

Reaction of isocyanides with thiophenols and gem-diactivated olefins: a one-pot synthesis of substituted 2-aminopyrroles

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Abstract A novel multicomponent reaction of isocyanides with thiophenols and gem-diactivated olefins has been discovered. Depending on the choice of isocyanides, substituted 2-aminopyrroles or thioimides have been prepared. The obtained scaffolds bearing four points of diversity can directly be used in combinatorial syntheses.

Keywords MCRs · Reaction design · Isocyanides · 2-Aminopyrroles · Thioimides · Multicomponent

Introduction

Multicomponent reactions (MCRs) are able to combine multiple reagents into a single core in one step giving an easy access to millions of small organic molecules. These compounds are widely used in biological screening and materials science [1]. Therefore, these reactions are regarded as a powerful tool in parallel organic synthesis and combinatorial chemistry [2]. Owing to the unique flexibility and multitude of variants, isocyanide-based MCRs are perfectly suited for the exploration of chemistry space [3]. Modern planning strategies in organic chemistry such as diversity-oriented synthesis aim at the development of short pathways (three- to five-step) leading to collections of small molecules having skeletal diversity [4]. However, collections of products with many distinct molecular skeletons are a difficult task for MCRs, because the number of MCRs, including all its variants, is limited. There are several most exploited reactions, including the Ugi and Passerini condensations, which

produce the main part of libraries. Therefore, finding of novel MCRs is a basis for design of libraries having broad skeletal diversity. During the last decade several original methods for the efficient finding of MCRs were proposed [5]. The goals of these methods include the discovery of collections of novel reactions that will be able to produce libraries of libraries, containing several distinctive scaffolds. However, the development of this approach is still a challenge.

During the last 5 years, our research group concentrated its efforts on finding novel isocyanide-based MCRs. We believe that a collection of these reactions can be used for parallel synthesis of a library containing several scaffolds. Previously, our research group discovered an original reaction of isocyanides with gem-dicyano olefins and nitrophenols via combinatorial finding of novel MCRs on the basis of well-known variant of the Ugi reaction [6]. Depending on conditions, this reaction can give access to two distinctive backbones: substituted propionamides **1** and succinimides **2**. Thus, in the presence of pyridine propionamides **1** were formed, while the use of strong base opens the way to succinimides **2**. Another direction is the formation of cyclopentene derivatives **3** [7] under heating (see Fig. 1). New generation of products can be obtained via combinatorial formation of precursors in this reaction. We present here novel isocyanide-based reactions leading to substituted 2-aminopyrroles **4** and thioimides **5** (routes D and E in Fig. 1, respectively). It should be noted that 2-aminopyrroles containing a cyano or carboxymethyl group at 3-position can be easily transformed into pyrrolo[2,3-d]pyrimidines with potential anti-HIV activities [8].

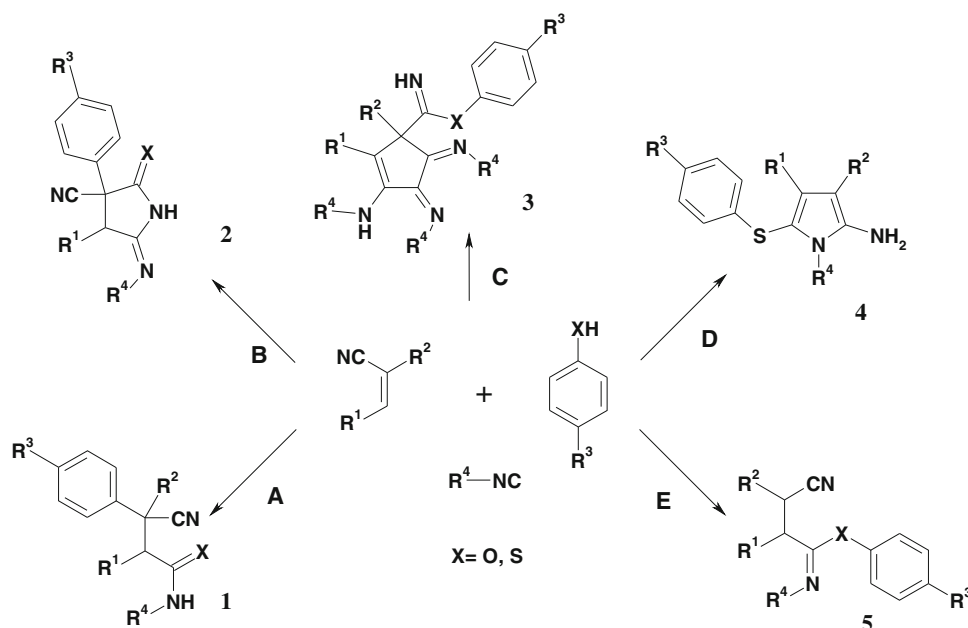
Results and discussion

The results previously obtained gave us the basis for the determination of appropriate reaction conditions and starting

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Fig. 1 Diversity of the products in the system: isocyanide-activated olefin–(thio)phenol



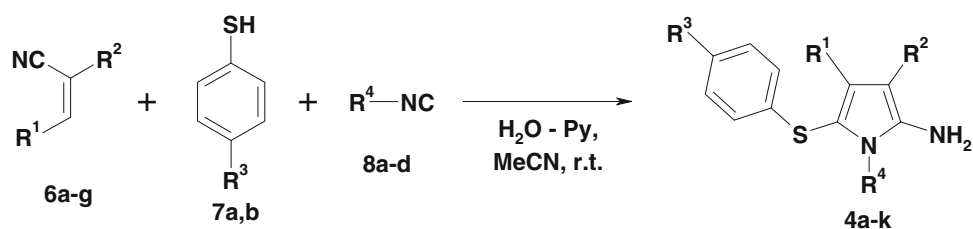
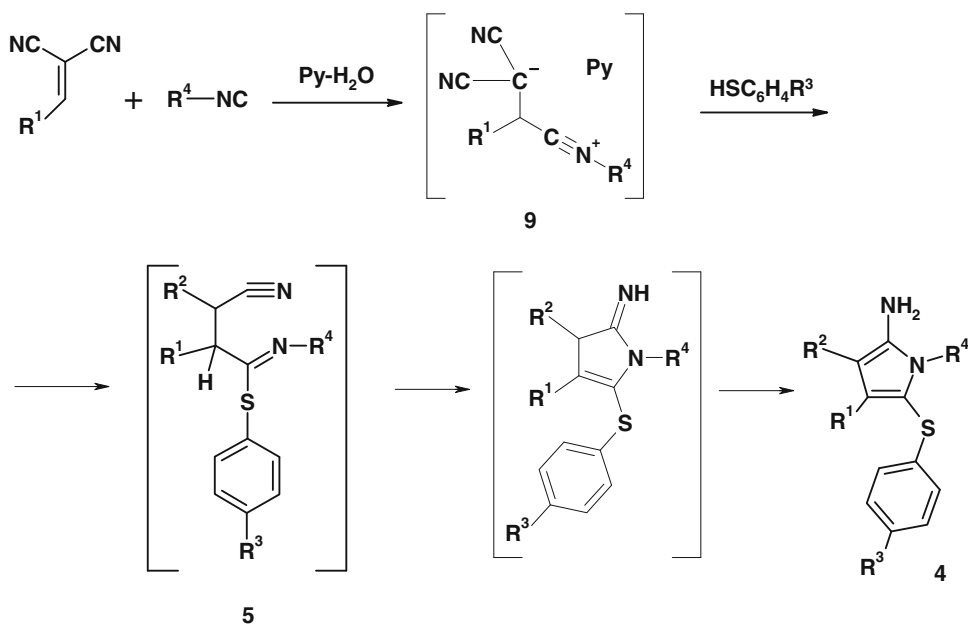
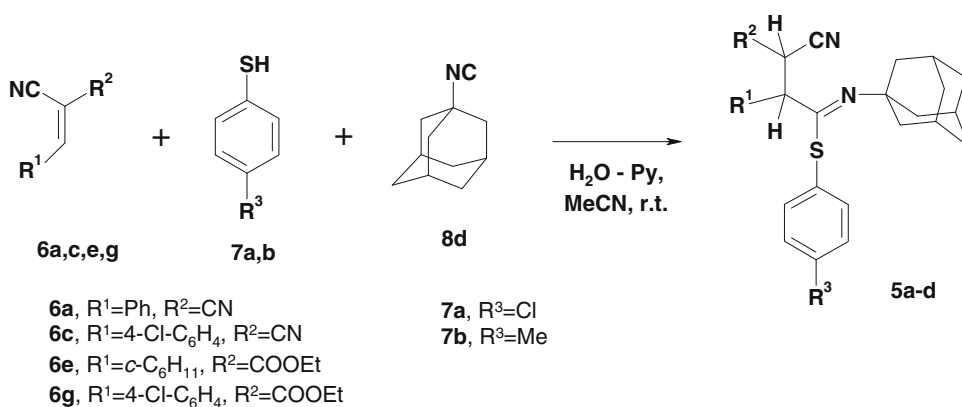
materials. Since we have previously used N-nucleophiles (e.g., isoquinoline [9]) and O-nucleophiles (e.g., 4-nitrophenols [6]), we envisioned that we could also use S-nucleophiles (e.g., thiophenols) in the reaction with isocyanides and gem-diactivated olefins. Although Kaim et al. have used thiophenols in Ugi-Smiles reactions [10], in such case, only thioamides were obtained. Note that reactions of isocyanides with nucleophiles and gem-diactivated olefins proceed in the presence of organic bases (e.g., pyridine). We also used water as an additive, which can increase the reaction rate.

In that way, we carried out all the experiments in mixture of solvents containing acetonitrile (80%), water (15%), and pyridine (5%). In our approach, we found that the reaction of benzylidenemalononitrile **6a** with 4-chlorothiophenol **7a** and cyclohexyl isocyanide **8a** in the mixed solvent affords only product **4a** with good yields (Scheme 1). Using other gem-diactivated olefins **6b–f**, 4-methylthiophenol **7b**, and isocyanides **8b,c** a set of products was obtained whose structures were determined by NMR spectroscopy and mass spectrometry. Surprisingly, no ¹³C thioamide signal (190–210 ppm) was observed. Along with the absence of 2-H in the range 4.4–4.6 ppm, these data suggested that the reaction of isocyanides and activated olefins with thiophenols does not lead to substituted propionthioamides. The distinctive feature of the NMR spectra for compounds **4a–k** was the presence of the ¹³C signals of only one cyano group from two, which were incorporated in the starting olefins **6a–d**. When we used the olefins with one cyano group **6e,f**, no signals corresponding to CN have been revealed. Instead of CN group, the ¹H resonance of amino group has been detected in the ¹H NMR spectra of all compounds **4a–k**. The presence of primary amino group was also proved through acylation of compound **4d** with acetic anhydride. Resulting acetamide was identified

with the help of IR spectroscopy. In addition, four signals corresponding to new aromatic system were observed in the ¹³C NMR spectra (see “Experimental” section). In summary, the character of the spectra pointed out intramolecular cyclization with the participation of cyano group completed by the formation of an aromatic system. Taking these data into account, we have proposed the structure of 2-aminopyrrole as the most appropriate for compounds **4a–k**. Analysis of previously reported data gave us information about similar 2-aminopyrroles obtained via conversion of 5-aminothiazolium salts under basic conditions [11] or by the multi-step synthesis [8,12]. Comparison of these NMR spectra confirmed the structure of the final products. It should be noted that the C-1 of 2-aminopyrrole system is usually observed in the range 140–150 ppm, while C-2 of ones in the range 80–90 ppm. This fact may be accounted for tautomerization, which is typical for 2-aminopyrroles. In that way, the reaction results in the formation of 2-amino-5-arylthiopyrroles via intramolecular addition of cyano group to N atom of thioimide group and further H-shift (Scheme 2).

Using 1-adamantyl isocyanide **8d**, we have succeeded in obtaining some other products—thioimides **5a–d** (Scheme 3), which can easily be identified by the presence of the ¹H signals of 2-H in the range of 4.1–4.2 ppm and 3-H in the range of 4.6–4.7 ppm with a coupling constant of 6 Hz. Thus, steric hindrance appearing during the cyclization stage changes the reaction route.

The proposed reaction mechanism is based on existence of subsequent thioimides **5** which are formed by the addition of thiophenols as an external nucleophile to the zwitterionic intermediate **9** (Scheme 2). Previously, we have registered unstable zwitter-ionic intermediates in the mixtures of isocyanides and gem-diactivated olefins [7]. In turn, isolation

Scheme 1 Synthesis of 2-aminopyrroles **4****Scheme 2** Proposed mechanism of the reaction of isocyanides with activated olefins and thiophenols**Scheme 3** Synthesis of thioimidates **5**

of products **5** in the reaction with 1-adamantyl isocyanide **8d** confirms our initial suggestion about the mechanism. In addition, we carried out the direct conversion of isolated product **5a** into **4k** in the presence of triethylamine (see “Experimental” section).

Depending on the choice of isocyanides, the reaction can give access to two different backbones: 2-aminopyrroles **4** and thioimides **5**. Most of them were obtained in good or moderate yields (Table 1). Note that use of alkyl-substituted reagents **6d–f** leads to a decrease in the reaction time and an increase in the yields of the target products. The reaction gives satisfactory results only in the case of aromatic thiols. No products were obtained when aliphatic thiols were used even in the presence of a strong base.

Conclusion

Our method gives a possibility to vary all four substituent in the pyrrole ring. In addition, the presence of primary amino group in the compounds opens the way to a further modification of obtained compounds. Note that bicyclic derivatives obtained on the basis of 2-aminopyrrole scaffold are of interest for medicinal chemistry as potential antiviral agents. Now, we concentrated our efforts on diversity-oriented cyclizations using 2-aminopyrroles **4** as a starting point. The results of these investigations will be reported in due course. Thus, this protocol is amenable to the automated synthesis of combinatorial libraries.

In summary, we have studied the behavior of thiophenols as a nucleophile in the system: isocyanide-activated olefin-nucleophile. As a result, new directions leading to 2-aminopyrroles **4** and thioimides **5** have been revealed.

Experimental

Most of products **4** were isolated by the simple filtration, while **5** and **4k** by flash-chromatography. Starting reagents are commercially available or can be obtained in one step from common products. Isocyanides **8a–d** were synthesized according to published protocols [13]. Other reagents were purchased from commercial sources and used without purification. Melting points were measured with a Buchi melting point apparatus and were not corrected. Elemental analyses for all the compounds were carried out at the Institute of Organic Synthesis (Ekaterinburg). ^1H NMR and ^{13}C NMR were recorded on a Bruker DRX-400 (400 MHz for ^1H and 100 MHz for ^{13}C) spectrometer in $\text{DMSO}-d_6$ using TMS as an internal standard. Chemical shifts are reported in ppm (δ scale), and coupling constants are reported in hertz. Mass spectra were recorded on a Varian MAT 311A.

General procedure

Pyridine (25 μL , 0.3 mmol), water (0.1 mL), isocyanide (0.5 mmol), gem-diactivated olefin (0.5 mmol), and thiophenol (0.5 mmol) were mixed together in MeCN (0.4 mL). The resulting solution was stirred at r.t. for 4–15 h. After the reaction was complete according to thin-layer chromatography, the solution was concentrated, and the product was collected by filtration. Crystallization from ethanol–water mixtures was used for purification of products **4a–j**, while compounds **4k** and **5a–d** were purified via flash-chromatography (Silica gel 60 HF₂₅₄ Merck KGaA, chloroform:hexane 9:1).

Conversion of **5a** into **4k**

Compound **5a** (50 mg) was dissolved in MeCN (1 mL). Triethylamine (10 μL) was added to the solution and resulting mixture was stirred at 65 °C for 8 h. After the reaction was complete, the solution was evaporated and purified via flash-chromatography (Silica gel 60 HF₂₅₄ Merck KGaA, chloroform:hexane 8:2). Compound **4k** was obtained in 82% yield.

2-Amino-5-(4-chlorophenylthio)-1-cyclohexyl-4-phenyl-1H-pyrrole-3-carbonitrile (**4a**)

Mp. 184 °C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 7.46 (1H, d, J = 8.9 Hz, C_6H_5); 7.38 (2H, d, J = 6.7 Hz, C_6H_5); 7.30 (2H, d, J = 8.2 Hz, C_6H_5); 7.23 (2H, d, J = 8.6 Hz, $\text{C}_6\text{H}_4\text{Cl}$); 6.93 (2H, d, J = 7.9 Hz, $\text{C}_6\text{H}_4\text{Cl}$); 5.91 (2H, br.s, NH_2); 4.23–4.34 (1H, m, CH); 1.10–2.19 (2H, m, C_6H_{11}); 1.62–1.84 (2H, m, C_6H_{11}); 1.42–1.60 (3H, m, C_6H_{11}); 1.06–1.36 (3H, m, C_6H_{11}). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ : 149.30 (1C, C– NH_2), 139.25 (1C, C(4-Cl– C_6H_4 –S)), 136.33 (1C, C-4 (4-Cl– C_6H_4 –S)), 133.15 (1C, C(Ph)), 129.62 (1C, C-1 (4-Cl– C_6H_4 –S)), 129.17 (2C, C-2,6 (4-Cl– C_6H_4 –S)), 128.65 (2C, C-2,6 (Ph)), 127.55 (2C, C-3,5 (4-Cl– C_6H_4 –S)), 126.90 (2C, C-3,5 (Ph)), 126.75 (1C, C-4 (Ph)), 117.30 (1C, CN), 106.76 (1C, CPh), 72.48 (1C, C(CN)), 55.34 (1C, C-1, C_6H_{11}), 26.10 (2C, C-2,6, C_6H_{11}), 23.95 (2C, C-3,5 C_6H_{11}), 23.10 (1C, C-4, C_6H_{11}). MS (m/z , %): 441 [$\text{M}+4$]⁺ (2), 440 [$\text{M}+3$]⁺ (7), 409 [$\text{M}+2$]⁺ (26), 408 [$\text{M}+1$]⁺ (18), 407 [M]⁺ (64), 381 (11), 330 (7), 325 (100), 264 (13), 214 (17), 202 (14), 182 (23), 144 [$\text{C}_6\text{H}_5\text{ClS}$]⁺ (6), 114 (5), 83 [C_6H_{11}]⁺ (23), 67 [$\text{C}_4\text{H}_5\text{N}$]⁺ (5). Anal. Calcd for $\text{C}_{23}\text{H}_{22}\text{ClN}_3\text{S}$: C, 67.71; H, 5.44; N, 10.30. Found: C, 67.64; H, 5.47; N, 10.35.

2-Amino-5-(4-chlorophenylthio)-1-cyclohexyl-4-(3-methoxyphenyl)-1H-pyrrole-3-carbonitrile (**4b**)

Mp. 142 °C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 7.18–7.26 (3H, m, $\text{C}_6\text{H}_4\text{OCH}_3$); 6.87–6.97 (4H, m, $\text{C}_6\text{H}_4\text{Cl}$); 6.80 (1H, d, J = 8.2 Hz, $\text{C}_6\text{H}_4\text{OCH}_3$); 5.99 (2H, br.s, NH_2); 4.23–4.28 (1H, m, CH); 3.65 (3H, s, OCH_3); 2.09–2.24 (2H, m, C_6H_{11});

Table 1 Synthesis of 2-aminopyrroles **4** and thioimides **5**

Compound	R ¹	R ²	R ³	R ⁴	Reaction time	Isolated yield (%)
4a	Ph	CN	Cl	<i>c</i> -C ₆ H ₁₁	12	44
4b	3-OMe-C ₆ H ₄	CN	Cl	<i>c</i> -C ₆ H ₁₁	12	35
4c	<i>i</i> -Pr	CN	Cl	<i>c</i> -C ₆ H ₁₁	4	91
4d	<i>i</i> -Pr	CN	Cl	CH ₃ O(CH ₂) ₂	4	83
4e	<i>c</i> -C ₆ H ₁₁	COOEt	Cl	<i>c</i> -C ₆ H ₁₁	8	46
4f	Ph	CN	CH ₃	<i>c</i> -C ₆ H ₁₁	12	45
4g	4-Cl-C ₆ H ₄	CN	CH ₃	CH ₃ O(CH ₂) ₂	13	67
4h	<i>i</i> -Pr	CN	CH ₃	<i>c</i> -C ₆ H ₁₁	4	90
4i	<i>c</i> -C ₆ H ₁₁	COOEt	CH ₃	<i>c</i> -C ₆ H ₁₁	9	59
4j	<i>i</i> -Pr	COOEt	CH ₃	<i>c</i> -C ₅ H ₉	8	85
4k	<i>c</i> -C ₆ H ₁₁	COOEt	Cl	1-Adamantyl	8 ^a	56
5a	<i>c</i> -C ₆ H ₁₁	COOEt	Cl	1-Adamantyl	7	40 ^b
5b	Ph	CN	Cl	1-Adamantyl	12	53
5c	4-Cl-C ₆ H ₄	CN	Cl	1-Adamantyl	12	66
5d	4-Cl-C ₆ H ₄	COOEt	CH ₃	1-Adamantyl	15	25

^a 80 °C^b The formation of **4k** (~ 5%) is observed

1.63–1.77 (2H, m, C₆H₁₁); 1.43–1.60 (3H, m, C₆H₁₁); 1.15–1.32 (3H, m, C₆H₁₁). MS (*m/z*, %): 441 [M + 4]⁺ (3), 440 [M + 3]⁺ (9), 439 [M + 2]⁺ (32), 438 [M + 1]⁺ (23), 437 [M]⁺ (79), 436 [M – 1]⁺ (1), 368 (1), 355 (100), 287 (9), 244 (19), 212 (16), 185 (7), 144 [C₆H₅ClS]⁺ (6), 114 (5), 83 [C₆H₁₁]⁺ (23), 67 [C₄H₅N]⁺ (5). Anal. Calcd for C₂₄H₂₄ClN₃OS: C, 65.81; H, 5.52; N, 9.59. Found: C, 65.87; H, 5.46; N, 9.51.

2-Amino-5-(4-chlorophenylthio)-1-cyclohexyl-4-isopropyl-1H-pyrrole-3-carbonitrile (4c)

Mp. 160 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.22 (2H, d, *J* = 8.6 Hz, C₆H₄Cl); 6.90 (2H, d, *J* = 8.9 Hz, C₆H₄Cl); 5.78 (2H, br.s, NH₂); 4.08–4.14 (1H, m, CH); 3.06–3.12 (1H, m, CH); 2.00–2.20 (2H, m, C₆H₁₁); 1.63–1.74 (2H, m, C₆H₁₁); 1.36–1.60 (3H, m, C₆H₁₁); 1.11–1.34 (3H, m, C₆H₁₁); 1.20 (6H, d, *J* = 7.0 Hz, 2CH₃). ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 149.57 (1C, C–NH₂), 139.39 (1C, C(4-Cl-C₆H₄-S)), 137.15 (1C, C-4 (4-Cl-C₆H₄-S)), 129.94 (1C, C-1 (4-Cl-C₆H₄-S)), 129.04 (2C, C-2,6 (4-Cl-C₆H₄-S)), 126.32 (2C, C-3,5 (4-Cl-C₆H₄-S)), 117.25 (1C, CN), 104.11 (1C, C(CH(CH₃)₂)), 71.36 (1C, C(CN)), 54.89 (1C, C-1, C₆H₁₁), 28.94 (1C, C(CH₃)₂), 26.45 (2C, 2CH₃), 25.78 (2C, C-2,6, C₆H₁₁), 24.00 (2C, C-3,5 C₆H₁₁), 22.19 (1C, C-4, C₆H₁₁). MS (*m/z*, %): 376 [M + 3]⁺ (6), 375 [M + 2]⁺ (24), 374 [M + 1]⁺ (15), 373 [M]⁺ (61), 372 [M – 1]⁺ (1), 340 [M-Cl]⁺ (1), 291 (68), 276 (35), 180 (8), 164 (6), 147 (25), 133 (8), 121 (16), 105 [C₅H₃N₃]⁺ (12), 94 (16), 83 [C₆H₁₁]⁺ (29), 79 (7), 67 [C₄H₅N]⁺ (10). Anal. Calcd for C₂₀H₂₄ClN₃S: C, 64.24; H, 6.47; N, 11.24. Found: C, 64.13; H, 6.44; N, 11.35.

2-Amino-5-(4-chlorophenylthio)-1-(2-methoxyethyl)-4-isopropyl-1H-pyrrole-3-carbonitrile (4d)

Mp. 132 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.24 (2H, d, *J* = 8.5 Hz, C₆H₄Cl); 6.90 (2H, d, *J* = 8.9 Hz, C₆H₄Cl); 5.91 (2H, br.s, NH₂); 3.88 (2H, t, *J* = 5.8 Hz, CH₂); 3.32 (2H, t, *J* = 5.8 Hz, CH₂); 3.17 (3H, s, OCH₃); 3.05–3.10 (1H, m, CH); 1.22 (6H, d, *J* = 7.0 Hz, 2CH₃). ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 150.39 (1C, C–NH₂), 139.32 (1C, C(4-Cl-C₆H₄-S)), 137.87 (1C, C-4 (4-Cl-C₆H₄-S)), 130.02 (1C, C-1 (4-Cl-C₆H₄-S)), 129.09 (2C, C-2,6 (4-Cl-C₆H₄-S)), 126.28 (2C, C-3,5 (4-Cl-C₆H₄-S)), 117.15 (1C, CN), 104.11 (1C, C(CH(CH₃)₂)), 70.53 (1C, C(CN)), 70.08 (1C, CH₂), 58.16 (1C, OCH₃), 41.92 (1C, CH₂), 26.49 (1C, C(CH₃)₂), 22.24 (2C, 2CH₃). MS (*m/z*, %): 353 [M + 4]⁺ (2), 352 [M + 3]⁺ (8), 351 [M + 2]⁺ (39), 350 [M + 1]⁺ (21), 349 [M]⁺ (100), 348 [M – 1]⁺ (1), 334 [M-CH₃]⁺ (10), 316 [M-Cl]⁺ (18), 290 (10), 258 (13), 238 (50), 206 (29), 191 (31), 173 (9), 148 (47), 143 [C₆H₄ClS]⁺ (29), 133 (16), 121 (13), 108 (21), 94 (10), 78 (10), 67 [C₄H₅N]⁺ (6), 59 [C₃H₇O]⁺ (65). Anal. Calcd for C₁₇H₂₀ClN₃OS: C, 58.36; H, 5.76; N, 12.01. Found: C, 58.48; H, 5.69; N, 11.95.

2-Amino-5-(4-chlorophenylthio)-1,4-dicyclohexyl-1H-pyrrole-3-ethylcarboxylate (4e)

Mp. 160 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 7.47 (1H, d, *J* = 7.0 Hz, C₆H₄Cl); 7.34 (1H, d, *J* = 8.5 Hz, C₆H₄Cl); 7.21 (1H, d, *J* = 8.5 Hz, C₆H₄Cl); 6.92 (1H, d, *J* = 7.9 Hz, C₆H₄Cl); 6.17 (2H, br.s, NH₂); 4.14–4.26 (3H, m, CH and CH₂); 3.10–3.20 (1H, m, CH); 1.87–2.16 (4H, m, C₆H₁₁); 1.58–1.79 (6H, m, C₆H₁₁); 1.44–1.53 (4H, m, C₆H₁₁); 1.36 (3H, t, *J* = 7.0 Hz, CH₃); 1.02–1.30 (6H, m, C₆H₁₁).

MS (m/z , %): 464 $[M + 4]^+$ (3), 463 $[M + 3]^+$ (11), 462 $[M + 2]^+$ (39), 461 $[M + 1]^+$ (29), 460 $[M]^+$ (100), 427 $[M - Cl]^+$ (13), 377 (22), 331 (36), 288 (4), 271 (15), 188 (29), 144 $[C_6H_5ClS]^+$ (15), 134 (9), 108 $[C_5H_4N_2O]^+$ (11), 98 (7), 83 $[C_6H_{11}]^+$ (38), 67 $[C_4H_5N]^+$ (16). Anal. Calcd for $C_{25}H_{33}ClN_2O_2S$: C, 65.13; H, 7.12; N, 6.08. Found: C, 65.01; H, 7.13; N, 5.99.

2-Amino-5-(4-methylphenylthio)-1-cyclohexyl-4-phenyl-1H-pyrrole-3-carbonitrile (4f)

Mp. 85 °C. 1H NMR (400 MHz, DMSO- d_6) δ : 7.17–7.40 (5H, m, C_6H_5); 7.10 (2H, d, $J = 7.3$ Hz, $C_6H_4CH_3$); 6.87 (2H, d, $J = 7.3$ Hz, $C_6H_4CH_3$); 6.14 (2H, br.s, NH_2); 4.25–4.40 (1H, m, CH); 2.28–2.40 (1H, m, C_6H_{11}); 2.22 (3H, s, CH_3); 2.11–2.20 (1H, m, C_6H_{11}); 1.61–1.71 (2H, m, C_6H_{11}); 1.33–1.58 (3H, m, C_6H_{11}); 1.05–1.29 (3H, m, C_6H_{11}). MS (m/z , %): 390 $[M + 3]^+$ (2), 389 $[M + 2]^+$ (7), 388 $[M + 1]^+$ (22), 387 $[M]^+$ (79), 386 $[M - 1]^+$ (1), 305 (100), 290 (5), 273 (7), 213 (17), 197 (10), 180 (9), 155 (9), 128 (8), 123 $[C_7H_7S]^+$ (5), 106 $[C_5H_4N_3]^+$ (5), 91 (19), 83 $[C_6H_{11}]^+$ (14), 65 $[C_4H_3N]^+$ (7). Anal. Calcd for $C_{24}H_{25}N_3S$: C, 74.38; H, 6.50; N, 10.84. Found: C, 74.47; H, 6.45; N, 10.89.

2-Amino-5-(4-methylphenylthio)-1-(2-methoxyethyl)-4-(4-chlorophenyl)-1H-pyrrole-3-carbonitrile (4g)

Mp. 160 °C. 1H NMR (400 MHz, DMSO- d_6) δ : 7.37–7.51 (4H, m, C_6H_4Cl); 7.10 (2H, d, $J = 7.9$ Hz, $C_6H_4CH_3$); 6.83 (2H, d, $J = 8.2$ Hz, $C_6H_4CH_3$); 6.34 (2H, br.s, NH_2); 3.98 (2H, t, $J = 5.8$ Hz, CH_2); 3.37 (2H, t, $J = 5.6$ Hz, CH_2); 3.27 (3H, s, OCH_3); 2.23 (3H, s, CH_3). ^{13}C NMR (100 MHz, DMSO- d_6) δ : 150.30 (1C, C- NH_2), 135.10 (1C, $C(4-CH_3-C_6H_4-S)$), 134.36 (1C, C-4 (4- $CH_3-C_6H_4-S$)), 132.14 (1C, C-1 (4- $CH_3-C_6H_4-S$)), 131.54 (1C, C-4 (4- $Cl-C_6H_4$)), 131.29 (1C, C-1 (4- $Cl-C_6H_4$)), 130.13 (2C, C-2,6 (4- $CH_3-C_6H_4-S$)), 130.07 (2C, C-2,6 (4- $Cl-C_6H_4$)), 128.27 (2C, C-3,5 (4- $CH_3-C_6H_4-S$)), 124.71 (2C, C-3,5 (4- $Cl-C_6H_4$)), 116.80 (1C, CN), 107.26 (1C, $C(C_6H_4Cl)$), 72.20 (1C, $C(CN)$), 69.93 (1C, C-2, (CH_2) $_2OCH_3$), 58.22 (1C, OCH_3), 42.17 (1C, C-1, (CH_2) $_2OCH_3$). MS (m/z , %): 401 $[M + 4]^+$ (3), 400 $[M + 3]^+$ (9), 399 $[M + 2]^+$ (40), 398 $[M + 1]^+$ (25), 397 $[M]^+$ (100), 396 $[M - 1]^+$ (1), 366 $[M - OCH_3]^+$ (2), 349 (2), 338 (16), 306 (60), 274 (10), 239 (9), 216 (30), 189 (6), 123 $[C_7H_7S]^+$ (14), 105 $[C_5H_3N_3]^+$ (14), 91 (22), 79 (8), 65 $[C_4H_3N]^+$ (9), 59 $[C_3H_7O]^+$ (33). Anal. Calcd for $C_{21}H_{20}ClN_3OS$: C, 63.39; H, 5.07; N, 10.56. Found: C, 63.48; H, 4.98; N, 10.66.

2-Amino-5-(4-methylphenylthio)-1-cyclohexyl-4-isopropyl-1H-pyrrole-3-carbonitrile (4h)

Mp. 180 °C. 1H NMR (400 MHz, DMSO- d_6) δ : 7.10 (2H, d, $J = 7.9$ Hz, $C_6H_4CH_3$); 6.85 (2H, d, $J = 7.9$ Hz, $C_6H_4CH_3$); 5.91 (2H, br.s, NH_2); 4.10–4.30 (1H, m, CH); 3.03–3.14 (1H, m, CH); 2.23 (3H, s, CH_3); 2.00–2.17 (2H, m, C_6H_{11}); 1.59–1.73 (2H, m, C_6H_{11}); 1.35–1.48 (3H, m, C_6H_{11}); 1.03–1.26 (3H, m, C_6H_{11}); 1.17 (6H, d, $J = 7.0$ Hz, 2 CH_3). ^{13}C NMR (100 MHz, DMSO- d_6) δ : 149.30 (1C, C- NH_2), 139.39 (1C, $C(4-CH_3-C_6H_4-S)$), 138.50 (1C, C-4 (4- $CH_3-C_6H_4-S$)), 134.74 (1C, C-1 (4- $CH_3-C_6H_4-S$)), 129.70 (2C, C-2,6 (4- $CH_3-C_6H_4-S$)), 125.08 (2C, C-3,5 (4- $CH_3-C_6H_4-S$)), 117.43 (1C, CN), 107.26 (1C, $C(CH(CH_3)_2)$), 71.36 (1C, $C(CN)$), 54.84 (1C, C-1, C_6H_{11}), 29.0 (1C, CH_3), 26.44 (1C, $C(CH_3)_2$), 25.81 (2C, 2 CH_3), 24.03 (2C, C-2,6, C_6H_{11}), 22.25 (2C, C-3,5 C_6H_{11}), 20.39 (1C, C-4, C_6H_{11}). MS (m/z , %): 356 $[M + 3]^+$ (1), 355 $[M + 2]^+$ (7), 354 $[M + 1]^+$ (25), 353 $[M]^+$ (100), 352 $[M - 1]^+$ (2), 320 (2), 271 (74), 256 (42), 238 (19), 147 (15), 123 $[C_7H_7S]^+$ (16), 121 (17), 105 $[C_5H_3N_3]^+$ (12), 91 (14), 83 $[C_6H_{11}]^+$ (10), 67 $[C_4H_5N]^+$ (6). Anal. Calcd for $C_{21}H_{27}N_3S$: C, 71.35; H, 7.70; N, 11.89. Found: C, 71.28; H, 7.81; N, 11.95.

2-Amino-5-(4-methylphenylthio)-1,4-dicyclohexyl-1H-pyrrole-3-ethylcarboxylate (4i)

Mp. 182 °C. 1H NMR (400 MHz, DMSO- d_6) δ : 7.08 (2H, d, $J = 7.9$ Hz, $C_6H_4CH_3$); 6.87 (2H, d, $J = 7.6$ Hz, $C_6H_4CH_3$); 6.26 (2H, br.s, NH_2); 4.15–4.25 (3H, m, CH and CH_2); 3.22–3.36 (1H, m, CH); 2.23 (3H, s, CH_3); 2.04–2.10 (4H, m, C_6H_{11}); 1.61–1.73 (5H, m, C_6H_{11}); 1.33–1.58 (5H, m, C_6H_{11}); 1.31 (3H, t, $J = 7.0$ Hz, CH_3); 1.07–1.23 (6H, m, C_6H_{11}). ^{13}C NMR (100 MHz, DMSO- d_6) δ : 165.25 (1C, C=O), 148.80 (1C, C- NH_2), 134.57 (1C, $C(4-CH_3-C_6H_4-S)$), 130.11 (1C, C-4 (4- $CH_3-C_6H_4-S$)), 129.63 (1C, C-1 (4- $CH_3-C_6H_4-S$)), 128.11 (2C, C-2,6 (4- $CH_3-C_6H_4-S$)), 125.21 (2C, C-3,5 (4- $CH_3-C_6H_4-S$)), 107.15 (1C, $C(C_6H_{11})$), 92.55 (1C, $C(COOEt)$), 58.56 (1C, CH_2), 54.37 (1C, C-1, C_5H_9), 46.12 (1C, C-1, C_6H_{11}), 37.42 (2C, C-2,6, C_6H_{11}), 30.92 (2C, C-2,5, C_5H_9), 28.67 (2C, C-3,5, C_6H_{11}), 26.89 (1C, C-4, C_6H_{11}), 25.87 (2C, C-3, C_5H_9), 25.53 (2C, C-4, C_5H_9), 20.41 (1C, CH_3), 14.53 (1C, $COOCH_2CH_3$). MS (m/z , %): 443 $[M + 3]^+$ (3), 442 $[M + 2]^+$ (12), 441 $[M + 1]^+$ (40), 440 $[M]^+$ (100), 439 $[M - 1]^+$ (2), 395 (5), 357 (31), 312 (45), 271 (13), 188 (30), 160 (12), 132 (8), 123 $[C_7H_7S]^+$ (12), 105 $[C_5H_3N_3]^+$ (8), 91 (16), 83 $[C_6H_{11}]^+$ (11), 67 $[C_4H_5N]^+$ (7). Anal. Calcd for $C_{26}H_{36}N_2O_2S$: C, 70.87; H, 8.23; N, 6.36. Found: C, 70.97; H, 8.15; N, 6.28.

2-Amino-5-(4-methylphenylthio)-1-cyclopentyl-4-isopropyl-1H-pyrrole-3-ethylcarboxylate (4j)

Mp. 145 °C. ^1H NMR (400 MHz, DMSO- d_6) δ : 6.99 (2H, d, $J = 7.9$ Hz, $\text{C}_6\text{H}_4\text{CH}_3$); 6.79 (2H, d, $J = 7.9$ Hz, $\text{C}_6\text{H}_4\text{CH}_3$); 6.00 (2H, br.s, NH_2); 4.76–4.84 (3H, m, CH (C_5H_9)); 4.22 (2H, q, $J = 7.0$ Hz, CH_2); 3.44–3.55 (1H, m, CH); 2.26 (3H, s, CH_3); 1.87–2.14 (2H, m, C_5H_9); 1.72–1.86 (2H, m, C_5H_9); 1.62–1.71 (2H, m, C_5H_9); 1.42–1.60 (2H, m, C_5H_9); 1.23 (3H, t, $J = 7.0$ Hz, CH_3); 1.19 (6H, d, $J = 7.0$ Hz, 2CH_3). ^{13}C NMR (100 MHz, DMSO- d_6) δ : 165.02 (1C, C=O), 149.04 (1C, C- NH_2), 137.79 (1C, C(4- CH_3 - C_6H_4 -S)), 135.81 (1C, C-4 (4- CH_3 - C_6H_4 -S)), 134.40 (1C, C-1 (4- CH_3 - C_6H_4 -S)), 129.67 (2C, C-2,6 (4- CH_3 - C_6H_4 -S)), 124.46 (2C, C-3,5 (4- CH_3 - C_6H_4 -S)), 106.59 (1C, C(CH(CH_3) $_2$)), 92.55 (1C, C(COOEt)), 58.53 (1C, CH_2), 54.11 (1C, C-1, C_5H_9), 28.57 (1C, CH_3), 26.59 (1C, C(CH $_3$) $_2$), 24.20 (2C, 2CH_3), 21.62 (2C, C-3,4, C_5H_9), 20.37 (2C, C-2,5, C_5H_9), 14.42 (1C, CH_3). MS (m/z , %): 389 [$\text{M} + 3$] $^+$ (2), 388 [$\text{M} + 2$] $^+$ (8), 387 [$\text{M} + 1$] $^+$ (27), 386 [M] $^+$ (100), 385 [$\text{M} - 1$] $^+$ (1), 341 (5), 317 (26), 307 (5), 295 (5), 272 (42), 257 (22), 181 (6), 148 (11), 122 [$\text{C}_7\text{H}_6\text{S}$] $^+$ (16), 105 (6), 94 (11), 79 (6), 69 [C_5H_9] $^+$ (9), 67 [$\text{C}_4\text{H}_5\text{N}$] $^+$ (12). Anal. Calcd for $\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_2\text{S}$: C, 68.36; H, 7.82; N, 7.25. Found: C, 68.27; H, 7.75; N, 7.28.

2-Amino-5-(4-chlorophenylthio)-1-(1-adamantyl)-4-cyclohexyl-1H-pyrrole-3-ethylcarboxylate (4k)

Oil. ^1H NMR (400 MHz, DMSO- d_6) δ : 7.47 (2H, d, $J = 8.5$ Hz, $\text{C}_6\text{H}_4\text{Cl}$); 7.35 (2H, d, $J = 8.5$ Hz, $\text{C}_6\text{H}_4\text{Cl}$); 5.89 (2H, br.s, NH_2); 4.11 (2H, q, $J = 7.0$ Hz, CH_2); 2.64–2.70 (1H, m, CH); 2.02–2.12 (2H, m, C_6H_{11}); 1.85–1.95 (3H, m, Ad); 1.78 (6H, br.s, Ad); 1.68 (6H, br.s, Ad); 1.25–1.40 (4H, m, C_6H_{11}); 1.29 (3H, t, $J = 7.0$ Hz, CH_3); 1.13–1.23 (4H, m, C_6H_{11}). MS (m/z , %): 516 [$\text{M} + 4$] $^+$ (1), 515 [$\text{M} + 3$] $^+$ (3), 514 [$\text{M} + 2$] $^+$ (12), 513 [$\text{M} + 1$] $^+$ (9), 512 [M] $^+$ (30), 377 (53), 295 (41), 224 (7), 195 (11), 178 (10), 144 [$\text{C}_6\text{H}_5\text{ClS}$] $^+$ (17), 135 (100), 108 [$\text{C}_5\text{H}_4\text{N}_2\text{O}$] $^+$ (13), 98 (7), 83 [C_6H_{11}] $^+$ (38), 67 [$\text{C}_4\text{H}_5\text{N}$] $^+$ (16). Anal. Calcd for $\text{C}_{29}\text{H}_{37}\text{ClN}_2\text{O}_2\text{S}$: C, 67.88; H, 7.27; N, 5.46. Found: C, 70.02; H, 7.25; N, 5.48.

***N*-(1-adamantyl)-*S*-(4-chlorophenyl)-3-cyano-3-carboxyethyl-2-cyclohexylpropionthioimide (5a)**

Oil. ^1H NMR (400 MHz, DMSO- d_6) δ : 7.47 (2H, d, $J = 8.5$ Hz, $\text{C}_6\text{H}_4\text{Cl}$); 7.35 (2H, d, $J = 8.5$ Hz, $\text{C}_6\text{H}_4\text{Cl}$); 5.89 (2H, br.s, NH_2); 4.11 (2H, q, $J = 7.0$ Hz, CH_2); 2.64–2.70 (1H, m, CH); 2.02–2.12 (2H, m, C_6H_{11}); 1.85–1.95 (3H, m, Ad); 1.78 (6H, br.s, Ad); 1.68 (6H, br.s, Ad); 1.25–1.40 (4H, m, C_6H_{11}); 1.29 (3H, t, $J = 7.0$ Hz, CH_3); 1.13–1.23 (4H, m, C_6H_{11}). Anal. Calcd for $\text{C}_{29}\text{H}_{37}\text{ClN}_2\text{O}_2\text{S}$: C, 67.88; H, 7.27; N, 5.46. Found: C, 67.79; H, 7.30; N, 5.41.

***N*-(1-adamantyl)-*S*-(4-chlorophenyl)-3,3-dicyano-2-phenylpropionthioimide (5b)**

Mp. 150 °C. ^1H NMR (400 MHz, DMSO- d_6) δ : 7.21–7.36 (5H, m, C_6H_5); 7.06 (2H, d, $J = 8.5$ Hz, $\text{C}_6\text{H}_4\text{Cl}$); 6.92 (2H, d, $J = 8.5$ Hz, $\text{C}_6\text{H}_4\text{Cl}$); 4.68 (1H, d, $J = 6.0$ Hz, CH); 4.23 (1H, d, $J = 5.8$ Hz, CH); 2.25 (3H, br.s, Ad); 2.15 (6H, m, Ad); 1.76 (6H, m, Ad). Anal. Calcd for $\text{C}_{27}\text{H}_{26}\text{ClN}_3\text{S}$: C, 70.49; H, 5.70; N, 9.13. Found: C, 70.43; H, 5.81; N, 9.02.

***N*-(1-adamantyl)-*S*-(4-chlorophenyl)-3,3-dicyano-2-(4-chlorophenyl)-propionthioimide (5c)**

Oil. ^1H NMR (400 MHz, DMSO- d_6) δ : 7.21–7.36 (4H, m, $\text{C}_6\text{H}_4\text{Cl}$); 7.06 (2H, d, $J = 8.5$ Hz, $\text{C}_6\text{H}_4\text{Cl}$); 6.92 (2H, d, $J = 8.6$ Hz, $\text{C}_6\text{H}_4\text{Cl}$); 4.69 (1H, d, $J = 6.0$ Hz, CH); 4.23 (1H, d, $J = 5.8$ Hz, CH); 2.25 (3H, m, Ad); 2.15 (6H, m, Ad); 1.76 (6H, m, Ad). Anal. Calcd for $\text{C}_{27}\text{H}_{25}\text{Cl}_2\text{N}_3\text{S}$: C, 65.58; H, 5.10; N, 8.50. Found: C, 65.77; H, 5.06; N, 8.60.

***N*-(1-adamantyl)-*S*-(4-methylphenyl)-3-cyano-3-carboxyethyl-2-(4-chlorophenyl)-propionthioimide (5d)**

Mp. 140 °C. ^1H NMR (400 MHz, DMSO- d_6) δ : 7.33 (2H, d, $J = 8.3$ Hz, $\text{C}_6\text{H}_4\text{Cl}$); 7.18 (2H, d, $J = 8.3$ Hz, $\text{C}_6\text{H}_4\text{Cl}$); 7.09 (1H, d, $J = 8.3$ Hz, $\text{C}_6\text{H}_4\text{CH}_3$); 6.96 (1H, d, $J = 8.0$ Hz, $\text{C}_6\text{H}_4\text{CH}_3$); 6.86 (1H, d, $J = 8.3$ Hz, $\text{C}_6\text{H}_4\text{CH}_3$); 6.76 (1H, d, $J = 8.5$ Hz, $\text{C}_6\text{H}_4\text{CH}_3$); 4.35 (1H, d, $J = 6.3$ Hz, CH); 4.11–4.26 (2H, m, CH_2); 4.05 (1H, d, $J = 6.2$ Hz, CH); 2.37 (3H, s, CH_3); 2.15–2.21 (6H, m, Ad); 1.96–2.13 (3H, m, Ad); 1.67–1.77 (6H, m, Ad); 1.29 (3H, t, $J = 7.0$ Hz, CH_3). Anal. Calcd for $\text{C}_{30}\text{H}_{33}\text{ClN}_2\text{O}_2\text{S}$: C, 69.14; H, 6.38; N, 5.38. Found: C, 69.22; H, 6.31; N, 5.33.

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