

Synthetic Development and Assessment of Antioxidant Activity of Imino[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitrile and Its Derivatives

N. B. Wadwale^a, D. Prasad^b, A. H. Jadhav^{b,*}, A. R. Karad^c, G. S. Khansole^d, S. S. Choudhare^e, S. V. Navhate^f, and V. N. Bhosale^{f,**}

^a P.G. Research Centre, Department of Chemistry, M.S.G. College Malegaon, Malegaon, Maharashtra, 423105 India

^b Centre for Nano and Material Science, JAIN University, Bangalore, Karnataka, 562112 India

^c Department of Chemistry, M. G. M. Ahmedpur, Ahmdepur, Latur District, Maharashtra, 413515 India

^d Department of Chemistry, D. A. B. N. College, Chikhali, Sangli District, Maharashtra, 415408 India

^e Department of Chemistry, S. D. College, Soegaon, Aurangabad District, Maharashtra, 431120 India

^f P.G. Research Centre, Department of Chemistry, Yeshwant Mahavidyalay Nanded, Nanded, Maharashtra, 431602 India

*e-mail: jadhav.ah@gmail.com

**e-mail: vijaynbhosale77@gmail.com

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Abstract—The reaction of 2-[bis(methylsulfanyl)methylidene]malononitrile with 1*H*-1,2,4-triazol-3-amine in *N,N*-dimethylformamide in the presence of anhydrous potassium carbonate led to the formation of 7-imino-5-(methylsulfanyl)-1,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitrile. The latter was then reacted with some nitrogen and carbon nucleophiles such as substituted anilines and active methylene compounds to afford the corresponding 5-substituted derivatives. The structure of the synthesized compounds was confirmed by IR, NMR, and mass spectra and elemental analyses. Furthermore, their potential as antioxidant agents was evaluated using DPPH and hydroxyl radical scavenging assays.

Keywords: multicomponent reactions (MCR), 1,2,4-triazole, [1,2,4]triazolo[1,5-*a*]pyrimidine, 2-[bis(methylsulfanyl)methylidene]malononitrile, antioxidant activity

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INTRODUCTION

Multicomponent reactions (MCRs) are classical examples of synthetic efficiency and reaction design for diversity-oriented synthesis in organic chemistry [1–3]. The simplest definition of MCR is that it is a one-pot reaction wherein two or more reactants rearrange into a single complex structure with functional diversity, without adding any external reagents or changing reaction conditions throughout the progress of the reaction [4, 5]. For the past few decades, significant research has been devoted both at academic

and industrial scale toward the development of new heterocyclic compounds in a one-pot synthetic protocol [4–7]. Usually, MCRs follow a one-pot multistep process and a complex mechanistic pathway where all the steps are reversible and the last step is irreversible [8].

However, the major challenge in the commercialization of novel MCRs and elementary heterocyclic synthesis is to master and gather expertise toward uncommon combinations and arrangements under similar reaction conditions [4–6, 8]. The most advantageous feature of MCRs is that it can be extended into various promising synthetic protocols which can further be

developed into novel targeted structural motifs [9]. These new lead molecules can be used as active agents for various applications, e.g., in the field of catalysis and medicinal and biological applications. MCRs have also been known to produce a wide range of structurally and stereochemically different heterocyclic compounds along with their polyheterocyclic derivatives, which have been further evaluated as potential biologically active compounds [9–11]. Without a doubt, most of these potential biologically active heterocyclic compounds are used as scaffolds in the pharmaceutical and drug industries [9, 10, 12]. However, the development of new types of MCRs for the discovery of new pairs of functional groups to access new scaffolds is still in flourishing demand to produce new drug-like molecules.

Over the years, it has been observed that triazolo[1,5-*a*]pyrimidinedione as a versatile compound holds a significant position in the field of synthetic and organic chemistry [13]. The fact that triazolo[1,5-*a*]pyrimidine can form stable coordination complexes and possesses a high binding capacity for metal ions has led to increased attention to the development of novel triazolo[1,5-*a*]pyrimidinedione derivatives [14–16]. In particular, due to their diverse agricultural, pharmacological, and biological properties, such compounds have attracted attention of a large number of organic chemists [17]. Their biological properties

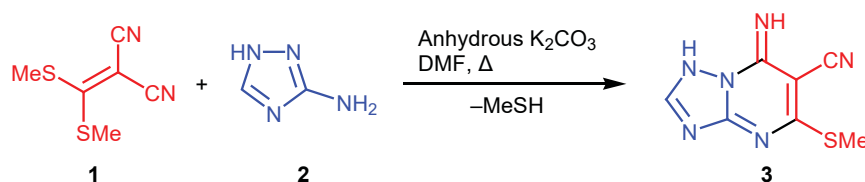
include antitumor [13], analgesic [18], anticancer [19], antifungal [15], antibiotic [20], and antileishmanial activities [21]. Compounds based on the [1,2,4]triazolo[1,5-*a*]pyrimidine core have recently been reported as phosphodiesterase inhibitors [22] for the treatment of Alzheimer's disease [23, 24], antimalarial agents [25], CB2 cannabinoid receptor inverse agonists [26], and hypnotic agents [27]. Owing to their beneficial biological applications, the use of [1,2,4]triazolo[1,5-*a*]pyrimidine in multicomponent reactions can definitely provide further opportunities. However, these compounds have not been tested for their anti-oxidant activity.

In the present article we report the synthesis of 7-imino-5-(methylsulfanyl)-1,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitrile and its derivatives in a facile and cost efficient one-pot route and their anti-oxidant activity.

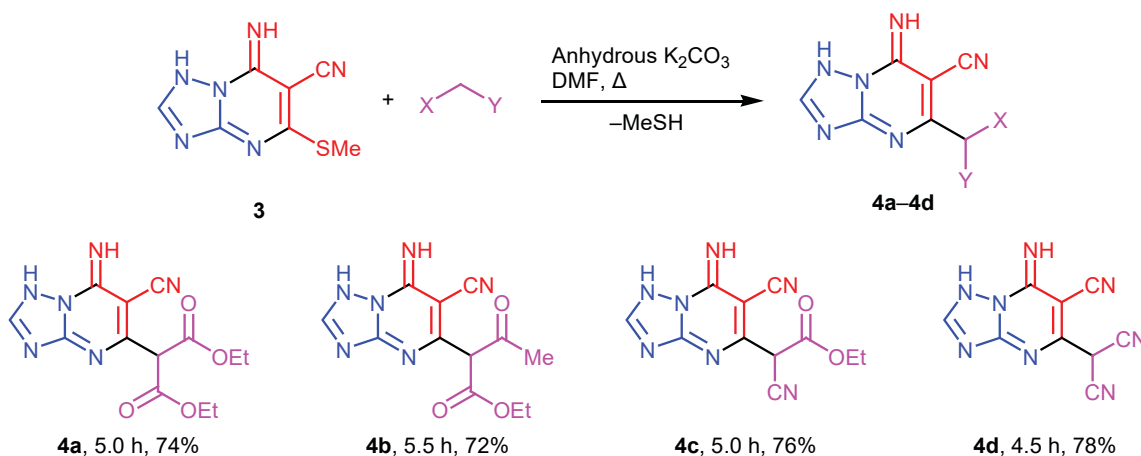
RESULTS AND DISCUSSION

Initially, we focused on the synthesis of 7-imino-5-(methylsulfanyl)-1,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitrile (**3**) as the parent compound. It was prepared by reacting 2-*bis*(methylsulfanyl)-methylidene]malononitrile (**1**) and 1*H*-1,2,4-triazol-3-amine (**2**) on heating in DMF in the presence of anhy-

Scheme 1.



Scheme 2.



drous potassium carbonate (Scheme 1). The synthetic details are given in Experimental.

Molecule **3** possesses a replaceable methylsulfanyl group at the 5-position, which is activated due to electron-withdrawing effects of the N¹ atom and cyano group on C⁶. Therefore, it can be presumed that compound **3** is a potential precursor for the synthesis of 5-substituted derivatives. In fact, 5-substituted derivatives of **3** were obtained by reacting it with different nucleophiles such as active methylene compounds and substituted anilines. Accordingly, the reactions of **3** with diethyl malonate, ethyl acetoacetate, ethyl cyanoacetate, and malononitrile in dimethylformamide in the presence of anhydrous potassium carbonate afforded the corresponding 5-substituted derivatives **4a–4d** as shown in Scheme 2.

Under similar experimental conditions, compound **3** reacted with substituted anilines to produce 5-(R-anilino)-7-imino-1,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitriles **5a–5j** (Scheme 3).

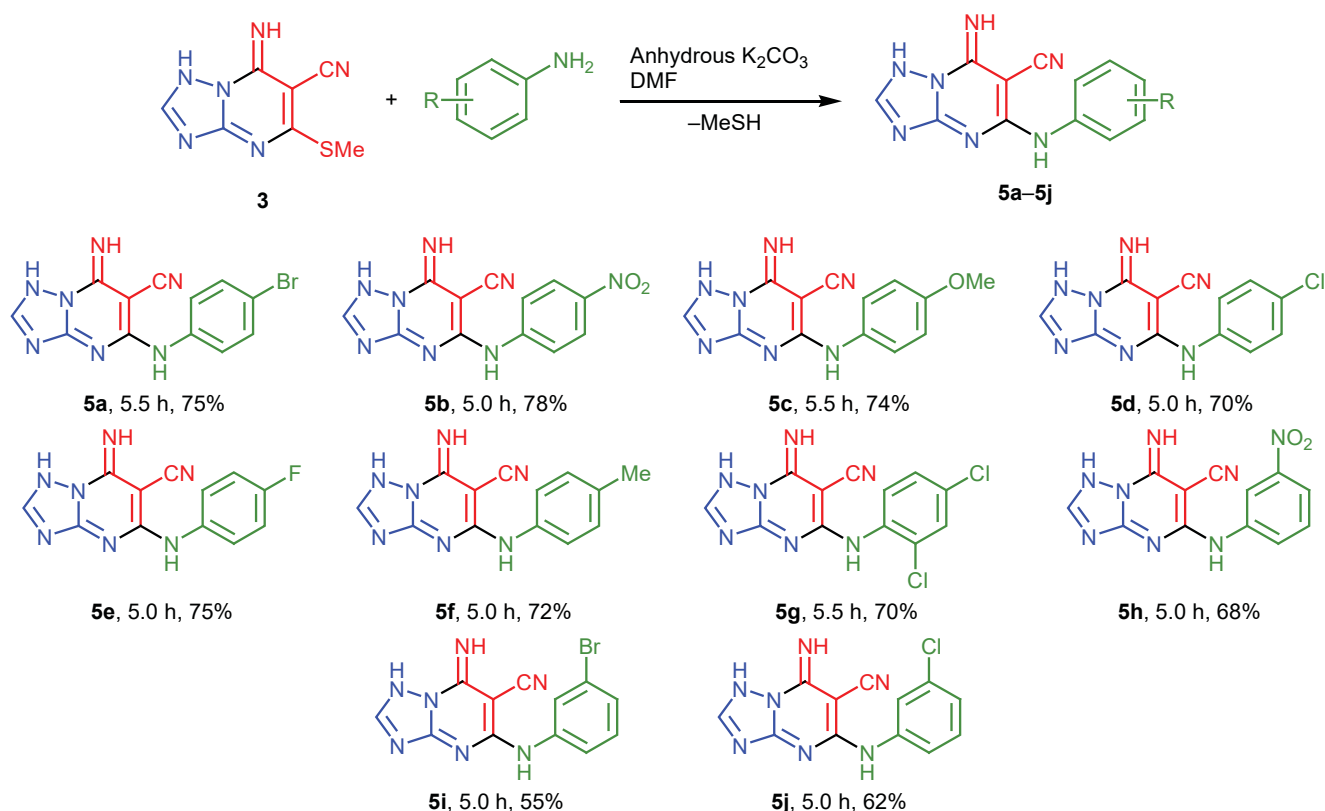
A tentative mechanism was proposed for the formation of parent compound **3** (Scheme 4). Initially, nucleophilic addition of 1*H*-1,2,4-triazol-3-amine (**2**) to 2-[bis(methylsulfanyl)methylidene]malononitrile (**1**) gives zwitterionic intermediate **A** [28] which is stabi-

lized via elimination of methanethiolate anion and deprotonation followed by proton migration to produce intermediates **B** and **C**, respectively. Finally, intramolecular Michael addition between the NH and C≡N groups of **C** leads to the formation of triazolopyrimidine **3** [29]. In the next stage, nucleophilic substitution of the 5-methylsulfanyl group in molecule **3** yields final compounds **4** and **5**.

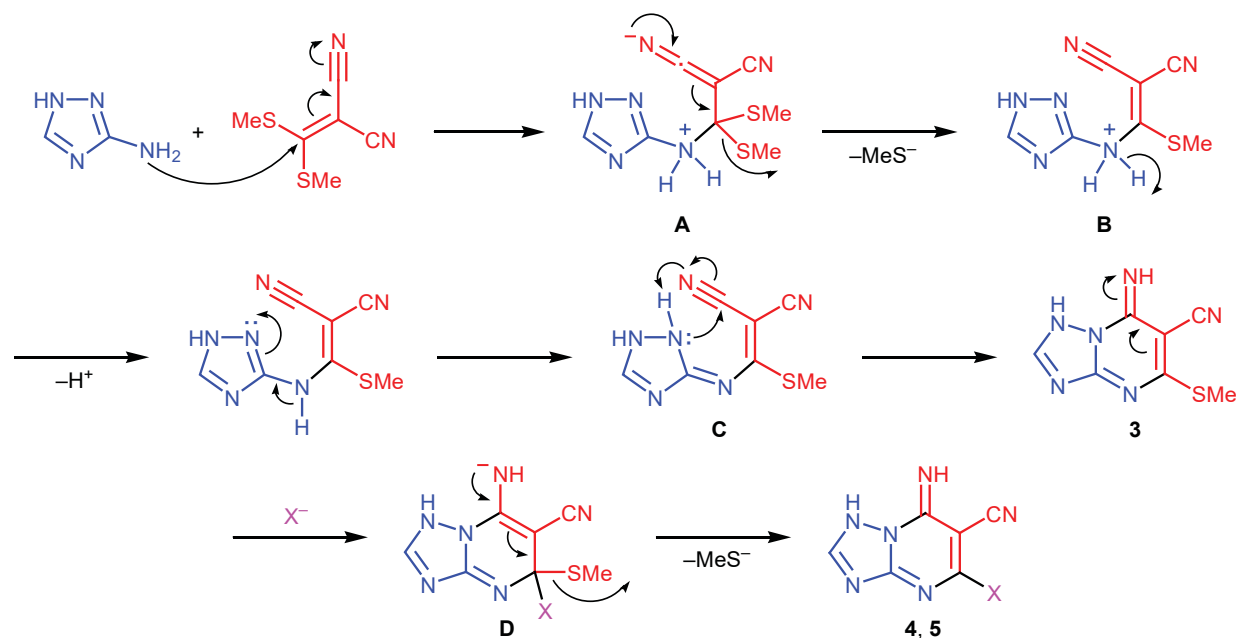
Antioxidant activity. *1,1-Diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay.* The antioxidant properties of newly synthesized compounds **4a–4d** and **5a–5d** were evaluated by the DPPH radical scavenging assay [17] using 1 mM ascorbic acid as the reference compound. Reaction mixtures were prepared by adding a solution of individual compound **4a–4d** or **5a–5d** in absolute ethanol to an equal volume of a 0.1 mM solution of DPPH radical. The mixture was incubated at room temperature for 20 min, and the absorbance at λ 517 nm was measured with a UV-Vis spectrophotometer. Compounds **5c** and **5b** showed the weakest activities by scavenging 60.2 and 40.6% of DPPH, respectively (Table 1).

Hydroxyl radical scavenging assay. The well-known Fenton reaction was used for measuring the OH radical scavenging activity [30]. In a typical Fenton

Scheme 3.



Scheme 4.



reaction, 60 μL of FeCl_2 (1 mM), 90 μL of 1,10-phenanthroline (1 mM), 2.4 mL of phosphate buffer (pH 7.8), and 150 μL of 0.17 M H_2O_2 were mixed together along with 1.5 mL of 1 mM solution of compound 3–5. After incubation at room temperature for 5 min, the absorbance at λ 560 nm was recorded. Ascorbic acid (1 mM) was used as reference compound. The results are shown in Table 1. Ascorbic acid as the reference compound showed a scavenging activity of 89.5%. Compound 3 showed OH radical scavenging activity of 45.6%. Compounds 4a, 4b, 4d, 5a, 5c, and 5d showed

Table 1. Antioxidant activity of compounds 3, 4a–4d, and 5a–5d according to DPPH and OH radical scavenging assays

Compound no.	Radical scavenging activity, %	
	DPPH	OH
3	48.7 \pm 1.23	45.6 \pm 1.06
4a	80.6 \pm 0.82	84.0 \pm 1.60
4b	78.2 \pm 1.84	82.2 \pm 1.06
4c	66.4 \pm 1.36	62.9 \pm 0.21
4d	85.4 \pm 0.30	80.2 \pm 1.25
5a	66.4 \pm 0.30	69.5 \pm 1.84
5b	40.6 \pm 0.82	45.2 \pm 1.06
5c	60.2 \pm 1.84	66.6 \pm 0.25
5d	80.4 \pm 1.36	78.2 \pm 1.28
Ascorbic acid	91.4 \pm 0.021	89.5 \pm 0.021

good OH radical scavenging activities. The highest OH radical scavenging activity was observed for compounds 4a and 4b, 84.0 and 82.2%, respectively. Compounds 4d and 5d were slightly less active (80.2 and 78.2%, respectively), and the activities of 4c, 5a, and 5c were estimated at 62.9, 69.5, and 66.6%, respectively. The lowest OH radical scavenging activity was found for compound 5b (45.2%). Based on the performance results of both radical scavenging assays, it can be said that newly synthesized compounds 4a–4d and 5a–5d showed significant antioxidant activity. It can also be said that quantitative difference in the antioxidant properties of the newly synthesized compounds were influenced by the nature of substituents attached to the parent compound.

In summary, a new series of substituted 7-imino-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitrile derivatives were synthesized using an efficient, green, and easy protocol. The products could be easily isolated by simple work-up techniques in a less time-consuming manner. Moreover, the proposed protocol is believed to be cost-economic, and it provided high yields under mild conditions. Most of the newly synthesized compounds showed promising antioxidant potential in DPPH and OH radical scavenging assays.

EXPERIMENTAL

All chemicals of reagent grade were supplied by Sigma–Aldrich (India) and were used without further purification. The melting points were determined using

open capillary tubes and are uncorrected. The IR spectra were recorded in KBr on a Perkin Elmer FT-IR spectrometer. The mass spectra (electrospray ionization) were run on a Shimadzu 2010EV LC/MS instrument. The ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using CDCl_3 as solvent and tetramethylsilane as an internal standard. The progress of reactions and the purity of the isolated compounds were monitored by TLC on UV-active silica gel plate (Merck).

7-Imino-5-(methylsulfanyl)-1,7-dihydro[1,2,4]-triazolo[1,5-*a*]pyrimidine-6-carbonitrile (3). A mixture of 1*H*-1,2,4-triazol-3-amine (**2**, 1.68 g, 20 mmol), 2-[bis(methylsulfanyl)methylidene]malononitrile (**1**, 3.40 g, 20 mmol), and anhydrous potassium carbonate (1.38 g, 1 equiv) in 30 mL of DMF was refluxed with continuous stirring for 4–5 h. After completion of the reaction (TLC), the mixture was cooled, and the solid product was collected by filtration, washed with water, and recrystallized from ethanol. Yield 3.26 g (80%), mp 203–205°C. IR spectrum, ν , cm^{-1} : 3347 (NH), 2228 ($\text{C}\equiv\text{N}$). ^1H NMR spectrum, δ , ppm: 9.20 br.s (1H, NH), 7.48 s (1H, CH), 4.08 br.s (1H, NH), 2.80 s (3H, SCH_3). ^{13}C NMR spectrum, δ_{C} , ppm: 164.8, 158.8, 157.8, 146.9, 115.7, 81.6, 15.07. Mass spectrum: m/z 205 (I_{rel} 100%) [$M + 1$]. Found, %: C 46.62; H 3.24; N 33.92; S 14.60. $\text{C}_7\text{H}_6\text{N}_6\text{S}$. Calculated, %: C 40.77; H 2.93; N 40.75; S 15.55.

General procedure for the synthesis of triazolo-pyrimidines 4a–4d and 5a–5j. A mixture of 1 mmol of compound **3**, 1 mmol of the corresponding CH acid or substituted aniline, and 1 equiv of anhydrous potassium carbonate in DMF was heated with continuous stirring for 4–5.5 h. After completion of the reaction (TLC), the mixture was cooled, and the solid product was collected by filtration, washed with water, and recrystallized from ethanol. If necessary, the product was additionally purified using a short silica gel column. The IR, ^1H and ^{13}C NMR, and mass spectra of **4a–4d** and **5a–5j** were in well agreement with the assigned structures and consistent with literature data for structurally related compounds [16, 31–43].

Diethyl 2-(6-cyano-7-imino-1,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidin-5-yl)malonate (4a). Yield 0.238 g (74%), mp 185–187°C. IR spectrum, ν , cm^{-1} : 3341 (NH), 3137 ($\text{C}=\text{NH}$), 2223 ($\text{C}\equiv\text{N}$), 1721 ($\text{C}=\text{O}$), 1154 ($\text{C}-\text{O}$); ^1H NMR spectrum, δ , ppm: 9.24 br.s (1H, NH), 7.56 s (1H, 2-H), 4.13 m (4H, OCH_2), 4.05 br.s (1H, NH), 3.84 s (1H, CH), 1.31 t (6H, CH_3). ^{13}C NMR spectrum, δ_{C} , ppm: 167.3, 166.0, 155.8, 146.7, 115.8, 91.7, 61.4, 60.0, 14.1. Mass spectrum: m/z 318

(I_{rel} 100%) [$M + 1$]. Found, %: C 49.09; H 4.38; N 26.48. $\text{C}_{13}\text{H}_{14}\text{N}_6\text{O}_4$. Calculated, %: C 49.06; H 4.43; N 26.40.

Ethyl 2-(6-cyano-7-imino-1,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidin-5-yl)-3-oxobutanoate (4b). Yield 0.207 g (72%), mp 190–192°C. IR spectrum, ν , cm^{-1} : 3352 (NH), 3124 ($=\text{N}-\text{H}$), 2218 ($\text{C}\equiv\text{N}$), 1725 ($\text{C}=\text{O}$), 1143 ($\text{C}-\text{O}$). ^1H NMR spectrum, δ , ppm: 9.12 br.s (1H, NH), 7.50 s (1H, 2-H), 4.21 m (2H, OCH_2), 4.17 br.s (1H, NH), 3.87 s (1H, CH), 2.18 s (3H, COCH_3), 1.25 t (3H, CH_3). ^{13}C NMR spectrum, δ_{C} , ppm: 202.4, 167.5, 166.2, 158.8, 146.7, 115.8, 91.7, 61.4, 57.8, 28.2, 14.1. Mass spectrum: m/z 288 (I_{rel} 100%) [$M + 1$]. Found, %: C 50.09; H 4.25; N 29.20. $\text{C}_{12}\text{H}_{12}\text{N}_6\text{O}_3$. Calculated, %: C 50.00; H 4.20; N 29.15.

Ethyl 2-cyano-2-(6-cyano-7-imino-1,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidin-5-yl)acetate (4c). Yield 0.205 g (76%), mp 186–188°C. IR spectrum, ν , cm^{-1} : 3343 (NH), 3131 ($=\text{N}-\text{H}$), 2219 ($\text{C}\equiv\text{N}$), 1724 ($\text{C}=\text{O}$), 1145 ($\text{C}-\text{O}$). ^1H NMR spectrum, δ , ppm: 9.04 br.s (1H, NH), 7.54 s (1H, 2-H), 4.18 m (2H, OCH_2), 4.12 br.s (1H, NH), 4.01 s (1H, CH), 1.29 t (3H, CH_3). ^{13}C NMR spectrum, δ_{C} , ppm: 171.2, 167.3, 158.9, 146.7, 115.8, 91.7, 63.8, 32.8, 14.1. Mass spectrum: m/z 271 (I_{rel} 100%) [$M + 1$]. Found, %: C 48.65; H 3.32; N 36.24; O 11.77. $\text{C}_{11}\text{H}_9\text{N}_7\text{O}_2$. Calculated, %: C 48.71; H 3.34; N 36.15.

2-(6-Cyano-7-imino-1,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidin-5-yl)malononitrile (4d). Yield 0.174 g (78%), mp 180–182°C. IR spectrum, ν , cm^{-1} : 3335 (NH), 3118 ($=\text{N}-\text{H}$), 2226 ($\text{C}\equiv\text{N}$). ^1H NMR spectrum, δ , ppm: 9.21 s (1H, NH), 7.50 d (1H, 2-H), 4.18 s (1H, CH), 4.15 br.s (1H, NH). ^{13}C NMR spectrum, δ_{C} , ppm: 167.35, 158.9, 158.8, 146.8, 115.8, 114.9, 91.7, 17.5. Mass spectrum: m/z 224 (I_{rel} 100%) [$M + 1$]. Found, %: C 48.05; H 1.65; N 49.73. $\text{C}_9\text{H}_4\text{N}_8$. Calculated, %: C 48.22; H 1.80; N 49.98.

5-(4-Bromoanilino)-7-imino-1,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitrile (5a). Yield 0.246 g (75%), mp 208–210°C. IR spectrum, ν , cm^{-1} : 3326 (NH), 3114 ($=\text{N}-\text{H}$), 2219 ($\text{C}\equiv\text{N}$), 779 ($\text{C}-\text{Br}$). ^1H NMR spectrum, δ , ppm: 10.59 s (1H, NH), 9.07 s (1H, $=\text{NH}$), 7.58 s (1H, 2-H), 7.31 d (2H, H_{arom}), 6.68 d (2H, H_{arom}), 4.08 br.s (1H, NH). ^{13}C NMR spectrum, δ_{C} , ppm: 174.7, 159.7, 158.3, 146.8, 138.1, 120.7, 116.6, 69.7. Mass spectrum: m/z 329 (I_{rel} 100%) [$M + 1$]. Found, %: C 43.60; H 2.47; Br 24.28; N 29.68. $\text{C}_{12}\text{H}_8\text{BrN}_7$. Calculated, %: C 43.66; H 2.44; Br 24.20; N 29.70.

7-Imino-5-(4-nitroanilino)-1,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitrile (5b). Yield 0.230 g (78%), mp 210–212°C. IR spectrum, ν , cm^{-1} : 3318 (NH), 3104 (=N–H), 2220 (C≡N), 1328 (NO₂), 1158 (NO₂). ¹H NMR spectrum, δ , ppm: 10.50 s (1H, NH), 9.10 s (1H, =NH), 8.18–6.68 m (4H, H_{arom}), 4.01 br.s (1H, NH). ¹³C NMR spectrum, δ_{C} , ppm: 174.2, 159.1, 158.5, 146.8, 137.9, 124.5, 114.6, 69.1. Mass spectrum: m/z 296 (I_{rel} 100%) [$M + 1$]. Found, %: C 48.42; H 2.58; N 37.65. C₁₂H₈N₈O₂. Calculated, %: C 48.65; H 2.72; N 37.82.

7-Imino-5-(4-methoxyanilino)-1,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitrile (5c). Yield 0.207 g (74%), mp 214–216°C. IR spectrum, ν , cm^{-1} : 3337 (NH), 3121 (=N–H), 2215 (C≡N), 1178 (C–O). ¹H NMR spectrum, δ_{C} , ppm: 10.41 s (1H, NH), 9.12 s (1H, =NH), 7.51 s (1H, 2-H), 6.71 d (2H, H_{arom}), 6.23 d (2H, H_{arom}), 4.19 br.s (1H, NH), 3.83 s (3H, OMe). ¹³C NMR spectrum, δ_{C} , ppm: 174.2, 158.3, 153.8, 146.2, 131.1, 127.3, 115.8, 115.2, 69.2, 55.6. Mass spectrum: m/z 281 (I_{rel} 100%) [$M + 1$]. Found, %: C 55.47; H 3.93; N 34.82. C₁₃H₁₁N₇O. Calculated, %: C 55.51; H 3.94; N 34.86.

5-(4-Chloroanilino)-7-imino-1,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitrile (5d). Yield 0.199 g (70%), mp 219–221°C. IR spectrum, ν , cm^{-1} : 3317 (NH), 3145 (=N–H), 2229 (C≡N), 812 (C–Cl). ¹H NMR spectrum, δ , ppm: 10.72 s (1H, NH), 9.13 s (1H, =NH), 7.43 s (1H, 2-H), 7.38 d (2H, H_{arom}), 6.61 d (2H, H_{arom}), 4.02 br.s (1H, NH). ¹³C NMR spectrum, δ_{C} , ppm: 174.1, 158.8, 146.6, 137.1, 129.4, 127.3, 120.7, 115.6, 69.1. Mass spectrum: m/z 285 (I_{rel} 100%) [$M + 1$]. Found, %: C 50.43; H 2.83; Cl 12.42; N 34.31. C₁₂H₈ClN₇. Calculated, %: C 50.45; H 2.82; Cl 12.41; N 34.32.

5-(4-Fluoroanilino)-7-imino-1,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitrile (5e). Yield 0.201 g (75%), mp 218–220°C. IR spectrum, ν , cm^{-1} : 3310 (NH), 3142 (=N–H), 2227 (C≡N), 690 (C–F). ¹H NMR spectrum, δ , ppm: 10.61 s (1H, NH), 9.01 s (1H, =NH), 7.51 s (1H, 2-H), 6.93 d (2H, H_{arom}), 6.48 d (2H, H_{arom}), 4.17 br.s (1H, NH). ¹³C NMR spectrum, δ_{C} , ppm: 174.3, 158.4, 157.7, 146.2, 134.7, 120.8, 116.3, 115.5, 69.7. Mass spectrum: m/z 269 (I_{rel} 100%) [$M + 1$]. Found, %: C 53.57; H 2.97; F 7.08; N 36.42. C₁₂H₈FN₇. Calculated, %: C 53.53; H 2.99; F 7.06; N 36.42.

7-Imino-5-(4-methylanilino)-1,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitrile (5f). Yield 0.190 g (72%), mp 224–226°C. IR spectrum, ν , cm^{-1} :

3317 (NH), 3132 (=N–H), 2987 (CH₃), 2212 (C≡N). ¹H NMR spectrum, δ , ppm: 10.66 s (1H, NH), 9.07 s (1H, =NH), 7.52 s (1H, 2-H), 6.98 d (2H, H_{arom}), 6.36 d (2H, H_{arom}), 4.06 br.s (1H, NH), 1.24 s (3H, CH₃). ¹³C NMR spectrum, δ_{C} , ppm: 174.1, 158.3, 146.7, 136.7, 131.5, 129.8, 116.4, 115.8, 69.7, 21.3. Mass spectrum: m/z 265 (I_{rel} 100%) [$M + 1$]. Found, %: C 58.82; H 4.17; N 36.97. C₁₃H₁₁N₇. Calculated, %: C 58.86; H 4.18; N 36.96.

5-(2,4-Dichloroanilino)-7-imino-1,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitrile (5g). Yield 0.223 g (70%), mp 214–216°C. IR spectrum, ν , cm^{-1} : 3305 (NH), 3149 (=N–H), 2233 (C≡N), 809 (C–Cl). ¹H NMR spectrum, δ_{C} , ppm: 10.59 s (1H, NH), 9.09 s (1H, =NH), 8.04 s (1H, H_{arom}), 7.50 s (1H, 2-H), 7.29–7.21 m (2H, H_{arom}), 4.04 br.s (1H, NH). ¹³C NMR spectrum, δ_{C} , ppm: 174.3, 158.8, 146.7, 141.3, 131.2, 125.7, 123.6, 122.6, 121.9, 115.8, 69.3. Mass spectrum: m/z 319 (I_{rel} 100%) [$M + 1$]. Found, %: C 45.07; H 2.22; Cl 22.16; N 30.67. C₁₂H₇Cl₂N₇. Calculated, %: C 45.02; H 2.20; Cl 22.15; N 30.63.

7-Imino-5-(3-nitroanilino)-1,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitrile (5h). Yield 0.201 g (68%), mp 208–210°C. IR spectrum, ν , cm^{-1} : 3320 (NH), 3112 (=N–H), 2220 (C≡N), 1322 (NO₂), 1152 (NO₂). ¹H NMR spectrum, δ , ppm: 10.42 s (1H, NH), 9.14 s (1H, =NH), 7.62 d (1H, H_{arom}), 7.56 s (1H, H_{arom}), 7.50 s (1H, 2-H), 7.46 m (1H, H_{arom}), 6.82 d (1H, H_{arom}), 4.11 br.s (1H, NH). ¹³C NMR spectrum, δ_{C} , ppm: 174.4, 158.9, 148.5, 146.8, 145.3, 130.4, 122.8, 115.6, 113.8, 109.2, 69.5. Mass spectrum: m/z 296 (I_{rel} 100%) [$M + 1$]. Found, %: C 48.58; H 2.76; N 37.86. C₁₂H₈N₈O₂. Calculated, %: C 48.65; H 2.72; N 37.82.

5-(3-Bromoanilino)-7-imino-1,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitrile (5i). Yield 0.180 g (55%), mp 210–212°C. IR spectrum, ν , cm^{-1} : 3337 (NH), 3121 (=N–H), 2215 (C≡N), 772 (C–Br). ¹H NMR spectrum, δ , ppm: 10.61 s (1H, NH), 9.11 s (1H, =NH), 7.51 s (1H, 2-H), 6.96–6.91 m (2H, H_{arom}), 6.69 s (1H, H_{arom}), 6.37 m (1H, H_{arom}), 4.13 br.s (1H, NH). ¹³C NMR spectrum, δ_{C} , ppm: 174.2, 158.8, 146.8, 130.1, 123.7, 121.7, 115.6, 69.2. Mass spectrum: m/z 329 (I_{rel} 100%) [$M + 1$]. Found, %: C 43.63; H 2.47; Br 24.28; N 29.71. C₁₂H₈BrN₇. Calculated, %: C 43.66; H 2.44; Br 24.20; N 29.70.

5-(3-Chloroanilino)-7-imino-1,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitrile (5j). Yield 0.176 g (62%), mp 219–221°C. IR spectrum, ν , cm^{-1} : 3328 (NH), 3132 (=N–H), 2228 (C≡N), 805 (C–Cl).

¹H NMR spectrum, δ , ppm: 10.63 s (1H, NH), 9.21 s (1H, =NH), 7.51 s (1H, 2-H), 7.17 s (1H, H_{arom}), 6.86–6.79 m (2H, H_{arom}), 6.31 s (1H, H_{arom}), 4.08 br.s (1H, NH). ¹³C NMR spectrum, δ_C , ppm: 174.1, 158.7, 146.2, 145.6, 135.2, 130.8, 122.8, 116.5, 115.4, 114.2, 69.7. Mass spectrum: *m/z* 285 (I_{rel} 100%) [*M* + 1]. Found, %: C 50.49; H 2.82; Cl 12.47; N 34.28. C₁₂H₈ClN₇. Calculated, %: C 50.45; H 2.82; Cl 12.41; N 34.32.

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CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

REFERENCES

- Toure, B.B. and Hall, D.G., *Chem. Rev.*, 2009, vol. 109, p. 4439.
<https://doi.org/10.1021/cr800296p>
- Multicomponent Reactions*, Zhu, J. and Bienaymé, H., Eds., Weinheim: Wiley, 2005.
<https://doi.org/10.1002/3527605118>
- Atar, A.B., Kang, J., and Jadhav, A.H., *New J. Chem.*, 2020, vol. 44, p. 3241.
<https://doi.org/10.1039/C9NJ05738B>
- Dömling, A., *Chem. Rev.*, 2006, vol. 106, p. 17.
<https://doi.org/10.1021/cr0505728>
- Shaaban, M.R. and Elwahy, A.H.M., *Curr. Org. Synth.*, 2014, vol. 11, p. 471.
<https://doi.org/10.2174/15701794113106660076>
- D'Souza, D.M. and Müller, T.J.J., *Chem. Soc. Rev.*, 2007, vol. 36, p. 1095.
<https://doi.org/10.1039/B608235C>
- Mathapati, S.R., Jadhav, A.H., Swami, M.B., and Dawle, J.K., *Lett. Org. Chem.*, 2019, vol. 16, p. 740.
<https://doi.org/10.2174/1570178616666181211094040>
- Dömling, A., Wang, W., and Wang, K., *Chem. Rev.*, 2012, vol. 112, p. 3083.
<https://doi.org/10.1021/cr100233r>
- Sunderhaus, J.D. and Martin, S.F., *Chem. Eur. J.*, 2009, vol. 15, p. 1300.
<https://doi.org/10.1002/chem.200802140>
- Nair, V., Rajesh, C., Vinod, A.U., Bindu, S., Sreekanth, A.R., Mathen, J.S., and Balagopal, L., *Acc. Chem. Res.*, 2003, vol. 36, p. 899.
<https://doi.org/10.1021/ar020258p>
- Mathapati, S.R., Prasad, D., Atar, A.B., Nagaraja, B.M., and Jadhav, A.H., *Mater. Today: Proc.*, 2019, vol. 9, p. 661.
<https://doi.org/10.1016/j.matpr.2018.10.390>
- Jiang, B., Rajale, T., Wever, W., Tu, S., and Li, G., *Chem. Asian J.*, 2010, vol. 5, p. 2318.
<https://doi.org/10.1002/asia.201000310>
- Zhao, X.-L., Zhao, Y.-F., Guo, S.-C., Song, H.-S., Wang, D., and Gong, P., *Molecules*, 2007, vol. 12, p. 1136.
<https://doi.org/10.3390/12051136>
- Navarro, J.A.R., Salas, J.M., Romero, M.A., Vila-plana, R., Gonzalez-Vilchez, F., and Faure, R., *J. Med. Chem.*, 1998, vol. 41, p. 332.
<https://doi.org/10.1021/jm970358e>
- Chen, Q., Zhu, X.-L., Jiang, L.-L., Liu, Z.-M., and Yang, G.-F., *Eur. J. Med. Chem.*, 2008, vol. 43, p. 595.
<https://doi.org/10.1016/j.ejmech.2007.04.021>
- Bhosale, V.N., Khansole, G.S., and Angulwar, J.A., *World J. Pharm. Pharm. Sci.*, 2016, vol. 5, no. 5, p. 1434.
- Molyneux, P. and Songklanakarin, J., *Sci. Technol.*, 2004, vol. 26, p. 211.
- Hour, M.-J., Huang, L.-J., Kuo, S.-C., Xia, Y., Bastow, K., Nakanishi, Y., Hamel, E., and Lee, K.-H., *J. Med. Chem.*, 2000, vol. 43, p. 4479.
<https://doi.org/10.1021/jm000151c>
- Holla, B.S., Poojary, K.N., Rao, B.S., and Shivananda, M.K., *Eur. J. Med. Chem.*, 2002, vol. 37, p. 511.
[https://doi.org/10.1016/S0223-5234\(02\)01358-2](https://doi.org/10.1016/S0223-5234(02)01358-2)
- Cei, M., Pardelli, R., Sani, S., and Mumoli, N., *Clin. Exp. Med.*, 2014, vol. 14, p. 77.
<https://doi.org/10.1007/s10238-012-0219-0>
- Süleymanoğlu, N., Ünver, Y., Ustabas, R., Direkel, Ş., and Alpaslan, G., *J. Mol. Struct.*, 2017, vol. 1144, p. 80.
<https://doi.org/10.1016/j.molstruc.2017.05.017>
- Gomez, L., Massari, M.E., Vickers, T., Freestone, G., Vernier, W., Ly, K., Xu, R., McCarrick, M., Marrone, T., and Metz, M., *J. Med. Chem.*, 2017, vol. 60, p. 2037.
<https://doi.org/10.1021/acs.jmedchem.6b01793>
- Kumar, J., Meena, P., Singh, A., Jameel, E., Maqbool, M., Mobashir, M., Shandilya, A., Tiwari, M., Hoda, N., and Jayaram, B., *Eur. J. Med. Chem.*, 2016, vol. 119, p. 260.
<https://doi.org/10.1016/j.ejmech.2016.04.053>
- Kovalevich, J., Cornec, A.-S., Yao, Y., James, M., Crowe, A., Lee, V.M.-Y., Trojanowski, J.Q., Smith, A.B., Ballatore, C., and Brunden, K.R., *J. Pharmacol. Exp. Ther.*, 2016, vol. 357, p. 432.
<https://doi.org/10.1124/jpet.115.231175>

25. Phillips, M.A., White, K.L., Kokkonda, S., Deng, X., White, J., El Mazouni, F., Marsh, K., Tomchick, D.R., Manjаланagara, K., and Rudra, K.R., *ACS Infect. Dis.* 2016, vol. 2, p. 945.
<https://doi.org/10.1021/acsinfecdis.6b00144>
26. Tabrizi, M.A., Baraldi, P.G., Ruggiero, E., Saponaro, G., Baraldi, S., Poli, G., Tuccinardi, T., Ravani, A., Vincenzi, F., and Borea, P.A., *Eur. J. Med. Chem.*, 2016, vol. 113, p. 11.
<https://doi.org/10.1016/j.ejmech.2016.02.032>
27. Faizi, M., Dabirian, S., Tajali, H., Ahmadi, F., Zavareh, E.R., Shahhosseini, S., and Tabatabai, S.A., *Bioorg. Med. Chem.* 2015, vol. 23, p. 480.
<https://doi.org/10.1016/j.bmc.2014.12.016>
28. Singh, M., Fatma, S., Ankit, P., Singh, S.B., and Singh, J., *Tetrahedron Lett.*, 2014, vol. 55, p. 525.
<https://doi.org/10.1016/j.tetlet.2013.11.090>
29. Alluri, H., Gonthina, H., Ganta, R.K., Ch, M., and Rao, B.V., *Pharma Chem.*, 2015, vol. 7, no. 10, p. 515.
30. Khansole, G.S., Prasad, D., Angulwar, J.A., Atar, A.B., Nagaraja, B.M., Jadhav, A.H., and Bhosale, V.N., *Mater. Today: Proc.*, 2019, vol. 9, p. 653.
<https://doi.org/10.1016/j.matpr.2018.10.389>
31. Vartale, S.P., Halikar, N.K., Pawar, Y.D., and Tawde, K.V., *Arab. J. Chem.*, 2016, vol. 9, p. S1117.
<https://doi.org/10.1016/j.arabjc.2011.12.007>
32. Danagulyan, G.G., Boyakhchyan, A.P., Danagulyan, A.G., and Panosyan, H.A., *Chem. Heterocycl. Compd.*, 2011, vol. 47, p. 321.
<https://doi.org/10.1007/s10593-011-0760-x>
33. Wendt, M.D., Kunzer, A., Henry, R.F., Cross, J., and Pagano, T.G., *Tetrahedron Lett.*, 2007, vol. 48, p. 6360.
<https://doi.org/10.1016/j.tetlet.2007.07.039>
34. Abdel-Rahman, H.M., El-Koussi, N.A., and Hassan, H.Y., *Arch. Pharm.*, 2009, vol. 342, p. 94.
<https://doi.org/10.1002/ardp.200800113>
35. Ranjbar-Karimi, R., Beiki-Shoraki, K., and Amiri, A., *Monatsh. Chem.*, 2010, vol. 141, p. 1101.
<https://doi.org/10.1007/s00706-010-0371-8>
36. Bhosale, V.N., Khansole, G.S., Angulwar, J.A., and Choudhare, S.S., *World J. Pharm. Res.*, 2015, vol. 5, no. 2, p. 1261.
37. Hassan, A.Y., Sarg, M.T., Bayoumi, A.H., and El-Deeb, M.A., *J. Heterocycl. Chem.*, 2018, vol. 55, p. 1450.
<https://doi.org/10.1002/jhet.3184>
38. Bhosale, V.N., Choudhare, S.S., Khansole, G.S., and Wadwale, N.B., *Pharma Chem.*, 2017, vol. 9, no. 5, p. 66.
39. Khansole, G.S., Angulwar, J.A., and Bhosale, V.N., *Indian J. Heterocycl. Chem.*, 2018, vol. 28, p. 267.
40. Hassaneen, H.M.E., Hassaneen, H.M., Khiry, S.F.M., and Pagni, R.M., *Z. Naturforsch., Teil B*, 2008, vol. 63, p. 217. <https://doi.org/10.1515/znb-2008-0216>
41. Karoui, A., Allouche, F., Deghrigue, M., Agrebi, A., Bouraoui, A., and Chabchoub, F., *Med. Chem. Res.* 2014, vol. 23, p. 1591.
<https://doi.org/10.1007/s00044-013-0742-x>
42. Lipson, V.V., Karnozhitskaya, T.M., Desenko, S.M., Shishkina, S.V., Shishkin, O.E., and Musatov, V.I., *Russ. J. Org. Chem.*, 2007, vol. 43, p. 249.
<https://doi.org/10.1134/S1070428007020169>
43. Erkin, A.V. and Krutikov, V.I., *Russ. J. Gen. Chem.*, 2009, vol. 79, p. 1204.
<https://doi.org/10.1134/S1070363209060309>