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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME NOVEL THIAZOLO[3,2-A]PYRIDINE, PYRANO[2,3-D]THIAZOLE AND PYRANO [2',3':4,5]THIAZOLO[3,2-A]PYRIDINE DERIVATIVES USING N-CYCLOHEXYL-2-CYANOACETAMIDE

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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME NOVEL THIAZOLO[3,2-A]PYRIDINE, PYRANO[2,3-D]THIAZOLE AND PYRANO [2',3':4,5]THIAZOLO[3,2-A]PYRIDINE DERIVATIVES USING N-CYCLOHEXYL-2-CYANOACETAMIDE

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Abstract

A novel and efficient method for the synthesis of a new variety of 2-(N-cyclohexyl-2-cyanoacetamide)-2-thiazolin-4-one and its corresponding thiazolo[3,2-a] pyridines and pyrano[2,3-d]thiazoles by the reaction of N-cyclohexyl-2-cyano-acetamide with thioglycolic acid. The synthetic potential of the method is demonstrated and antimicrobial evaluation.

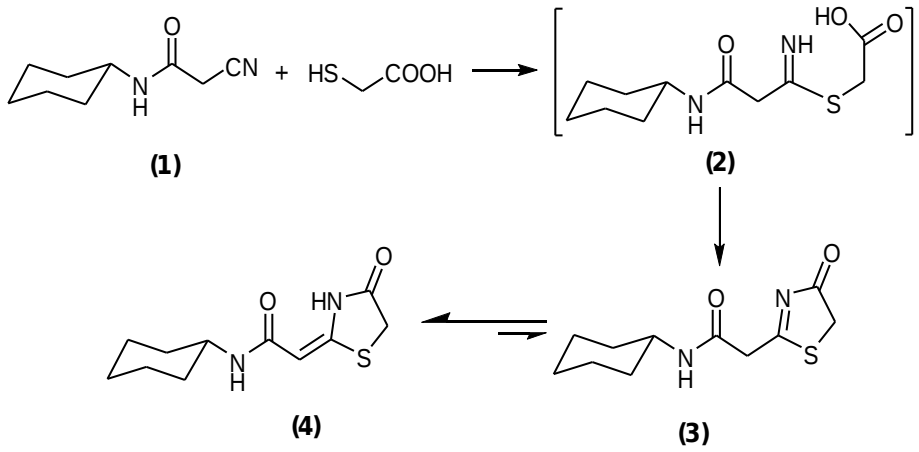
Keywrds: 4-Thiazolidinone, thiazolo[3,2-a]pyridines, pyrano[2,3-d]thiazoles, pyranothiazolopyridine derivatives.

Introduction

Thiazolo[3,2-a]pyridines were reported to furnish various biological and pharmacological activities such as antimicrobial[1], antifungal[2], bactericide[3], coronary dilator, antihypertensive[4], anticancer[5] and muscle relaxant[6] activities. Pyrano[2,3-d]thiazoles are useful in the treatment of diseases such as diabetes, obesity, hyperlipidemia, and atherosclerotic diseases[7]. They also are known to show bactericidal, fungicidal[8] and molluscicidal[9].Based on these facts and in a continuation of our studies on the chemistry of 4-thiazolidinone[10-16], we report here the synthesis and antimicrobial activity of some novel thiazolo[3,2-a]pyridine, pyrano-[2,3-d]thiazole and pyrano[2',3':4,5]thiazolo[3,2-a]pyridine derivatives.

Results and discussion

The starting material N-cyclohexyl-2-cynaoacetamide **(1)** was synthesized in accordance with the reported procedure[17]. Cyclo-condensation of N-(cyclohexyl)-2-cyanoacetamide **(1)** with thioglycolic acid furnished 4-thiazolidinone derivative **4**.



Scheme 1

The molecular structure of **4** was established on the basis of elemental analysis and spectral data. The infrared spectrum of compound **4** showed absorption bands at 3310 (NH), 2918 (CH-aliph.), and two carbonyl groups at 1708, 1638 cm^{-1}. Two tautomeric structures were considered in solutions. The structure of the 2-functionally substituted methyl-2-thiazolin-4-one **(3)** was readily ruled out based on ^{1}HNMR spectrum, which revealed one proton signal at δ 5.28 ppm. This signal can be only interpreted in terms of the 2-substituted methylidene form. Moreover, ^{13}C-NMR spectrum (DMSO-d_6) of compound **4** revealed a signal at δ 38.65 ppm corresponding to C5 of thiazoline ring. In addition, the mass spectrum of compound **4** revealed a molecular ion peak at m/z 240 (12%) in addition to the presence of peaks at m/z 243 (M+3; 3%), 242 (M+2; 8%), 241 (M+1; 33%) together with a base peak at 56.

The formation of compound **4** is assumed to proceed via intermediate **2** which formed by addition of thioglycolic acid to the cyano group in compound **1** followed by intramolecular cyclization through elimination of water, scheme 1.

Compound **4** bearing latent functional substituents were found useful to synthesize its fused ring derivatives. Thus, compound **4** readily reacted with benzylidenemalononitriles **(5a-f)** in refluxing ethanol conta-ining a catalytic amount of piperidine in a 1 : 2 molar ratio to yield 1 : 2 Michael adduct **6** as intermediate which underwent cyclization and elimination of malononitrile affording thiazolo[3,2-a]pyridine derivative **(9a-c)** as the final products but in case of α-cyano-p-methoxycinnamo-nitrile, α-cyano-p-chlorocinnamonitrile, α-cyano-o-chlorocinna-monitrile gave pyrano[2,3-d]thiazole derivatives **(10a-c)**. The structures of **(9a-c)** and **(10a-c)** were established on the basis of elemental analysis and spectral data (IR, MS, ^{1}HNMR). Thus, analytical and spectral data for compound **(9a)** revealed a molecular ion peak at m/z 484 (M+2; 3.2%) together with base peak at m/z 95. The ^{1}HNMR spectrum of **(9c)** indicated the presence of pyridine-H at 5.72 ppm besides the expected signals for $N(CH_3)_2$. Moreover, the IR spectrum revealed the presence of two carbonyl groups at 1687 and 1713 cm^{-1}. The formation of **(9a-c)** is assumed to proceed via formation of 1 : 2 Michael adduct intermediates **(6)**, which losses a malononitrile to give the intermediate **(7)**, which cyclized via intramolecular cyclization and tautomerized to give compound **(9)**. Each structure of **(10)** was confirmed on the basis of elemental analysis and spectral data (IR, Ms, ^{1}HNMR). Thus, infrared spectrum of **(10a)** showed absorption bands at 3399, 3329 (NH, NH_2), 2928 (CH-aliph.), 2189 (CN), 1657 (C=O, amide) and absence of carbonyl group of 4-thiazolidinone. ^{1}HNMR spectrum of **(10b)** revealed a signal at 5.81 ppm assignable to a pyran-H4, and broad signal at 11.98 for NH. Also, mass spectrum of compound **(10a)** showed a molecular ion peak at m/z 542 (M^+; 1.88%) together with a base peak at m/z 382. Moreover, the mass spectrum of compound **(10b)** exhibited the molecular ion peak at m/z 550 (M^+; 2.30%) with a base peak at m/z 168. In addition, the mass spectrum of compound **(10c)** exhibited the molecular ion peak at m/z 551 (M^+; 16.25) with abase peak at m/z 168. The formation of compound **(10)** can be explained by the reaction pathway depicted in scheme 2.

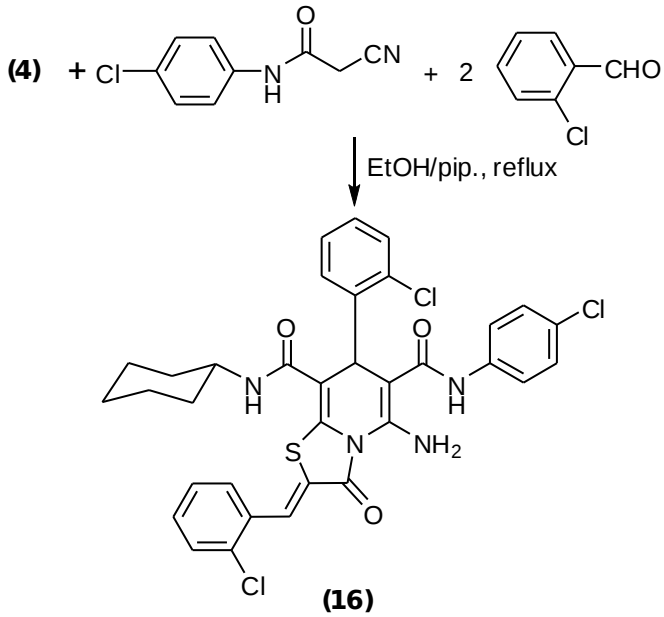
The reaction occurs via formation of 1 : 2 Michael adduct intermediate **(6)** which losses malononitrile to give intermediate **(8)**, which underwent cyclization through addition of oxygen to the nitrile function followed by tautomerization to give compounds **(10)**, scheme 2.

Scheme 2

This investigation was extended to study the reactivity of compound **(4)** towards arylidenecyanoacetate. Thus, the reaction of compound **(4)** with arylidenecyanoacetate **(11a,b)** in refluxing ethanol catalyzed with piperidine in a 1 : 2 molar ratio gave thiazolopyridines **(14)** and **(15)**. The analytical and spectral data were in consistence with thiazolopyridine structure **(14)** and **(15)**. The infrared spectrum of compound **(14)** displayed absorption bands at 3308 (OH), 3139 (NH), 2924 (CH-aliph.) 2052 (CN) and 1689, 1658 (C=O). ^{1}HNMR spectrum of compound **(15)** recorded on (DMSO-d_6) revealed signals at 1.02 to CH_3, 3.98 quartet for CH_2 and broad band at 11.98 for NH. Moreover, mass spectrum of compound **(15)** exhibited a molecular ion peak at m/z 597 (M-1; 5%) together with a base peak at m/z 433. The formation of **(14)** and **(15)** may be assumed to proceed via formation of the intermediates **12** and **13** which cyclized with loss of ethyl cyanoacetate and ethanol to give compound **(14)**, while compound **(15)** formed by cyclization with loss of ethyl cyanoacetate and tatuomerization, scheme 3.

Scheme 3

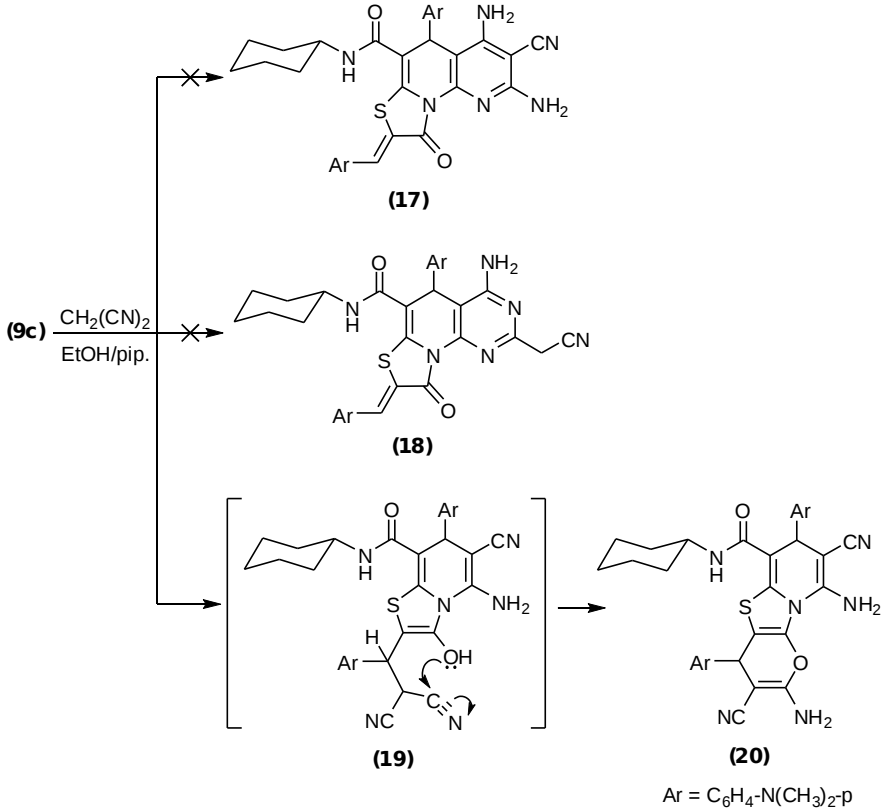
Ternary condensation of compound **(4)**, p-chlorocyanoacetanilide and o-chlorobenzaldehyde (1 : 1: 2 molar ratio) in absolute ethanol cont-aining a catalytic amount of piperidine gave thiazolo[3,2-a]pyridine **(16)**, scheme 4. The structure of compound **(16)** was supported by analytical and spectral data. Thus, the infrared spectrum showed absorption bands due to NH_2, NH, CO functional groups. Its mass spectrum exhibited a molecular ion peak at m/z 680 (M^+; 15%) together with a base peak at m/z 168.



Scheme 4

The reactivity of thiazolopyridine **(9c)**, which contains chalcone, and enaminonitrile moieties was investigated towards malononitrile. Thus, upon treatment of thiazolopyridine derivative **(9c)** with malono-nitrile in ethanolic solution catalyzed with piperidine afforded pyrano-[2',3':4,5]-thiazolo[3,2-a]pyridine derivative **(20)**. On the basis of analytical and spectral data and the other structures **(17)** and **(18)** were ruled out. The structure of compound **(20)** is in agreement with its spectral data. The infrared spectrum displayed disappearance of carbonyl group of thiazolidinone moiety. Its ^{1}HNMR spectrum recorded in (DMSO-d_6) revealed five

singlets for two -$N(CH_3)_2$, pyridine-H, pyran-H, and NH. The formation of compound **(20)** was assumed to proceed via initial nucleophilic attack of active methylene function group of malononitrile to activated double bond of chalcone of compound **(9c)** to form the non-isolable acyclic intermediate **(19)** followed by intramolecular cyclization via the addition of hydroxyl group to one of the two cyano groups and tautomerization to form **(20)**, scheme 5.



Scheme 5

Antimicrobial Activity:

The most of the synthesized compounds were screened in vitro for their antimicrobial activity. The diameter of inhibition zone was measured as an indicator for the activity of the compounds; Ampillicin is used as reference drug.

The results for antibacterial activities depicted in table 1 revealed that compounds **4, 9a, 9b, 9c, 10a,** and **16** exhibited good activities against the reference chemotherapeutics, while compounds **10b** and **10c** showed low activity against the reference chemotherapeutic, on the other hand, most of the prepared compounds

exhibitedmoderate antifungal activities against the reference drugs, whereas, **9b**, **9c**, **10b**, and **16** exhibited good antifungal activities against Fusariumoxysporum. Also, compounds **9a**, and **10c** exhibited good antifungal activities against Fusariumoxysporum and low activity against *Aspergillusochraceus Wilhelm.*

In conclusion, we report herein a simple and convenient route for the synthesis of some heterocyclic bases on thiazolo[3,2-a]pyridine for antimicrobial evaluation.

In vitro antimicrobial activity

The tested compounds were evaluated by the agar diffusion technique[18] using a 1 mg ml^{-1} solution in DMSO. The test organisms were four bacterial strains: *Bacilliustheringiensis*, *P. aeruginosa*, *Serratiam-arcescens*and S. aureus and two fungi: *Candida albicans*, *Aspergillus-ochraceus Wilhelm.* A control using DMSO without the test compound was included for each organism. Ampicillin was purchased from the Egyptian market and used in a concentration 2 mg/ml as reference drugs. The bacterial and fungi were tested on nutrient agar and potato dextrose agar media, respectively. Three plates were used for each compound as replicates. The plates were incubated for 24 h, and seven days for bacteria and fungi, respectively. After the incubation period, the diameter of inhibition zone was measured as an indicator for the activity of the compounds.

Table 1: Inhibition zone (mean diameter of inhibition in mm) as a criterion of antibacterial and antifungal activities of the newly synthesized compounds

Compd. No.	Bacteria				Fungi	
	Bacilliusther i ngiensis	*Serratiamar cescens*	*K. pneum oniae*	*Proteus mirabilis*	*F. oxysporum*	*Aspergillusoc hraceus Wilhelm*
4	15	14.5	14	18	4.5	5
9a	15.5	25	15	16	8	2
9b	14.5	16	12	12	9	8
9c	16	17	13	20	7	9
15	10	12	11	11	5	8
10a	15	21	15	11	7	5
10b	12	11	15	19	8	7
10c	11	12.5	13.5	16	11.5	3
16	14	26	15.5	18	9.5	6
Ampicillin	17	40	20	40	15	10

Experimental

All melting points are uncorrected. IR spectra (KBr) were measured on Shimadzu 440 spectrometer, ^{1}H NMR spectra were obtained in DMSO on a Varian Gemini 200 MHz spectrometer using TMS as internal standard; chemical shifts are reported as (ppm). Mass spectra were obtained on GCMS\QP 1000 Ex mass spectrometer at 70 ev. Elemental analyses were carried out at the Micro-analytical Center, Faculty of Science (Cairo University, Egypt).

N-Cyclohexyl-2-(4-oxo-4,5-dihydrothiazol-2-yl)acetamide (4).

A mixture of **(1)** (0.01 mol) and thioglycolic acid (0.01 mol) in acetic acid (20 ml) was heated under reflux for 3hrs, then allowed to cool and poured into cold water (50 ml). The solid product was collected and recrystallized from ethanol as faint yellow to give **4.**

Yield: 75%, m.p. 225-227°C. IR (KBr): ν = 3310 (NH), 2918 (CH-aliph.), 1708, 1638 cm^{-1} (C=O). ^{1}H NMR (DMSO-d_6): δ= 1.12-1.69, 3.60 (m, 11H, cyclohexyl), 3.87 (s, 2H, CH_2-thiazolidinone), 5.50 (s, 1H, methylidene), 7.8, 11.26 (2s, 2H, 2NH-exchangeable with D_2O).^{13}C-NMR (DMSO-d_6): δ= 173.89, 165.51, 151.16, 92.80, 47.06, 38.66, 31.82, 25.24, 24.58. MS, m/z (%):243 (M+3; 3), 242 (M+2; 8), 241 (M+1; 33), 240 (M^+; 12), 193 (13), 167 (12), 159 (26), 158 (64), 142 (83), 140 (25), 139 (12), 98 (68), 56 (100). Anal.Calcd.for$C_{11}H_{16}N_2O_2S$ (240): C, 55.00; H, 6.66; N, 11.66. Found: C, 55.00; H, 6.60; N, 11.60.

Synthesis of thiazolo[3,2-a]pyridine derivatives (9a-c).*General procedure:*

A mixture of 4-thiazolidinone derivative **(4)** (0.01 mol), cinnamonitriles **(5a-f)** (0.02 mol) in absolute ethanol (20 ml) having few drops of piperidine was refluxed for 4 hrs. The solid product was collected and recrystallized from the proper solvent to give **(9a-c)**,

5-Amino-2-benzylidene-6-cyano-N-cyclohexyl-3-oxo-7-phenyl-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-8-carboxamide (9a)

This compound was obtained in 80% yield as orange crystals (dioxane), m.p. 240-242°C. IR (KBr): ν = 3332, 3260, 3180 (NH/NH_2), 2220 (C≡N ,1720, 1660 cm^{-1} (C=O). MS, m/z (%): 484 (M+2; 3.2%), 95 (100%). Anal.Calcd.for $C_{28}H_{26}N_4O_2S$ (482): C, 69.70; H, 5.39; N, 11.61. Found: C, 69.60; H, 5.30; N, 11.50.

5-amino-6-cyano-N-cyclohexyl-2-(4-methylbenzylidene)-3-oxo-7-p-tolyl-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-8-carbo-xamide (9b).

This compound was obtained in 75% yield as orange crystals (dioxane), m.p. 235-237°C. IR (KBr): ν = 3336 (NH_2), 2186 (C≡N), 1713, 1659 cm^{-1} (C=O). ^{1}HNMR (DMSO-d_6): δ= 1.09, 1.65 (m, 11H, cyclohexyl), 2.27, 2.30 (2s, 6H, $2CH_3$),

4.92 (s, 1H, pyridine-H), 7.15, 7.52 (m, 12H, Ar-H + NH_2 + NH + benzylidene-H).Anal.Calcd.for $C_{30}H_{30}N_4O_2S$ (510): C, 70.58; H, 5.88; N, 10.98. Found: C, 70.50; H, 5.80; N, 10.90.

5-amino-6-cyano-N-cyclohexyl-2-(4-(dimethylamino)benzylidene)-7-(4-(dimethylamino)phenyl)-3-oxo-3,7-dihydro-2H-thiazolo[3,2-a]-pyridine-8-carboxamide (9c).

This compound was obtained in 70% yield as brown crystals (dioxane),m.p. 220-222°C. IR (KBr): ν = 3340, 3139 (NH/NH_2), 2207 (C≡N), 1713, 1687 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ= 1.20, 1.72, 3.65 (m, 11H, cyclohexyl), 2.85, 3.00 (2s, 12H, 2($N(CH_3)_2$), 5.72 (s, 1H, pyridine-H), 6.8-8.18 (m, 11H, Ar-H + NH_2 + benzylidene-H), 11.68 (s, 1H, NH-exchangeable with D_2O).Anal.Calcd.for $C_{32}H_{36}N_6O_2S$ (568): C, 67.60; H, 6.33; N, 14.78. Found: C, 67.50; H, 6.30; N, 14.70.

Synthesis of pyrano[2,3-d]thiazole derivatives (10a-c):

General procedure A mixture of compound **(4)** (0.01 mol), cinnamonitriles (0.02 mole) and triethylamine (0.01 mol) in ethanol (30 ml) was heated under reflux for 3hrs. The solid product that obtained was collected and recrystallized from suitable solvent to give **(10a-c)**.

2-(5-Amino-6-cyano-7-(4-methoxyphenyl)-7H-pyrano[2,3-d]-thiazol-2-yl)-N-cyclohexyl-3-(4-methoxyphenyl)acrylamide (10a).

This compound was obtained in 65% yield as brown crystals (dioxane), m.p. 240-241°C. IR (KBr): ν = 3399, 3329 (NH/NH_2), 2928 (CH-aliph.), 2189 (C≡N), 1657 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ= 1.10-1.84, 3.51 (m, 11H, cyclohexyl), 3.73, 3.84 (2s, 6H, 2 OCH_3), 4.98 (s, 1H, pyran-H-4), 6.85-7.66 (m, 11H, Ar-H + benzylidine-H + NH_2-exchangeable with D_2O), 8.40 (br, 1H, NH-exchangeable with D_2O).MS m/z (%): 542 (M^+; 1.88%), 382 (100), 164 (94.56), 121 (2.91) and 66 (2.97). Anal.Calcd.for $C_{30}H_{30}N_4O_4S$ (542): C, 66.42; H, 5.53; N, 10.33. Found: C, 66.30; H, 5.50; N, 10.20.

2-(5-Amino-7-(4-chlorophenyl)-6-cyano-7H-pyrano[2,3-d]-thiazol-2-yl)-3-(4-chlorophenyl)-N-cyclohexylacrylamide (10b).

This compound was obtained in 67% yield as brown crystals (dioxane),m.p. 260-262°C. IR (KBr): ν = 3396, 3310 (NH/NH_2), 2927 (CH-aliph.), 2194 (C≡N), 1651 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ= 1.20-1.83, 3.52 (m, 11H, cyclohexyl), 5.81 (s,

1H, pyran-H4), 7.30-7.68 (m, 11H, Ar-H + bezylidene-H+ NH_2-exchangeable with D_2O), 11.98 (br, 1H, NH-exchangeable with D_2O).MS m/z (%): 550 (M^+; 2.30), 168 (100), 98 (49.20), 66 (13.10). Anal.Calcd.for $C_{27}H_{24}N_4O_2SCl_2$ (550): C, 58.90; H, 4.36; N, 10.18. Found: C, 58.80; H, 4.30; N, 10.10.

2-(5-Amino-7-(2-chlorophenyl)-6-cyano-7H-pyrano[2,3-d]-thiazol-2-yl)-3-(2-chlorophenyl)-N-cyclohexylacrylamide (10c).

This compound was obtained in 65% yield as brown crystals (dioxane),m.p. 250-252°C. IR (KBr): ν = 3379, 3285 (NH_2), 2925 (CH-aliph.), 2189 (C≡N), 1654 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ= 1.06-1.17, 3.51 (m, 11H, cyclohexyl), 5.33 (s, 1H, pyran-H-4), 7.31-7.79 (m, 12H, Ar-H + NH + CH-benzylidene+ NH_2-exchangeable with D_2O).MS m/z (%): 551 (M^+; 16.25), 386 (59.75), 168 (100) and 56 (22.56). Anal.Calcd.for $C_{28}H_{24}N_4O_2SCl_2$ (550): C, 58.90; H, 4.36; N, 10.18. Found: C, 58.80; H, 4.30; N, 10.10.

Formation of compounds (14) and (15): General procedure:

A mixture of compound **(4)** (0.01 mole), α-ethoxycinnamonitriles (0.01 mole) with piperidine catalyzed in ethanolic solution under reflux 3hr, the solid product that obtained was collected and recrystallized from the proper solvent.

6-Cyano-N-cyclohexyl-5-hydroxy-2-(4-methoxybenzylidene)-7-(4-methoxy-hnyl)-3-oxo-3,7-dihydro-2H-thiazolo[3,2-a]-pyridine-8-carboxamide (14).

This compound was obtained in 70% yield as yellow crystals (acetic acid), m.p. 240-243°C. IR (KBr): ν = 3308 (OH), 3139 (NH), 2924 (CH-aliph.), 2052 (C≡N), and 1689, 1658 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ= 1.15, 1.78, 3.70 (m, 11H, cyclohexyl), 3.82 (s, 6H, OCH_3), 5.70 (s, 1H, pyridine-H), 7.08-7.88 (m, 10H, Ar-H + benzylidene-H+ NH-exchangeable with D_2O), 11.83 (br, 1H, OH-exchangeable with D_2O).Anal.Calcd.for $C_{30}H_{29}$-$_3O_5S$ (543): C, 66.29; H, 5.34; N, 7.73. Found: C, 66.20; H, 5.30; N, 7.60.

Ethyl5-amino-2-(4-chlorobenzyli-dene)-7-(4-chlorophenyl)-8-(cyclohexyl-arbamoyl-3-oxo-3,7-dihydro-2H-thiazolo[3,2-a]-pyridine-6-carboxyate (15).

This compound was obtained in 65% yield as yellow crystals (acetic acid), m.p. 195-197°C. IR (KBr): ν = 3399, 3260 (NH/NH_2), 2929 (CH-aliph.), 1701, 1669 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ= 1.02 (t, 3H, CH_3), 1.09, 1.21, 3.62 (m, 11H, cyclohexyl), 3.98 (q, 2H, CH_2), 5.34 (s, 1H, pyridine-H), 7.21-7.80 (m, 11H, Ar-H +

benzylidene-H + NH_2- exchangeable with D_2O), 11.98 (br, 1H, NH-exchangeable with D_2O). MS, m/z (%): 597 (M-1; 5), 562 (8), 544 (6), 486 (20), 471 (4), 435 (45), 433 (100), 242 (15), 228 (12), 215 (10), 172 (12),and 55 (22). Anal.Calcd.for $C_{30}H_{29}N_3O_4SCl_2$ (597): C, 60.30; H, 4.85; N, 7.03. Found: C, 60.20; H, 4.80; N, 6.95.

5-Amino-2-(2-chlorobenzylidene)-7-(2-chlorophenyl)-N^6-(4-chloro-phenl) N^8-cyclohexyl-3-oxo-3,7-dihydro-2H-thiazo-lo[3,2-a]pyrid-ine-6,8-dica-bxmide (16).

A mixture of compound **(4)** (0.01 mol),p-chlorocyano-acetanilide (0.01 mol), o-chlorobenzaldehyde (0.02 mol) in ethanol containing a catalytic amount of piperidine was refluxed for 3hr, the solid product was collected and recrystallized from acetic acid as white crystals.

Yield: 65%, m.p. 250-252°C.IR (KBr): ν = 3424, 325, 3170 (NH/NH_2), 1677 cm^{-1} (C=O). ^{1}H NMR (DMSO-d_6): δ= 1.2, 1.60, 3.65 (m, 11H, cyclohexyl protons), 5.68 (s, 1H, pyridine-H), 7.30-7.80 (m, 11H, Ar-H + CH-benzylidene + NH_2-exchangeable with D_2O), 8.89 (s, 2H, 2NH-exchangeable with D_2O). MS, m/z (%): 680 (M^+; 15), 525 (35), 490 (35), 485 (20), 449 (30), 391 (25), 363 (22), 222 (30), 168 (100), 153 (55), 125 (45), 98 (75), 89 (30), and 55 (50). Anal.Calcd.for $C_{34}H_{29}N_4O_3SCl_3$ (679.5): C, 60.04; H, 4.26; N, 8.24. Found: C, 60.10; H, 4.20; N, 8.15.

Synthesis of pyrano[2',3':4,5][1,3]thiazolo[3,2-a]pyridine derivative (20).

A mixture of compound **(9a)** (0.01 mol), with malononitrile (0.01 mol) in ethanol containing a catalytic amount of piperidine (0.5 ml) was refluxed for 3hr, the solid product was collected and recrystallized from dioxane as white crystals.

Yield 70 %, m.p.250-253°C.IR (KBr): ν = 3342, 3323, 3174 (NH/NH_2), 2212 (CN), 1645cm^{-1} (C=O). ^{1}H NMR (DMSO-d_6): δ= 1.10-1.80, 3.50 (m, 11H, cyclohexyl protons), 2.50, 2.85 (2s, 12H, $2N(CH_3)_2$), 4.79 (s, 1H, pyridine-H), 5.72 (s, 1H, pyran-H), 6.81-7.86 (m, 12H, Ar-H + $2NH_2$-exchangeable with D_2O), 11.68 (s, 1H, NH-exchangeable with D_2O).Anal.Calcd.for $C_{35}H_{38}N_8O_2S$ (634): C, 66.62; H, 5.99; N, 17.66. Found: C, 66.50; H, 5.90; N, 17.60.

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