrimidine-3-carboxamide 20, respectively. The IR spectrum of 20 showed two strong absorption bands at 1690 and 1650 cm\(^{-1}\) attributed to two amidic C=O functions. The \(^1\)H-NMR spectrum revealed a singlet signal at \(\delta\) 2.30 ppm characteristic of methyl protons, a singlet signal at \(\delta\) 7.28 ppm assignable to aromatic protons (H\(_5\)), two doublets at \(\delta\) 6.22 and 6.89 ppm assignable to aromatic protons (H\(_6\) and H\(_7\)), a singlet signal at \(\delta\) 8.18 ppm owing to pyrimidine-H2 proton and an aromatic multiplet at \(\delta\) 7.31–7.92 ppm region. The mass spectrum showed a molecular ion peak at \(m/z = 362\), corresponding to a molecular formula C\(_{19}\)H\(_{14}\)N\(_4\)O\(_2\)S.
In a similar manner, refluxing of 2 with 2-aminobenzothiazole in acetic acid afforded 4-oxo-N-(4-phenylthiazol-2-yl)-4H-pyrimido[2,1-b]benzothiazole-3-carboxamide 21 in quantitative yield.

The reaction of 2 with 2-aminobenzimidazole as potential precursor for pyrimido[1,2-a]benzimidazole was also investigated. Thus, the enaminonitrile 2 was refluxed with 2-aminobenzimidazole in ethanol containing a catalytic amount of piperidine to afford the corresponding pyrimido[1,2-a]benzimidazole derivative 23. The structure of 23 was established on the basis of its elemental analyses and spectral data, besides its independent synthesis via the reaction of \( N-1H \)-benzimidazol-2-yl-\( N,N \)-dimethylformamidine with 2-cyano-N-(4-phenylthiazol-2-yl)acetamide 1 which afforded a product identical in all respects (mp., mixed mp., and IR spectra) with those obtained previously from the reaction of the enaminonitrile 2 with 2-aminobenzimidazole. The presence of an amino group in 23 was evidenced by the presence of two absorption bands at 3445 and 3300 cm\(^{-1}\) in its IR spectrum and as a broad D\(_2\)O-exchangeable signal at \( \delta \) 6.35 ppm in its \( ^1\)H-NMR spectrum. The formation of 23 is therefore assumed to take place via the addition of the exocyclic amino group of 2-aminobenzimidazole to the activated double in 2 to give the acyclic non-isolable intermediate 22, which undergoes cyclization and aromatization via loss of dimethylamine molecule affording the final isolated product.

\[ \text{Scheme 4. Synthesis of bridgehead heterocyclic nitrogen compounds 19-23.} \]
Conclusions

The results of the present study indicate that the enaminonitrile and N-nucleophiles are useful precursors for the synthesis of different functionalized 2-hetarylthiazoles. In addition, they indicate that reactions of studied N-nucleophiles with enaminonitrile are regiospecific as they yielded, in each case, one product in good yield. The compounds prepared are expected to be of pharmacological interest.

Experimental Section

General. All melting points were determined on an electrothermal Gallenkamp apparatus. The IR spectra were measured on a Mattson 5000 FTIR Spectrometer in potassium bromide discs. The $^1$H NMR and $^{13}$C NMR spectra were recorded in DMSO-$d_6$ or CDCl$_3$ on a Bruker WP 212 instrument, the ionizing voltage was 70 ev, at Faculty of Science, Cairo University. Elemental analyses were carried out by the Microanalytical unit of Faculty of Science, Mansoura University, Masoura, Egypt. All reactions were followed by TLC (Silica gel, aluminum sheets 60 F$_{254}$, Merck). 2-Cyano-N-(4-phenylthiazol-2-yl)acetamide 1 was prepared according to previously reported procedure.29

2-Cyano-3-(dimethylamino)-N-(4-phenylthiazol-2-yl)acrylamide (2). A mixture of 2-cyano-N-(4-phenylthiazol-2-yl)acetamide 1 (3.65 g, 0.015 mole) and dimethylformamide-dimethylacetal (2 ml, 0.015 mole) in dry toluene (30 ml) was heated under reflux for 4 h, then left to cool at room temperature. The orange precipitate product was filtered off, washed with petroleum ether, dried well, and recrystallized from toluene to give compound 2. Orange crystals; Yield 82%; mp 248°C; IR (KBr): $v_{	ext{max.}}$/cm$^{-1}$ = 3230 (NH), 2196 (C≡N), 1668 (amidic C=O). $^1$H NMR (DMSO-$d_6$): $\delta$ppm = 3.27 (s, 3H, NCH$_3$), 3.33 (s, 3H, NCH$_3$), 7.20 – 7.95 (m, 5H, Ar-H), 7.57 (s, 1H, thiazole H-5), 8.07 (s, 1H, CH=), 11.44 (s, br, 1H, NH). MS m/z (%): 298 (M$^+$, 21.8), 124 (7.6), 123 (100), 104 (1.2), 95 (5.2), 80 (9.6), 51 (3.7). Anal. For C$_{15}$H$_{14}$N$_4$OS (298.36) Calcd.: C 60.38; H 4.73; N 18.78. Found: C 60.24; H 4.65; N 18.62 %.

5-Amino-N-(4-phenylthiazol-2-yl)-isoxazole-4-carboxamide (4). A mixture of enaminonitrile 2 (0.298 g, 0.001 mole) and hydroxylamine hydrochloride (0.07 g, 0.001 mole) in a mixture of ethanol and dimethylformamide (1:1) (30 ml) containing anhydrous potassium carbonate (0.28 g, 0.002 mole) was heated under refluxed for 6 h, then allowed to cool at room temperature and diluted with ice cold water (30 ml). The solid product so formed was filtered off, washed with water, dried well, and recrystallized from ethanol to afford compound 4. Yellow crystals; Yield 73 %; mp 265°C; IR (KBr): $v_{	ext{max.}}$/cm$^{-1}$ = 3405, 3345 (NH$_2$), 3234 (NH), 1666, (amidic C=O). $^1$H NMR (DMSO–$d_6$): $\delta$ppm = 5.79 (s, br, 2H, NH$_2$), 7.28 – 8.01 (m, 5H, Ar-H), 7.56 (s, 1H, thiazole
H-5), 8.88 (s, 1H, isoxazole H-3), 11.44 (s, br, 1H, NH). MS m/z (%): 286 (M⁺, 48.6), 202 (75.2), 176 (53.9), 160 (100), 111 (35.6), 77 (27.5). Anal. For C₁₃H₁₀N₄O₂S (286.31) Calcd. C 54.54; H 3.54; N 19.42 %.

5-Amino-N-((4-phenylthiazol-2-yl)-1H-pyrazole-4-carboxamide (6). To a solution of enammonitrile 2 (0.298 g, 0.001 mole) in ethanol (20 ml), hydrazine hydrate (80% 0.1 ml, 0.002 mole) was added. The reaction mixture was refluxed for 4 h, then allowed to cool at room temperature. The resultant solid product, so precipitated was collected by filtration, dried well, and recrystallized from a mixture of ethanol and dimethylformamide (1:1) to give compound 6. Yellow crystals; Yield 76%; mp 122°C; IR (KBr): v max./cm⁻¹ = 3382 – 3122 (NH₂, NH). MS m/z (%): 285 (M⁺, 40.5), 203 (49.8), 175 (64.2), 160 (57.2), 127 (32.6), 110 (100), 77 (52.2), 51 (48.9). Anal. For C₁₃H₁₁N₅OS (285.32) Calcd.: C 54.72; H 3.95; N 26.99 %.

2,4-Diamino-N-(4-phenylthiazole-2-yl)pyrimidine-5-carboxamide (8). A mixture of enammonitrile 2 (0.298 g, 0.001 mole) and guanidine nitrate (0.12 g, 0.001 mole) in a mixture of ethanol and dimethylformamide (1:1) (30 ml) containing anhydrous potassium carbonate (0.28 g, 0.002 mole) was heated under reflux for 8 h, then allowed to cool at room temperature. The reaction mixture was then triturated with cold water (50 ml), and few drops of dilute HCl were added (till pH = 7). The resultant solid product, so precipitated was collected by filtration, dried well, and crystallized from a mixture of ethanol and dimethylformamide (1:1) to give compound 8. Yellow crystals; Yield 71%; mp 274°C; IR (KBr): v max./cm⁻¹ = 3382 – 3122 (NH₂, NH), 1664 (amidic C=O). ¹H NMR (DMSO – d₆): δppm = 6.53 (s, br, 2H, NH₂), 7.31 – 7.96 (m, 5H, Ar-H), 7.68 (s, 1H, thiazole H-5), 8.67 (s, br, 2H, NH₂), 8.79 (s, H, pyrimidine H-6), 11.51 (s, br, 1H, NH). MS m/z (%): 312 (M⁺, 15.8), 279 (4.3), 176 (3.1), 136 (7.6), 137 (100), 134 (5.6), 95 (33.6), 68 (10.2), 53 (5.8). Anal. For C₁₄H₁₂N₆OS (312.35) Calcd.: C 53.83; H 3.87; N 26.91. Found: C 53.94; H 3.73; N 26.99 %.

4-Oxo-N-(4-phenylthiazole-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (9). A mixture of enammonitrile 2 (0.298 g, 0.001 mole) and thiourea (0.076 g, 0.001 mole) in a mixture of ethanol and dimethylformamide (1:1) (20 ml) containing a catalytic amount of piperidine (3 drops) was refluxed for 8 h and then left overnight at room temperature. The solid product so formed was filtered off, washed with ethanol, dried well, and recrystallized from a mixture of ethanol and dimethylformamide (1:1) to give compound 9. Pale yellow powder; Yield 63%; mp 278°C; IR (KBr): v max./cm⁻¹ = 3395 – 3162 (3NH), 1670, 1635 (2 amidic C=O), 1279 (C=S). ¹H NMR (DMSO – d₆): δppm = 7.21 – 7.96 (m, 5H, Ar-H), 7.49 (s, 1H, thiazole H-5), 8.22 (d, J = 6.8 Hz, 1H, pyrimidine H-6), 8.98 (s, br, 1H, NH), 11.02 (s, br, 1H, NH), 11.74 (s, br, 1H, NH). ¹³C NMR (DMSO – d₆): δppm = 105.6, 108.4, 125.8, 127.7, 129.2, 131.4, 151.5, 155.6, 163.2, 165.5, 166.7, 175.7. MS m/z (%): 330 (M⁺, 30), 302 (26.8), 286 (22.5), 252 (31), 203 (32.8), 175 (50.4), 170 (62.2), 160 (60), 155 (100), 127 (41.5), 99 (28.7), 77 (50). Anal. For C₁₄H₁₀N₄O₂S₂ (330.38) Calcd.: C 50.90; H 3.05; N 16.96. Found: C 50.74; H 3.13; N 16.84 %.
3,5-Dioxo-4-(4-phenylthiazol-2-yl)-2,3,4,5-tetrahydro-1H-1,4-diazepine-6-carbonitrile (14).
A mixture of enaminonitrile 2 (0.298 g, 0.001 mole) and ethyl glycinate hydrochloride (0.139 g, 0.001 mole) in a mixture of ethanol and dimethylformamide (1:1) (30 ml) containing a catalytic amount of triethylamine (3 drops) was refluxed for 12 h. The solid product so formed was filtered off, washed with ethanol, dried well, and recrystallized from a mixture of ethanol and dimethylformamide (1:1) to give compound 14. White crystals; Yield 57%; mp 286ºC; IR (KBr): \( \nu_{\text{max}}/\text{cm}^{-1} = 2205 \) (C=N), 1672, 1665 (2 amideic C=O). \(^1\)H NMR (DMSO-d\(_6\)): \( \delta_{\text{ppm}} = 3.45 \) (d, \( J = 8.6 \text{ Hz}, 2\text{H}, \text{diazepine-2-CH}_2\)), 7.28 – 7.92 (m, 5H, Ar-H), 7.52 (s, 1H, thiazole H-5), 8.31 (s, br, 1H, NH), 8.63 (d, \( J = 8.6 \text{ Hz}, 1\text{H}, \text{diazepine-7-CH}_2\)), \(^13\)C NMR (DMSO-d\(_6\)): \( \delta_{\text{ppm}} = 48.2, 83.5, 105.2, 115.6, 125.8, 127.7, 129.2, 131.4, 151.4, 152.3, 155.6, 160.9, 164.9. \) MS \( m/z \) (%): 310 (M\(^+\), 13.7), 285 (25.9), 254 (18.9), 233 (17.2), 202 (26.9), 174 (74.8), 151 (37.5), 150 (100), 122 (39.6), 110 (20.5), 84 (48.5), 77 (75.6). Anal. For C\(_{15}\)H\(_10\)N\(_4\)O\(_2\)S (310.33) Calcd.: C 58.05; H 3.28; N 18.05. Found: C 58.24; H 3.43; N 18.16 %.

2-Cyano-N’-(4-phenylthiazol-2-yl)-3-(4-phenylthiazol-2-ylamino)-acrylamide (17). A mixture of enaminonitrile 2 (0.298 g, 0.001 mole) and 2-amine-4-phenylthiazole (0.176 g, 0.01 mole) in a mixture of ethanol and dimethylformamide (1:1) (30 ml) was refluxed for 8 h and then evaporated in vacuo. The residue was triturated with ethanol and the resulting solid product was collected by filtration, washed with ethanol, dried well, and crystallized from ethanol-dimethylformamide to give compound 17. Pale yellow crystals; Yield 52%: mp 267ºC; \(^1\)H NMR (DMSO-d\(_6\)): \( \delta_{\text{ppm}} = 7.52 \) (s, 1H, thiazole H-5), 7.56 (s, 1H, thiazole H-5), 7.27–7.82 (m, 10H, Ar-H), 8.22 (d, \( J = 3.6 \text{ Hz}, 1\text{H}, =\text{CH-NH}\)), 11.16 (s, br, 1H, NH), 12.80 (s, br, 1H, NH). MS \( m/z \) (%): 429 (M\(^+\), 2.5), 376 (12.4), 227 (50.4), 203 (100), 175 (27.5), 77 (50). Anal. For C\(_{22}\)H\(_{15}\)N\(_3\)O\(_2\)S (429.52) Calcd.: C 61.52; H 3.43; N 16.22 %.

2-Cyano-N’-(4-phenylthiazol-2-yl)-3-(4-phenylthiazol-2-ylamino)-acrylamide (17). A mixture of enaminonitrile 2 (0.298 g, 0.001 mole) and 2-amine-4-phenylthiazole (0.176 g, 0.01 mole) in a mixture of ethanol and dimethylformamide (1:1) (30 ml) was refluxed for 8 h and then evaporated in vacuo. The residue was triturated with ethanol and the resulting solid product was collected by filtration, washed with ethanol, dried well, and crystallized from ethanol-dimethylformamide to give compound 17. Pale yellow crystals; Yield 52%: mp 267ºC; \(^1\)H NMR (DMSO-d\(_6\)): \( \delta_{\text{ppm}} = 7.52 \) (s, 1H, thiazole H-5), 7.56 (s, 1H, thiazole H-5), 7.27–7.82 (m, 10H, Ar-H), 8.22 (d, \( J = 3.6 \text{ Hz}, 1\text{H}, =\text{CH-NH}\)), 11.16 (s, br, 1H, NH), 12.80 (s, br, 1H, NH). MS \( m/z \) (%): 429 (M\(^+\), 2.5), 376 (12.4), 227 (50.4), 203 (100), 175 (27.5), 77 (50). Anal. For C\(_{22}\)H\(_{15}\)N\(_3\)O\(_2\)S (429.52) Calcd.: C 61.52; H 3.43; N 16.22 %.

General procedure for the reaction of enaminonitrile (2) with heterocyclic amines
To a solution of enaminonitrile 2 (0.298 g, 0.001 mole) in glacial acetic acid (3-5 ml), an equimolar amount of the appropriate heterocyclic amines was added and the mixture was heated in oil bath under reflux for 10–16 h, then evaporated in vacuo. The residue was triturated with ethanol and the resulting solid product was collected by filtration, dried well, and recrystallized from the appropriate solvent to give compounds 18, 19, 20 and 21.

5-Oxo-3-phenyl-N-(4-phenylthiazol-2-yl)-5H-thiazolo[3,2-a]pyrimidine-6-carboxamide (18). Prepared from 2-amino-4-phenylthiazole (0.176 g) by heating for 10 h under reflux and recrystallized from a mixture of ethanol and dimethylformamide (1:1). Yellow crystals; Yield 53%: mp 286ºC; IR (KBr): \( \nu_{\text{max}}/\text{cm}^{-1} = 3385 \) (NH), 1680, 1652 (2 amideic C=O). \(^1\)H-NMR (DMSO-d\(_6\)): \( \delta_{\text{ppm}} = 6.13 \) (s, 1H, thiazolopyrimidine H-2), 7.29–7.97 (m, 10H, Ar-H), 7.52 (s, 1H, thiazole H-5), 8.38 (s, 1H, thiazolopyrimidine H-7), 12.74 (s, br, 1H, NH). MS \( m/z \) (%): 430 (M\(^+\), 25.4), 418 (27.6), 376 (28), 255 (100), 227 (64.3), 203 (48.2), 175 (26.9), 77 (30), 51 (21.6). Anal. For C\(_{22}\)H\(_{14}\)N\(_4\)O\(_2\)S\(_2\) (430.50) Calcd.: C 61.38; H 3.28; N 13.01. Found: C 61.24; H 3.43; N 13.13 %.
7-Oxo-N-(4-phenylthiazol-2-yl)-3,7-dihydotetrazolo[1,5-a]pyrimidine-6-carboxamide (19). Prepared from 5-aminotetrazole (0.085 g) by heating for 10 h under reflux and recrystallized from a mixture of ethanol and dimethylformamide (1:1). Greenish brown powder; Yield 61%; mp 276°C; IR (KBr): νmax/cm⁻¹ = 3361, 3226 (2NH), 1690, 1655 (2 amic C=O). ¹H NMR (DMSO – d₆): δppm = 7.20 – 7.95 (m, 5H, Ar-H), 7.57 (s, 1H, thiazole H-5), 8.56 (s, 1H, tetrazolopyrimidine H-5), 9.46 (s, br, 1H, NH), 11.62 (s, br, 1H, NH). MS m/z (%): 339 (M⁺, 31.7), 311 (19.8), 263 (32.8), 256 (20.9), 229 (36.6), 203 (65), 175 (52.6), 160 (100), 136 (40), 122 (20), 109 (60.2), 77 (45.6). Anal. For C₁₄H₉N₇O₂S (339.33) Calcd.: C 49.74; H 2.78; N 28.89. Found: C 49.74; H 2.78; N 28.76 %.

8-Methyl-4-oxo-N-(4-phenylthiazol-2-yl)-4H-pyrido[1,2-a]pyrimidine-3-carboxamide (20). Prepared from 2-amino-3-methylpyridine (0.108 g) by heating for 10 h under reflux and recrystallized from a mixture of ethanol and dimethylformamide (1:1). Yellowish green powder; Yield 62%; mp 277°C; IR (KBr): νmax/cm⁻¹ = 3385 (NH), 1690, 1650 (2 amic C=O). ¹H NMR (DMSO – d₆): δppm = 2.30 (s, 3H, CH₃), 6.22 (d, J = 2.8 Hz, 1H, pyridopyrimidine H-7), 6.89 (d, J = 5.6 Hz, 1H, pyridopyrimidine H-6), 7.28 (s, 1H, pyridopyrimidine H-9), 7.31 – 7.92 (m, 5H, Ar-H), 7.52 (s, 1H, thiazole H-5), 8.18 (s, 1H, pyridopyrimidine H-2), 12.74 (s, br, 1H, NH). MS m/z (%): 362 (M⁺, 31.5), 347 (20.1), 320 (29.8), 296 (41.5), 268 (39.8), 243 (29.2), 203 (68.5), 187 (100), 175 (62.5), 160 (68.2), 145 (44.7), 132 (62.6), 118 (40.2), 107 (39.7), 91 (61.5), 58 (55.6). Anal. For C₁₉H₁₄N₄O₂S (362.41) Calcd.: C 62.97; H 3.89; N 15.46. Found: C 62.78; H 3.83; N 15.28 %.

4-Oxo-N-(4-phenyl-1,3-thiazol-2-yl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxamide (21). Prepared from 2-aminobenzothiazole (0.15 g) by heating for 10 h under reflux and recrystallized from a mixture of ethanol and dimethylformamide (1:1). Brown powder; Yield 51%; mp 281°C; IR (KBr): νmax/cm⁻¹ = 3364 (NH), 1686, 1648 (2 amic C=O). ¹H NMR (DMSO – d₆): δppm = 6.69 – 8.01 (m, 9H, Ar-H), 7.49 (s, 1H, thiazole H-5), 8.51 (s, 1H, pyrimidobenzothiazole H-2), 12.52 (s, br, 1H, NH). MS m/z (%): 404 (M⁺, 39.4), 376 (22.7), 352 (41.5), 327 (20.2), 300 (25.4), 251 (15.2), 229 (37.4), 201 (100), 194 (38.6), 175 (31.2), 160 (50), 153 (31.5), 134 (44.8), 127 (21.4), 77 (68.5). Anal. For C₂₀H₁₂N₄O₂S₂ (404.46) Calcd.: C 59.39; H 2.99; N 13.85. Found: C 59.27; H 3.06; N 13.97 %.

Synthesis of 4-amino-N-(4-phenyl-1,3-thiazol-2-yl)pyrimido[1,2-a]benzimidazole-3-carboxamide (23)

Method A. A mixture of enaminonitrile 2 (0.298 g, 0.001 mole) and 2-aminobenzimidazole (0.133 g, 0.001 mole) in a mixture of ethanol and dimethylformamide (1:1) (20 ml) containing a catalytic amount of piperidine (3 drops) was refluxed for 12 h. The precipitated product was filtered off, washed with ethanol, dried well, and crystallized from a mixture of ethanol and dimethylformamide (1:1) to give compound 23.

Method B. A mixture of 2-cyano-N-(4-phenylthiazol-2-yl)acetamide 1 (0.243 g, 0.001 mole) and N-1H-benzimidazol-2-yl-N,N-dimethylformamidine (0.188 g, 0.001 mole) in refluxing ethanol (20 ml) containing a catalytic amount of piperidine (3 drops) was refluxed for 8 h. The
precipitated product was filtered off, washed with ethanol, dried well, and crystallized from a mixture of ethanol and dimethylformamide (1:1) to give compound 23. Brown powder; Yield 57%; mp 266 °C; IR (KBr): \( \nu_{\text{max}} / \text{cm}^{-1} = 3445, 3300 (\text{NH}_2), 3215 (\text{NH}), 1648 (\text{C}=\text{O}) \). \(^1\)H-NMR (DMSO–d_6): \( \delta_{\text{ppm}} = 6.35 (s, \text{br}, 2\text{H}, \text{NH}_2), 7.29 – 8.02 (m, 9\text{H}, \text{Ar-H}), 7.58 (s, 1\text{H}, \text{thiazole H-5}), 8.6 (s, 1\text{H}, \text{pyrimidobenzimidazole H-2}), 12.01 (s, \text{br}, 1\text{H}, \text{NH}) \). MS m/z (%): 386 (M\(^+\), 25.6), 255 (15.2), 229 (37.4), 201 (65.2), 194 (32.3), 127 (29.9), 77 (70). Anal. For C\(_{20}\)H\(_{14}\)N\(_6\)OS (386.43) Calcd.: C 62.16; H 3.65; N 21.75. Found: C 62.24; H 3.58; N 21.82 %.

References

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