Synthesis, characterisation and antimicrobial activity of thiazole, bisthiazole, pyridone and bispyridone derivatives

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N-cyclohexyl-2-cyano-acetamide was reacted with phenyl isothiocyanates and sulfur to give thiazolidine and bisthiazolidine derivatives. Treatment of *N*-cyclohexyl-2-cyanoacetamide with phenyl isothiocyanate and KOH followed by *in situ* heterocyclisation with α-halo compounds gave thiazole derivatives. Treatment of *N*-cyclohexyl-2-cyano-acetamides with cinnamonitriles gave pyridone and bispyridone derivatives. *N*-cyclohexyl-2-cyanoacetamide coupled smoothly with benzene-diazonium chloride in pyridine. Cyclocondensation of *N*-cyclohexyl-2-cyanoacetamide with acetylacetone gave 1,1′-(ethane-1,2-diyl)bis(4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile). Ternary condensation of *N*-cyclohexyl-2-cyanoacetamide, malononitrile and acetaldehyde gave a bispyridone derivative. Some of the new compounds were tested against bacteria and some fungi.

Keywords: thiazole, bisthiazole, pyridone and bispyridone derivatives, antimicrobial activity

Heterocyclic compounds play an important role in all spheres of life including pharmaceuticals, natural resources, veterinary, agricultural products analytical reagents and dyes.[1,2] Cyanoacetamide derivatives are highly reactive reagents and their use in heterocyclic synthesis has recently received considerable attention.[3–5] The development of effective therapeutic agents for the treatment of inflammation continues to be a challenge in medicinal chemistry. Compounds containing thiazole have been reported to exhibit anti-inflammatory activity.[6–11] Furthermore, the antimicrobial activity of thiazoles is well documented.[12,13] On the other hand, the synthesis of polyfunctionalised pyridines is important because of their widespread occurrence in nature.[14–16] The pyridine ring is a basic unit of numerous biologically active alkaloids and pharmaceutical products.[17,18] Oligopyridines and their complexation with metal ions have been extensively studied because of their application in coordination and super molecular chemistry.[19,20] Some bipyridine derivatives are used in catalysis, molecular electronics, photoactivated species, and as optoelectronic devices.[21–24]

Encouraged by the above finding, the present investigation deals with the synthesis of compounds having thiazole, bisthiazole, pyridine and bispyridine moieties in order to investigate their antimicrobial activities.

Combination of NH–C=O and CH_2CN in *N*-alkyl-2-cyanoacetamide molecule opens synthetic opportunities for further reaction and utilisation as a starting material in the synthesis of many heterocyclic compounds. Therefore *N*-alkyl-2-cyanoacetamide derivatives **1a**,**b** were prepared in high yield from the reaction of aliphatic amines with ethyl cyanoacetate.[25] The reactivity of the methylene group in **1a** towards isothiocyanates and sulfur in the presence of triethylamine was investigated. Thus, the reaction of *N*-cyclohexyl-2-cyano-acetamide **1a** with isothiocyanate derivatives and/or biphenyl isothiocyanate and sulfur in ethanol catalysed with triethylamine gave thiazolidine and bisthiazolidine derivatives **2a**,**b** and **3** (Scheme 1). The structures of compounds **2a**,**b** and **3** were established on the basis of analytical analysis and spectral data (see Fig.1).

The reactivity of the methylene group in cyanoacetamide derivative **1a** towards isothiocyanate in the presence of potassium hydroxide followed by *in situ* heterocyclisation with *α*-halocarbonyl compounds was studied. Thus, the reaction of cyanoacetamide derivative **1a** with phenyl isothiocyanate in the presence of potassium hydroxide at room temperature gave the non-isolable potassium salt **4**. The potassium sulfide salt **3** on treatment with ethyl chloroacetate **5a** at room temperature gave the novel 4-thiaozlidinone derivative **6** in good yield. Cycloalkylation of the intermediate **4** with chloroacetone **5b** at room temperature gave the corresponding 4-methyl thiazole **7** and the structure of thiophene derivative **8** was rejected according to the spectral data (Scheme 1). The structure of 4-thiazolidinone **6** and 4-methylthiazole **7** derivatives were elucidated on the basis of elemental analysis and spectral data.

The reaction of N-cyclohexyl-2-cyanoacetamide **1a** with triethyl orthoformate in acetic anhydride gave *N*-(cyclohexyl)-2-ethoxymethylidene-2-cyanoacetamide **9** (Scheme 2). As a part of this research, the reaction of compound **1a** with *α*-cyanocinnamonitrile was investigated. Thus, Michael addition of cyanoacetamide derivative **1a** on the activated double bond of *α*-cyano-*o*-chlorocinnamonitrile gave 2-pyridone derivative **13** (Scheme 2). The formation of 2-pyridone **13** proceed via Michael type addition of the methylene function of **1a** to the activated double bond in *α*-cyanocinnamonitrile to yield Michael adduct **10** which underwent intramolecular cyclisation and auto-oxidation to give **13** (Scheme 2). Structure **13** was established on the basis of spectral data.

Attention has been increasingly paid to the synthesis of bisheterocyclic compounds, which displayed much better antibacterial activity than heterocyclic compounds.[26] Thus, compound **1b** coupled smoothly with benzene diazonium chloride in pyridine to give 2,2′-[ethane-1,2-diylbis(azanediyl)]bis (2-oxo-N'-phenylacetohydrazonoyl cyanide) **14** (Scheme 3 and Fig. 2)).

Cyclocondensation of compound **1b** with acetylacetone gave 1,1′-(ethane-1,2-diyl)bis(4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile) **16**, via intramolecular heterocyclisation of the non-isolable intermediate **15** by loss of water.[27] Ternary condensation of biscyanoacetamide derivative **1b**, malononitrile and acetaldehyde (1:2:2 molar ratio) in ethanol solution containing a catalytic amount of piperidine gave bispyridone **17**. Similarly, bispyridone **18** was obtained via reaction of compound **1b** with *α*-cyano-*p*-methylcinnamonitrile in refluxing ethanol in presence of a catalytic amount of piperidine (Scheme 3). The structures of bispyridine derivatives **16–18** were confirmed on the basis of elemental analysis and spectral data (see Fig. 3).

Antimicrobial activity

Most of the synthesised compounds were screened 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.

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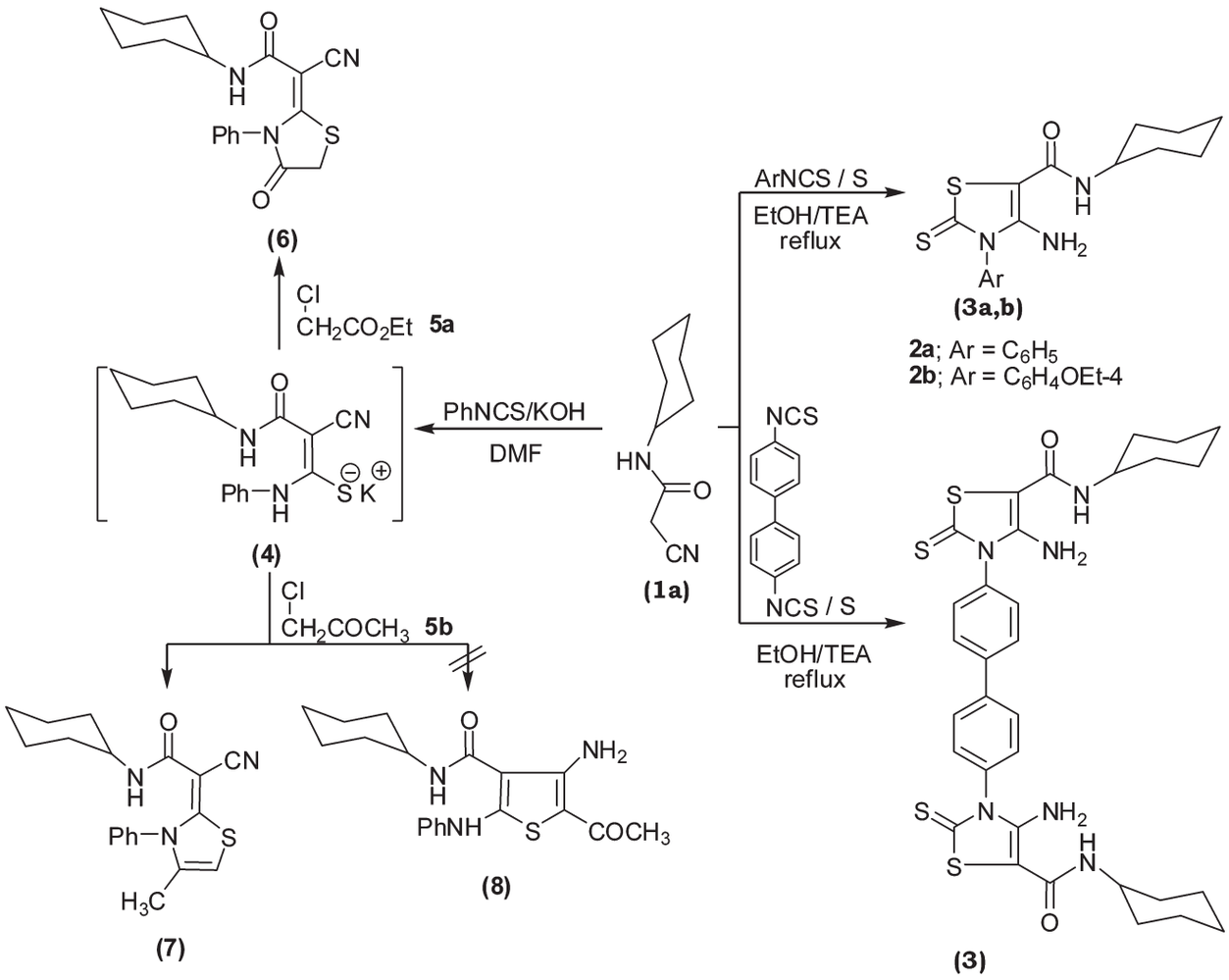
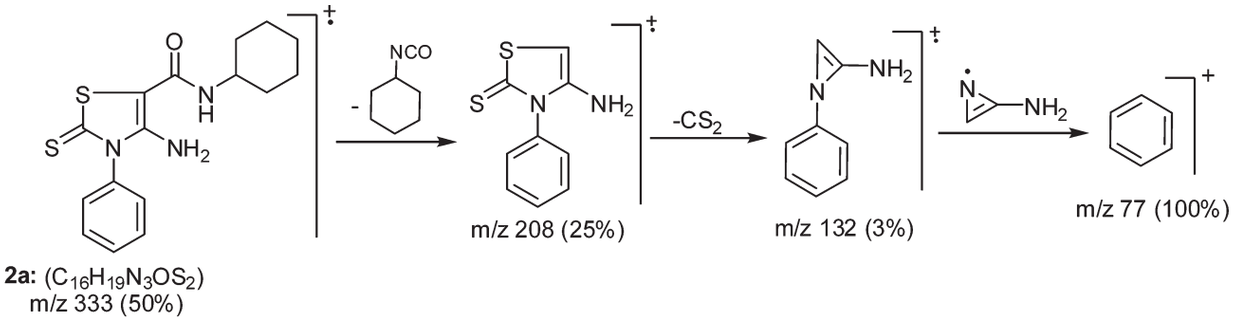


Scheme 1



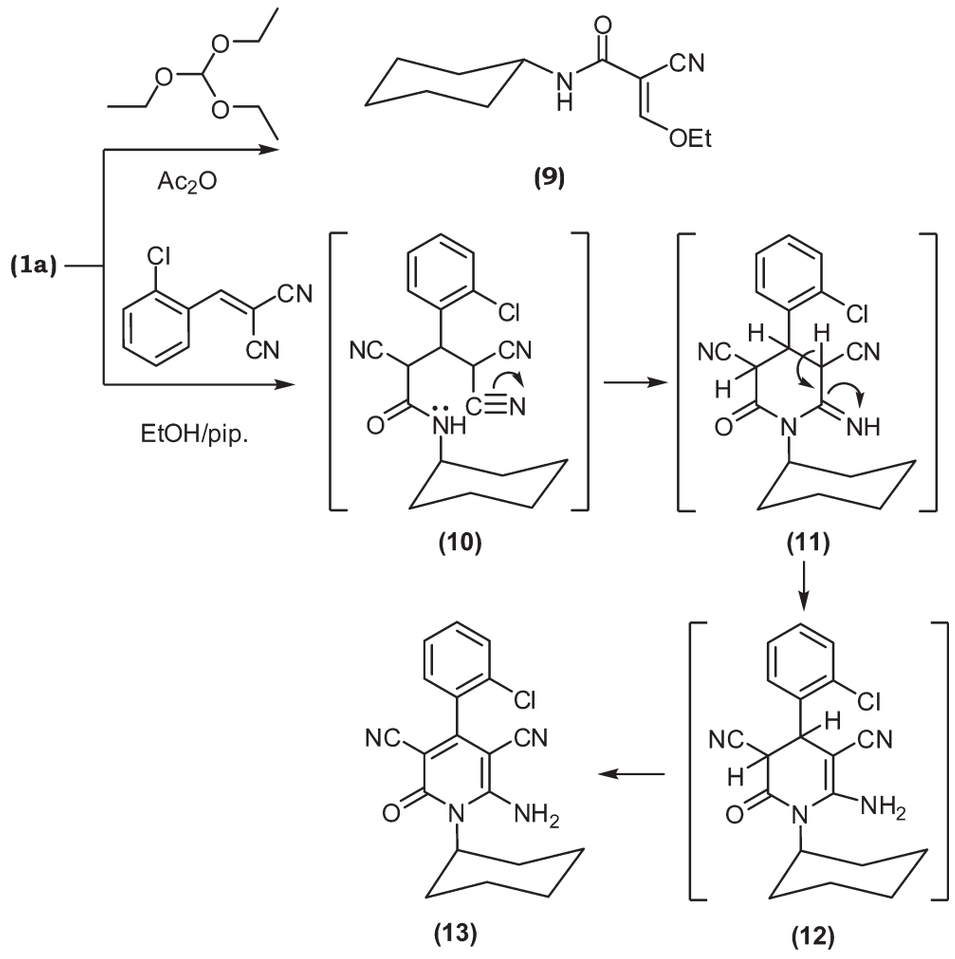
2a: ($C_{16}H_{19}N_3OS_2$)
m/z 333 (50%)

Fig. 1 Fragmentation pattern of **2a**.

The results for antibacterial activities depicted in Table 1 revealed that compounds **2a**, **6**, **13**, **14**, and **18** exhibited good activities against the reference chemotherapeutics, while compounds **2b**, **3**, **7** and **16** showed moderate antibacterial activity. On the other hand, most of the prepared compounds exhibited moderate antifungal activities against the reference drugs, whereas, **2a**, **6**, **9**, **16** and **18** exhibited good antifungal activities against *Fusariumoxy sporum* and low activity against *Aspergillus ochraceus.*

In conclusion, we have described a simple and convenient route for the synthesis of some heterocyclic bases on thiazole, bisthiazole, pyridine, and bispyridine derivatives for antimicrobial evaluation.

The tested compounds were evaluated by the agar diffusion technique[28] using a 1 mg mL^{-1} solution in DMSO. The test organisms were four bacterial strains: *Bacillius theringiensis, Serratia marcescens, Klebsiella pneumoniae*, and *Proteus mirabilis* and two fungi: *Fusarium oxysporum*, and *Aspergillus ochraceus.* A control using DMSO without the test compound was included for each organism. Ampicillin was purchased in Egypt and used in a concentration 2 mg mL^{-1} as a reference drug. 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



Scheme 2

zone was measured as an indicator for the activity of the compounds.

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 Microanalytical Center, Faculty of Science (Cairo University, Egypt). Microbiology screening was carried out in the Botany Department, Faculty of Science, Al-Azhar University.

Synthesis of dihydrothiazole derivatives (**2a**,**b**)

A mixture of compound **1a** (0.01 mol), the requisite aryl isothiocyanate (0.01 mol) and elemental sulfur (0.01 mol) in ethanol (30 mL) containing few drops of triethylamine were refluxed for 3h, the solid product so formed on heating was collected and recrystallised from suitable solvent to give **2a**,**b**.

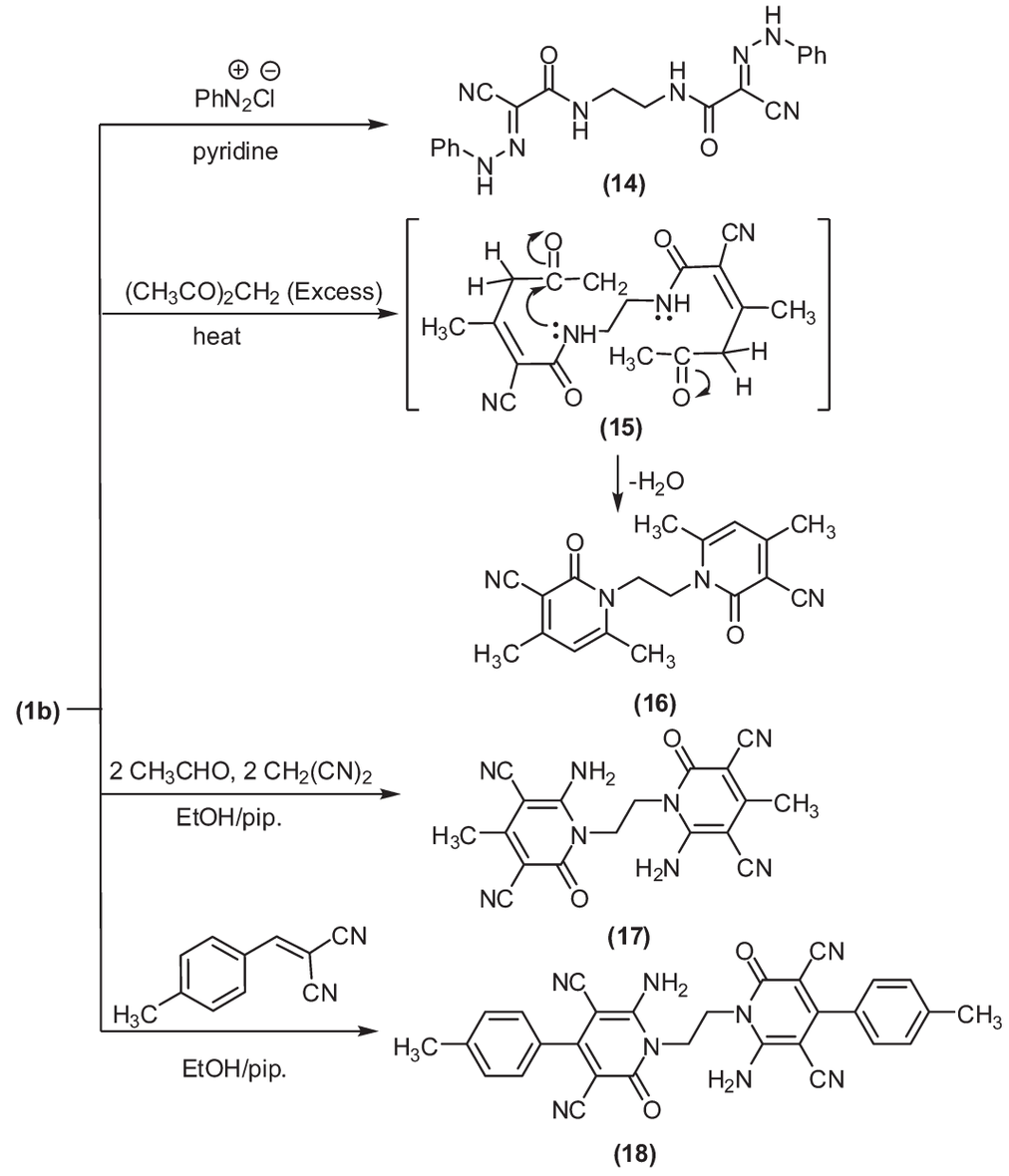
4-Amino-N-cyclohexyl-3-phenyl-2-thioxo-2,3-dihydrothiazole-5-carboxamide (**2a**): 70% yield; brown crystals (acetic acid), m.p. 266–268°C. IR (KBr): ν = 3461, 3301, 3213 (NH and NH_2) and 1654 cm^{-1} (C=O). ^{1}H NMR (DMSO-d_6): δ = 1.24–1.35 (m, 6H, cyclohexyl protons), 1.57–1.76 (m, 4H, cyclohexyl protons), 3.82 (hump, 1H, cyclohexyl proton), 6.50 (s, 2H, NH_2), 6.81–7.42 (m, 5H, ArH), 8.26 (s, 1H, NH). MS: *m/z* = 333 (M+; 50%), 250 (0.2%), 208 (25%), 136 (40%), 77 (100%). Anal. Calcd for $C_{16}H_{19}N_3OS_2$ (333.47): C, 57.63; H, 5.74; N, 12.60. Found: C, 57.60; H, 5.60; N, 12.55%.

4-Amino-N-cyclohexyl-3-(4-ethoxyphenyl)-2-thioxo-2,3-dihydrothiazole-5-carboxamide (**2b**): 65% yield; brown crystals (acetic acid), m.p. 266–268°C. IR (KBr): ν = 3332, 3280, 3258 (NH/NH_2) and 1630 cm^{-1} (C=O). ^{1}H NMR (DMSO-d_6): δ =1.21–1.31 (m, 6H, cyclohexyl protons), 1.37 (t, 3H, CH_3),1.53–1.72 (m, 4H, cyclohexyl protons), 3.71 (hump, 1H, cyclohexyl proton), 4.08 (q, 2H, CH_2), 6.70 (s, 2H, NH_2; exchangeable with D_2O), 7.07–7.29 (m, 5H, ArH+ NH; exchangeable with D_2O).^{13}C NMR (DMSO-d_6): δ = 24.92, 25.10, 32.35, 47.96, 83.57, 129.81, 129.85, 134.95, 150.72, 160.88, 185.01. MS: *m/z* = 376 (M-1; 50%), 332 (75%), 235 (100%), 161 (98%). Anal. Calcd For $C_{18}H_{23}N_3O_2S_2$ (377.52): C, 57.27; H, 6.14; N, 11.13. Found: C, 57.20; H, 6.00; N, 11.10%.

3,3′-(Biphenyl-4,4′-diyl)bis(4-amino-N-cyclohexyl-2-thioxo-2,3-dihydrothia-zole-5-carboxamide) (**3**): A mixture of compound **1a** (0.02 mol), biphenylisothio-cyanate (0.01 mol) and elemental sulfur (0.02 mol) in ethanol (30 mL) containing few drops of triethylamine were refluxed for 3h, The solid product which produced on heating was collected by filtration. 60% yield; brown crystals (acetic acid), m.p. 280–282°C. IR (KBr): ν = 3258 (NH), 2931 (stretching CH) and 1639 cm^{-1} (C=O).^{1}H NMR (DMSO-d_6): δ =1.22–1.26 (m, 6H, cyclohexyl protons), 1.63–1.74 (m, 4H, cyclohexyl protons), 3.72 (hump, 1H, cyclohexyl proton),6.82 (s, 4H, 2NH_2; exchangeable with D_2O), 7.36–8.00 (m, 10H, ArH and 2NH; exchangeable with D_2O). Anal. Calcd for $C_{32}H_{36}N_6O_2S_4$ (664.93): C, 57.80; H, 5.46; N, 12.64. Found: C, 57.60; H, 5.30; N, 12.60%.

Preparation of compounds **6** *and* **7**

To a suspension of finely powdered potassium hydroxide (0.01 mol) in dry dimethylformamide (10 mL), cyanoacetamide derivative (**1a**) (0.01 mol) and then the phenyl isothiocyanate (0.01 mol) were added in portions. The reaction mixture was stirred at room temperature with α-halocarbonyl compounds (namely, ethyl chloroacetate, chloroacetone; 0.01 mol) and left at room temperature for 3h, then it was placed into ice-water and acidified with 0.1 N HC1 at pH 3–4. The resulting precipitate was filtered off, dried and recrystallised from the proper solvent.



Scheme 3

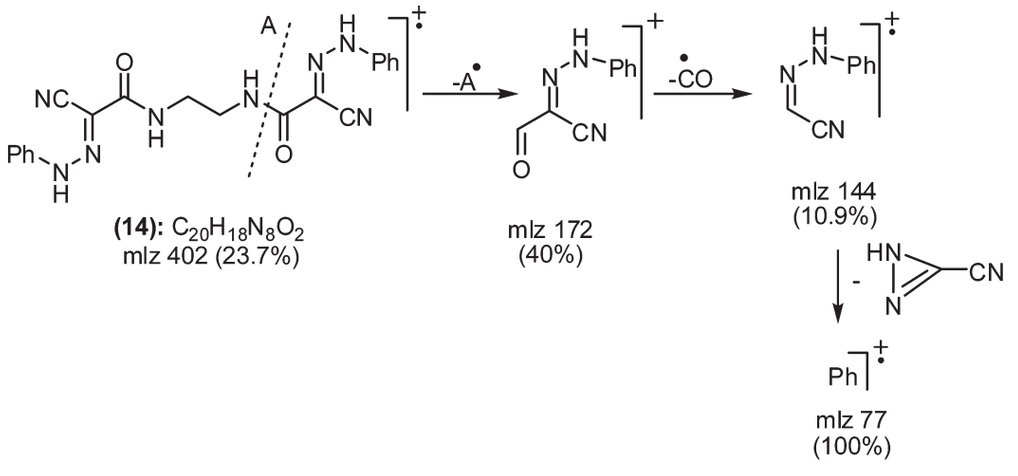


Fig. 2 Fragmentation pattern of **14**.

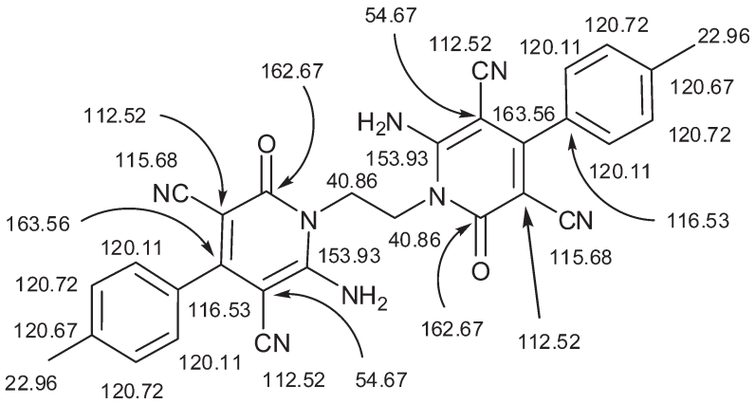


Fig. 3 ^{13}CNMR of **18**.

Table 1 Zone (mean diameter of inhibition in mm) as a criterion of antibacetrial and antifungal activities of the newly synthesised compounds

Compound	Bacteria				Fungi	
	Bacillius theringiensis	*Serratia marcescens*	*Klebsiella pneumoniae*	*Proteus mirabilis*	*Fusarium oxysporum*	*Aspergillus ochraceus*
2a	13	27.55	15	33	14.5	3
2b	11.5	21	6	22	7	4
3	10.5	21	12	24	9	2
6	15	28	17	31	13	–
7	12	21	11	11	5	5
9	9	9	15	19	14	1
13	15	26.5	16	31	6	3
14	13.5	26.5	16.5	27	7	3
16	10	22	14	24	13	2
18	16	31	17	31	14	–
Ampicillin	17	40	20	40	15	10

2-Cyano-N-cyclohexyl-2-(4-oxo-3-phenylthiazolidin-2-ylidene) acetamide (**6**): 70% yield; brown crystals (benzene), m.p. 270–272°C. IR (KBr): ν = 3332 (NH), 2189 (C≡N) and 1684, 1640 cm^{-1} (C=O). ^{1}H NMR (DMSO-d_6): δ = 1.34–1.47 (m, 6H, cyclohexyl protons), 1.57–1.77 (m, 4H, cyclohexyl protons), 3.74 (hump, 1H, cyclohexyl proton), 4.02 (s, 2H, CH_2), 7.16–7.31 (m, 5H, ArH), 9.37 (s, 1H, NH). MS: *m/z* = 341 (M$^+$; 25.6%), 284 (30.3%), 250 (26.7%), 172 (73.6%), 76 (100%). Anal. Calcd for $C_{18}H_{19}N_3O_2S$ (341.43): C, 63.32; H, 5.61; N, 12.31. Found: C, 63.33; H, 5.50; N, 12.25%.

2-Cyano-N-cyclohexyl-2-(4-methyl-3-phenylthiazol-2(3H)-ylidene) acetamide (**7**): 60% yield; brown crystals (benzene), m.p. 185–187°C. IR (KBr): ν = 3219, 3105 (NH), 2923 (aliph. CH), 2164 (C≡N) and 1635 cm^{-1} (C=O). ^{1}H NMR (DMSO-d_6): δ =1.16–1.21 (m, 6H, cyclohexyl protons), 1.63–1.67 (m, 4H, cyclohexyl protons), 1.79 (s, 3H, CH_3), 3.53 (hump, 1H, cyclohexyl proton), 6.21 (d, 1H, NH), 6.80 (s, 1H, thiazol-H5), 7.46–7.57 (m, 5H, ArH). MS: *m/z* = 339 (M$^+$; 49.2%), 241 (85.8%), 128 (23%), 93 (50%), 55 (100%). Anal.Calcd for $C_{19}H_{21}N_3OS$ (339.45): C, 67.23; H, 6.24; N, 12.38. Found: C, 67.22; H, 6.10; N, 12.30%.

2-Cyano-N-cyclohexyl-3-ethoxyacrylamide (**9**): A mixture of **1a** (0.01 mol), triethylorthoformate (0.01 mol) and acetic anhydride (20 mL) was heated under reflux for 3h. The solid product was collected and recrystallised from dioxane as white crystals. 75% yield, m.p. 140–142°C. IR (KBr): ν = 3258 (NH), 2968, 2922 (stretching CH), 2200 (C≡N) and 1661 cm^{-1} (C=O). ^{1}H NMR (DMSO-d_6): δ = 1.19–1.28 (m, 6H, cyclohexyl protons), 1.39 (t, 3H, CH_3), 1.56–1.75 (m, 4H, cyclohexyl protons), 3.84 (hump, 1H, cyclohexyl proton), 4.23 (q, 2H, CH_2), 8.15 (s, 1H, methine-H), 8.87 (s, 1H, NH). MS: *m/z* = 222 (M$^+$; 0.5%), 199 (8%), 185 (12%), 171 (10%), 157 (10%), 149 (16%), 129 (25%), 115 (15%), 98 (33%), 97 (38%), 73 (47%), 55 (100%). Anal. Calcd for $C_{12}H_{18}N_2O_2$ (222.28): C, 64.84; H, 8.16; N, 12.60. Found: C, 64.80; H, 8.00; N, 12.50%.

6-Amino-4-(2-chlorophenyl)-1-cyclohexyl-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**13**): To a solution of o-chlorobenzylidenemalononitrile (0.01 mol) in ethanol (30 mL) was added cyanoacetamide derivative **1a** (0.01 mol) and few drops of piperidine and the reaction mixture was heated under reflux for 2h, then left to cool to room temperature. The precipitated product was collected by filtration, and recrystallised from acetic acid as yellow crystals. 65% yield, m.p. >300°C. IR (KBr): ν = 3458, 3288 (NH_2), 2938 (stretching CH), 2213 (C≡N), and 1644 cm^{-1} (C=O). ^{1}H NMR (DMSO-d_6): δ =1.16–1.34 (m, 6H, cyclohexyl protons), 1.55–1.73 (m, 4H, cyclohexyl protons), 3.71 (hump, 1H, cyclohexyl proton), 7.12–7.63 (m, 6H, ArH+ NH_2). MS: *m/z* = 352 (M$^+$; 24.3%), 270 (75%), 245 (8%), 180 (10%), 68 (47%), 55 (100%). Anal. Calcd For $C_{19}H_{17}N_4OCl$ (352.82): C, 64.68; H, 4.86; N, 15.88. Found: C, 64.60; H, 4.80; N, 15.80%.

2,2′-(Ethane-1,2-diylbis(azanediyl))bis(2-oxo-N′-phenylacetohydrazonoyl cyanide) (**14**): A mixture of compound **1b** (0.01 mol), benzene diazonium chloride (0.02 mol) and pyridine (10 mL) was stirred at room temperature for 6 h. The resulting solution was poured into crushed ice with adding a few drops of conc. HCl and the precipitate product was collected and crystallised from dioxane as red crystals. 70% yield, m.p. 210–213°C. IR (KBr): ν = 3304 (NH), 2922 (CH-aliph.), 2216 (C≡N), and 1648 cm^{-1} (C=O). ^{1}H NMR (DMSO-d_6): δ = 4.01 (s, 4H, 2CH_2), 7.14–7.88 (m, 10H, ArH), 8.11, 9.8 (2s, 4H, 4NH). MS: *m/z* = 402 (M$^+$; 23.7%), 298 (30%), 172 (40%), 144 (10.9%), 109 (15%), 77 (100%). Anal. Calcd for $C_{20}H_{18}N_8O_2$ (402.41): C, 59.69; H, 4.51; N, 27.85. Found: C, 59.60; H, 4.40; N, 27.80%.

1,1′-(Ethane-1,2-diyl)bis(4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitr-ile) (**16**): Equimolar amounts of **1b** (0.01 mol) and acetylacetone (excess) with a few drops of piperidine in an oil bath were refluxed for 1 h at 160°C, then allowed to cool. The solid product was collected and recrystallised from ethanol as yellow crystals to give **16**. 70% yield, m.p. 240–243°C. IR (KBr): ν = 3304 (NH), 2922 (stretching CH), 2216 (C≡N), and 1648cm^{-1} (C=O).^{1}H NMR (DMSO-d_6): δ = 2.27, 2.50 (s, 12H, 4CH_3), 4.24 (s, 4H, 2CH_2),6.03 (s, 2H, pyridine-H). MS: *m/z* = 322 (M$^+$; 15%), 258 (30%), 256 (15%), 218 (17%), 173 (100%), 149 (95%), 104 (20%), and 77 (30%). Anal. Calcd for $C_{18}H_{18}N_4O_2$ (322.36): C, 67.07; H, 5.63; N, 17.38. Found: C, 67.00; H, 5.20; N, 17.30%.

1,1′-(Ethane-1,2-diyl)bis(6-amino-4-Methyl-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile) (**17**): A mixture of biscyanoacetanilide **1b** (0.01 mol), acetaldehyde (0.02 mol), malononitrile (0.02 mol) in ethanol (30 mL) containing piperidine (0.5 mL) was heated under reflux for 3hr. the resulting solid was filtered off and recrystallised from the suitable solvent to give **17.** 70% yield, m.p. 300–302°C. IR (KBr): ν = 3333, 3316 (NH_2), 2216 (C≡N) and 1642 cm^{-1} (C=O). ^{1}H NMR (DMSO-d_6): δ = 2.16 (s, 6H, $2CH_3$), 4.31 (s, 4H, $2CH_2$), 6.89 (s, 4H, $2NH_2$). MS: *m/z* = 376 (M+2; 15%), 342 (23%), 271 (26%), 163 (45%), 111 (100%), 67 (53%). Anal. Calcd for $C_{18}H_{14}N_8O_2$ (374.36): C, 57.75; H, 3.77; N, 29.93. Found: C, 57.70; H, 3.70; N, 29.90%.

1,1′-(Ethane-1,2-diyl)bis(6-amino-2-oxo-4-p-tolyl-1,2-dihydropyridine-3,5-dicarbonitrile) (**18**): To a mixture of biscyanoacetanilide derivative **1b** (0.01 mol), p-tolualdehyde (0.02 mol), malononitrile (0.02 mol) in ethanol (30 mL), piperidine (0.5 mL) was added. The reaction mixture was refluxed for 4 h. The solid product which produced on heating was collected and recrystallised from dioxane as brown crystals. 65% yield, m.p. >300°C. IR (KBr): ν = 3492, 3324 (NH_2), 2214 (C≡N), and 1640 cm^{-1} (C=O).^{1}H NMR (DMSO-d_6): δ = 2.34, 2.37 (2s, 6H, $2CH_3$),4.40 (s, 4H, $2CH_2$),7.18–7.41 (m, 8H, ArH), 8.58 (s, 4H, $2NH_2$; exchangeable with D_2O).^{13}C NMR (DMSO-d_6): δ = 22.96, 40.33, 40.86, 54.67, 115.65, 116.53, 129.11, 120.67, 120.72, 153.93, 162.67 and 163.56. MS: *m/z* = 526 (M^+; 6%), 423 (23%), 368 (21.4%), 360 (40%), 273 (60%), 290 (100%), 189 (55%), 143 (40%), 84 (72%). Anal. Calcd For $C_{30}H_{22}N_8O_2$ (526.55): C, 68.43; H, 4.21; N, 21.28. Found: C, 68.40; H, 4.10; N, 21.20%.

Received 9 May 2010; accepted 12 July 2010
Paper 1000111 doi: 10.3184/030823410X12812857779516
Published online: 30 August 2010

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