Molecular Diversity (2024) 28:51–60
https://doi.org/10.1007/s11030-022-10592-5

ORIGINAL ARTICLE

Catalyst-free synthesis of highly functionalized triazole hexahydroquinoline carbohydrazide scaffolds via four-component cyclocondensation reaction

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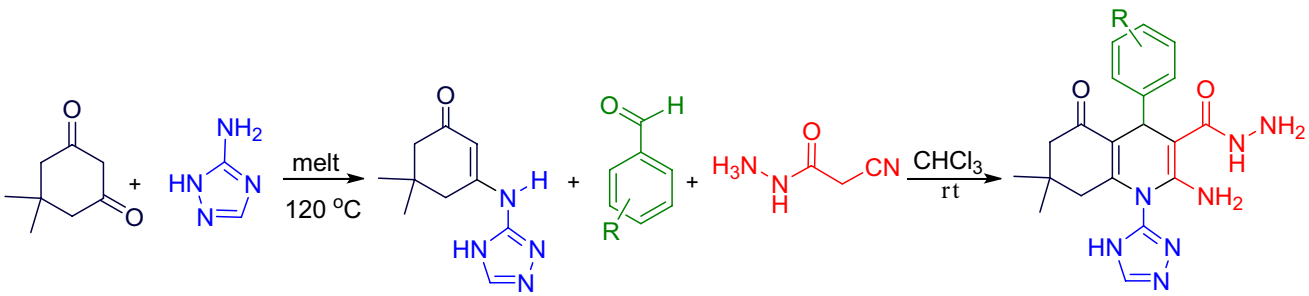
Received: 1 March 2022 / Accepted: 22 December 2022 / Published online: 31 December 2022

Abstract

A new class of multi-functional triazole hexahydroquinoline carbohydrazide named 2-amino-7,7-dimethyl-5-oxo-4-phenyl-1-(4*H*-1,2,4-triazol-3-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbohydrazide has been synthesized by a novel multi-component process involving the reaction of dimedone, 3-amino-1,2,4-triazole, various benzaldehyde with cyanoacetohydrazide under mild conditions in the stoichiometric melt and chloroform in sequence. The simple one-pot process, straight product isolation without applying tedious purification procedures, progression of the reaction without using any catalyst, the application of diverse aldehydes causing a high molecular diversity, the existence of several nitrogen atoms in the product structure, and the possibility of creating multiple hydrogen bonding in the final compound are attractive specifications of the present strategy.

Graphical abstract



Keywords Triazole · Hexahydroquinoline carbohydrazide · Four-component reaction · Catalyst-free approach · Cyanoacetohydrazide

Introduction

An important and valuable group among heterocyclic compounds comprising three nitrogen atoms within the five-membered cycle is identified as triazole with molecular formula $C_2H_3N_3$ acts as isosteres of amide, ester, and carboxylic acid [1, 2]. 1,2,4-Triazole derived compounds are a significant category of heterocyclic products existent in a broad scope of pharmaceuticals and bioactive compounds applied in the drug discovery research against cancer cells, microbes, and different kinds of disease in the human body [3, 4]. The possible therapeutic usages and chemotherapeutical importance of 1,2,4-triazole include anti-cancer [5], antioxidant [6], antibiotic [7], antihypertensive [8], anti-HIV [9], anti-inflammatory [10], and anticonvulsant [11]. This motif is an integral part of a variety of drugs available in clinical therapy including fluconazole, cyproconazole, and triazolam, and also as the third generation of antifungal medicines such as difenoconazole represented in Fig. 1 which are actively used in the pharmacological area [12].

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On the other hand, among the important azaheterocycles, quinoline and its derivatives are one of the most significant building blocks in various natural compounds and drugs that due to their diverse usages in the pharmaceutical fields dedicated a remarkable place compounds to themselves [13, 14]. Quinoline displays a library of pharmaceutically valuable products that has a broad range of biological activities of biological activities, including antipsychotic [15], antimalarial [16], antihypertensive [17], anti-inflammatory [18], anti-HIV [19], PDE4B inhibitors [20], and antibiotic activities [21]. Medicines possessing quinolone scaffold, such as mefloquine, and amodiaquine, are applied as useful medicines for the therapy of malaria, ciprofloxacin is a fluoroquinolone antibiotic used to treat a number of bacterial infections, bosutinib is used for the treatment of chronic myelogenous leukemia, neratinib is a tyrosine kinase inhibitor anti-cancer drug applied for the therapy of breast cancer, belotecan is a drug used in chemotherapy, and also, lenvatinib is an anti-cancer medication for the therapy of specified types of thyroid cancer, that the structures of quinoline-based drugs are shown in Fig. 2 [22–25]. The existence of nitrogen atoms remarkably enhances the fundamental property of products containing quinoline scaffold. In addition, the nitrogen in the quinoline structure may be connected to the target enzymes via hydrogen bonding. An additional important feature of quinoline is the polarity which can cause the reduction in the lipophilic nature, enhancing solubility in water, and subsequently better oral absorption which is required in medication design approaches [26]. In addition, 5-oxo-1,4,5,6,7,8-hexahyroquinolines (5-oxo-HHQs) are a class of heterocycles that have been considered by researchers because of their wide biological and pharmaceutical significance [27–29].

Designing new methods for the synthesis of new 5-oxo-HHQ and developing valuable remedial compounds bearing the 5-oxo-HHQ moiety will be useful for pharmaceutical chemists in the area of medication exploration. Accordingly, in the past years, multi-component reactions (MCRs) especially containing aldehydes, activated nitriles and enamines, have been designed for the synthesis of various quinoline and 5-oxo-HHQ compounds. For example, Abdelhamid and coworkers have reported an efficient formation of 1-(4*H*-1,2,4-triazol-3-yl)hexahydroquinoline-3-carbonitrile products via the condensation between dimedone, 3-amino-4*H*-1,2,4-triazole, and arylidenemalononitriles under reflux conditions in alcohol for 3 h. In the first step, *N*-(1,2,4-triazol-3-yl)enamine was created via the condensation of dimedone, and 3-amino-4*H*-1,2,4-triazole, in the presence of trichloroacetic acid (TCAA) as a catalyst without using a solvent which was used as an *β*-enaminone intermediate in the next step [30].

Due to the increasing request for convenient and rapid synthesis of bioactive heterocycles, the study of effective MCRs as a simple and potent protocol for the formation of diverse multi-substituted heterocyclic compounds is increasing. Furthermore, the MCR is introduced as an influential and green approach to the synthesis of different biologically active heterocyclic compounds and drug-like motifs from simple preliminary materials that led to eliminating the multiple steps and expensive purification process of the reaction, increasing the productivity, saving energy, and reducing the reaction time [31–36].

on the other hand, one of the main protocols for the construction of azaheterocycles is the design of the reactions based on 3-amino-1,2,4-triazole as a beneficial mono-, bi-, and polynucleophile substance with diverse electrophiles in one-pot MCRs. 3-Amino-1,2,4-triazoles contain multiple alternative reaction sites, so these compounds are effective synthetic substrates in controlled multidirectional reactions, and it is possible to synthesize a high molecular diversity of heterocyclic compounds [37, 38].

Results and discussion

Considering potential medicinal applications of hybrid molecules containing triazole and quinoline moieties, and with regard to our interest in the synthesis of valuable

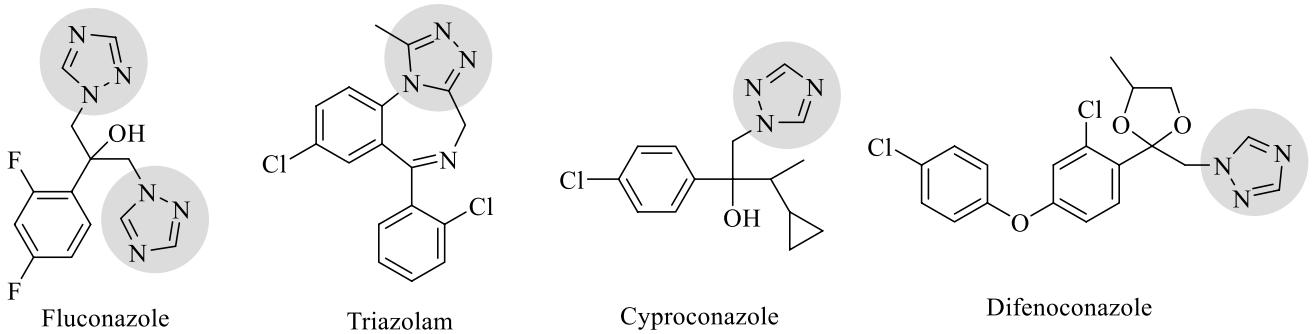


Fig. 1 Some important triazole derived scaffold with biological activities

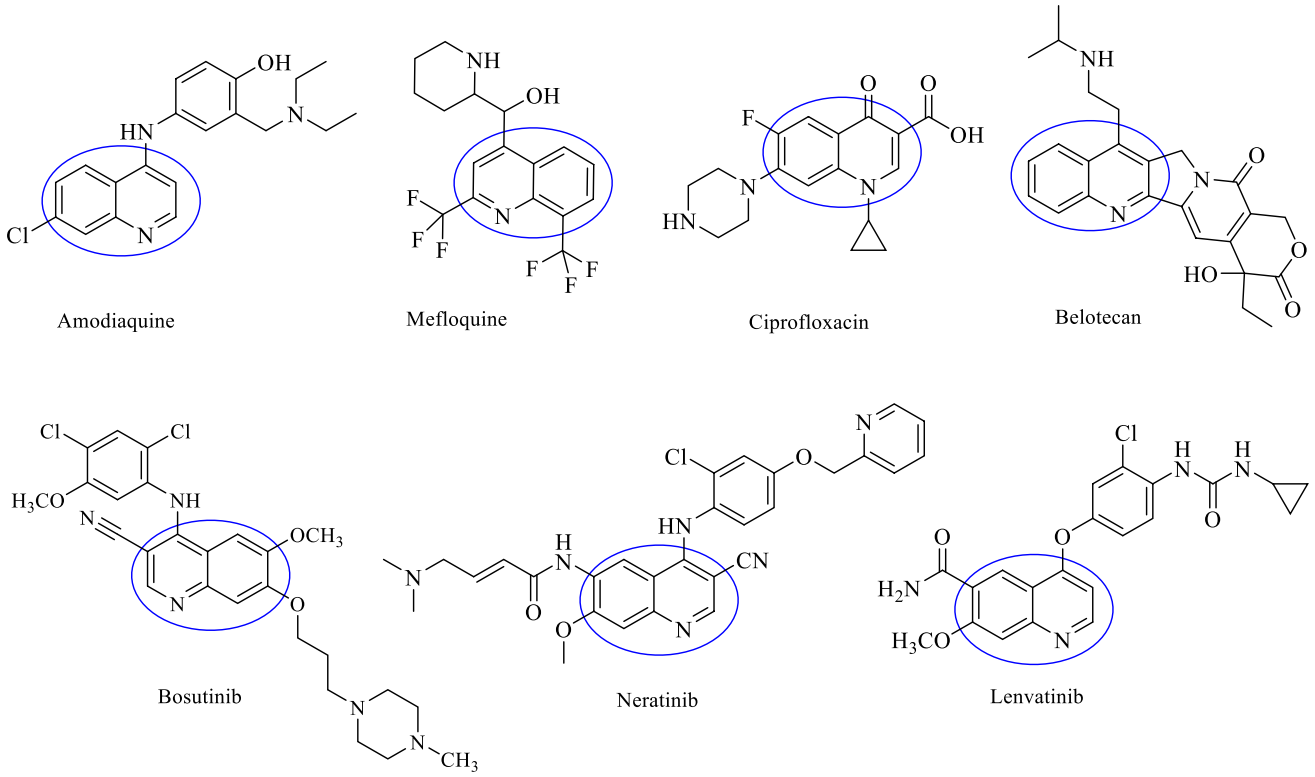
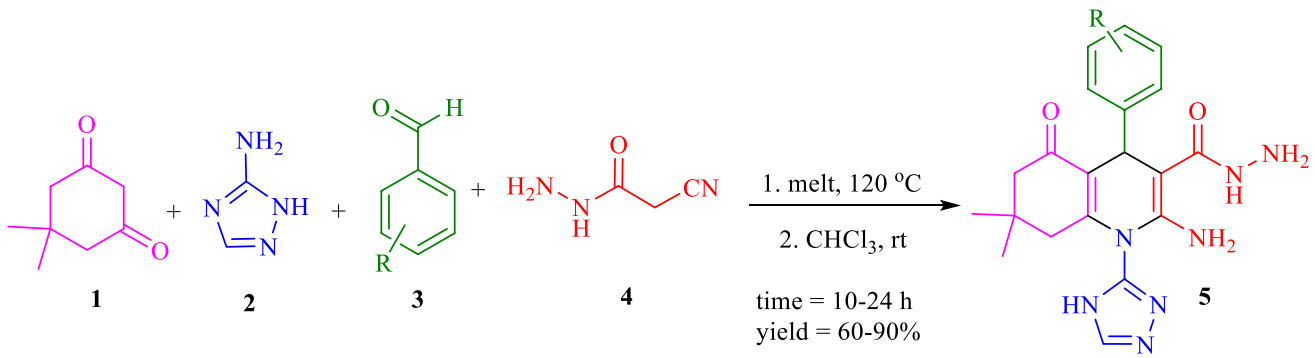


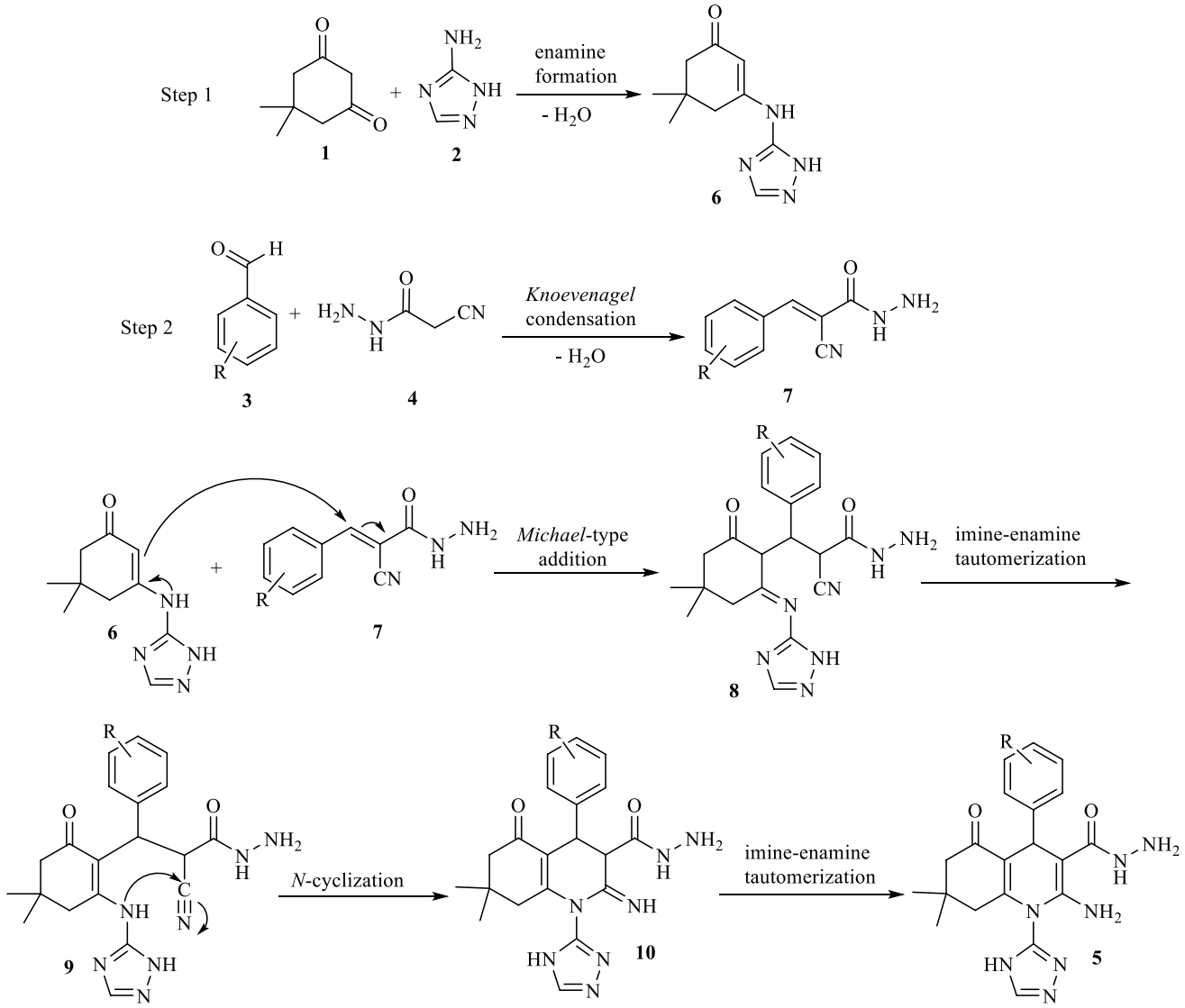
Fig. 2 Structure of quinoline-based drugs with therapeutic activity

biologically active compounds [39, 40], we described a one-pot four-component reaction of dimedone **1** and 3-amino-1,2,4-triazole **2** carries out under solvent-free conditions, at 120 °C to generate the enaminone intermediate **6** in high yields during 15–20 min. In the following, the addition of various benzaldehydes **3** and cyanoacetohydrazide **4** as valuable synthetic unit in chloroform at room temperature condition successfully gave the multifunctional triazole hexahydroquinoline carbohydrazide **5** as attractive synthetic targets, and the structure of final products was proved by spectroscopic data (Scheme 1). The products were obtained in good yields, with a simple workup technique through straightforward filtration. The synthesized derivatives are new hybrid molecules containing triazole and hexahydroquinoline moieties that it is possible to inherit biological activities of both triazole and hexahydroquinoline moieties.



R = H, 2-Cl, 3-Cl, 4-Cl, 3-F, 4-F, 3-OCH_3, 4-OCH_3, 4-OH, 3,4-diOCH_3, 2-OH-3-OCH_3, 2-OH-5-Br

Scheme 1 Synthetic approach for the construction of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-1-(4*H*-1,2,4-triazol-3-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbohydrazide **5**



Scheme 2 A plausible mechanism for the formation of **5** in catalyst-free condition

The acceptable pathway for the synthesis of expected product **5** is illustrated in Scheme 2. Based on ^{1}H NMR spectrum data of intermediate **6**, it is logical that at first, the reaction involves the initial generation of enaminone **6** via the reaction of dimedone **1** with 3-amino-1,2,4-triazole **2**. Next, the *Knoevenagel* condensation between benzaldehyde **3** and cyanoacetohydrazide **4** as an active methylene-containing compound leads to *Michael* acceptor **7**. Then the *Michael* addition between enaminone **6** and *Knoevenagel* intermediate **7** obtain open-chain intermediate **8**, which creates intermediate **9** after sequential imine-enamine tautomerization. This intermediate is transformed into **10** via intramolecular *N*-cyclization, and then imine-enamine tautomerization gives the desired product **5**.

As displayed in Fig. 3, we surveyed the structural variety of this reaction by applying aryl aldehydes **3** with various donor and acceptor substituents in produce products **5a-l**. Compounds named 2-amino-7,7-dimethyl-5-oxo-4-phenyl-1-(4*H*-1,2,4-triazol-3-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbohydrazide were acquired in moderate to high yields (60–90%) with relatively long reaction time (10–24 h). We also applied aliphatic aldehydes including pyruvic aldehyde and heterocyclic aldehydes such as indole-3-carboxaldehyde to enhance the structural diversity variety of the products, but the process did not proceed. The derivatives in Fig. 3 indicated that aromatic aldehydes carrying electron-withdrawing and one or two electron-donating groups showed reactivity and were involved in the reaction.

The structures of the derivatives were confirmed by their elemental analyses, IR, ^{1}H and ^{13}C NMR spectra. The mass spectra of **5b** demonstrated molecular ion peaks at proper *m*/*z* values. The ^{1}H NMR spectrum of **5b** in DMSO-d_6

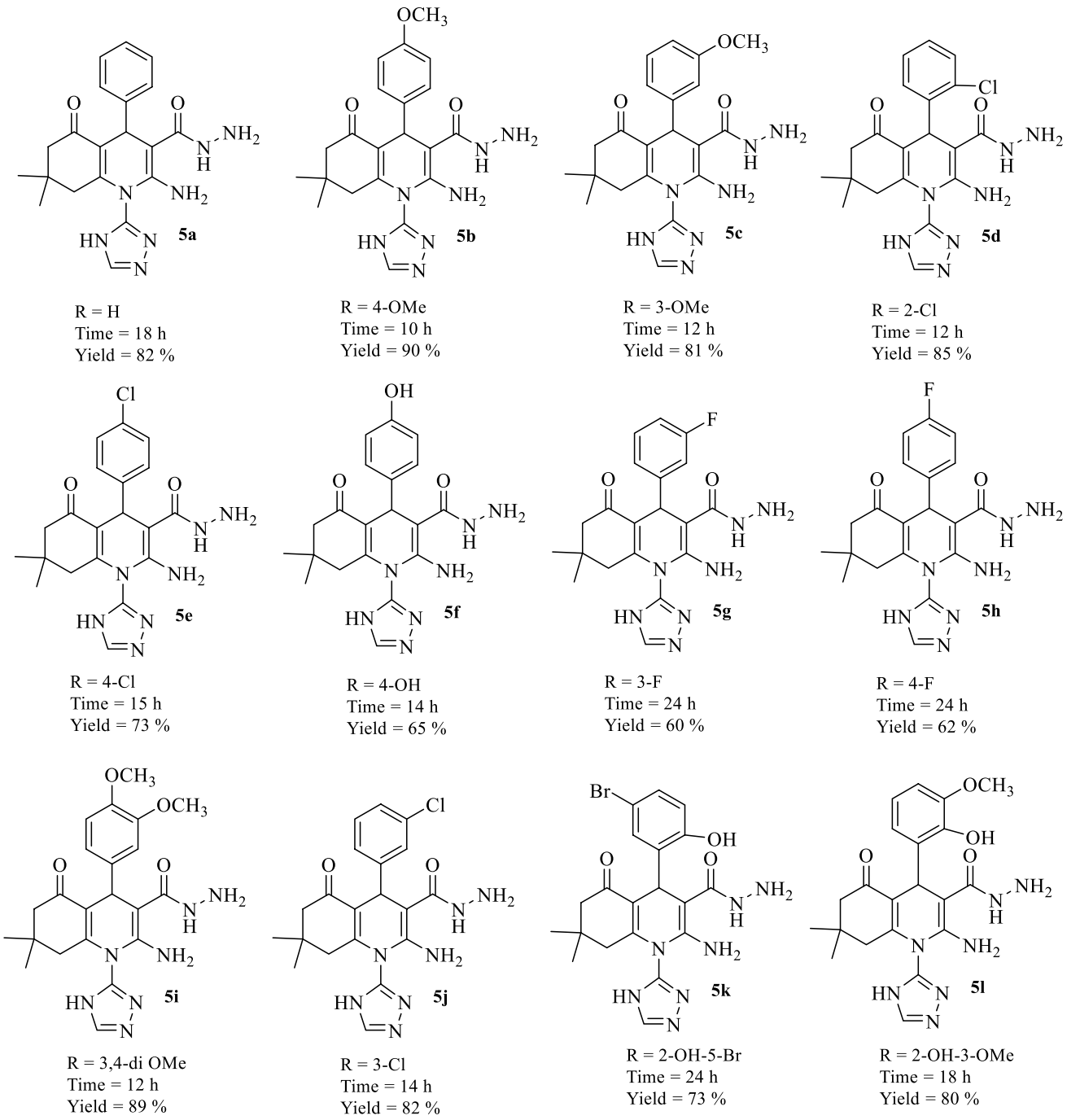


Fig. 3 Substrate scope study of diverse product **5** with a series of benzaldehydes

displayed one *singlet* (δ 0.98 ppm) for the two methyl groups, two *singlet* for the two methylene groups (δ 2.03 and 2.34 ppm), a singlet (δ 3.77 ppm) for methoxy, a *singlet* (δ 3.80 ppm) for methine proton, one *singlet* for the N–NH_2 protons (δ 4.20 ppm, D_2O exchangeable), along with special signals for the aromatic moiety (δ 6.96 and 7.61 ppm), one singlet (δ 7.93 ppm) for CH proton of triazole, and three *singlet* signals for the two NH and one NH_2 groups (δ 9.55, 11.66, 13.66 ppm, D_2O exchangeable). The ^1H decoupled ^{13}C NMR spectrum of **5b** displayed 18 separate signals according to the suggested structure. The particular signal of methine carbon was appeared at δ 32.8 ppm and the specific peaks of **C**=C–NH_2, N=CH and N–C=N were assigned at δ 79.6, 159.1 and 161.3 ppm which verified the selective synthesized of **5a**. Other signals of the product **5b** exhibited characteristic resonances with appropriate chemical shifts.

Conclusion

In the following of introducing novel and efficient protocols to access new scaffolds containing 1,2,4-triazole, which would be very beneficial for the finding of novel therapeutic candidates, we described a new four-component reaction between dimedone, 3-amino-1,2,4-triazole, various benzaldehyde, and cyanoacetohydrazide, for the one-pot synthesis of multi-functional triazole hexahydroquinoline carbohydrazide through sequential enaminone formation/ *Knoevenagel* condensation/*Michael* addition/enol-keto tautomerism /intramolecular *N*-cyclization sequences in chloroform without using any catalyst. The synthesized derivatives are new hybrid molecules containing triazole and hexahydroquinoline moieties that may inherit the biological activities of both triazole and hexahydroquinoline scaffolds.

Experimental

General

The dimedone, 3-amino-1,2,4-triazole, different benzaldehydes, cyanoacetohydrazide and solvents were obtained from Sigma Aldrich and Fluka Co. used without further purification. IR spectra: Bruker Tensor 27 spectrometer. NMR spectra: Bruker DRX-300 Avance instrument (300 MHz for ^{1}H and 75.4 MHz for ^{13}C) with DMSO-d_6 as solvents. Chemical shifts are expressed in parts per million (ppm), and coupling constant (*J*) are reported in hertz (Hz). Mass spectra: Agilent 5975C VL MSD with Triple-Axis detector operating at an ionization potential of 70 eV. Elemental analyses were performed using a PerkinElmer 2004 series [II] CHN elemental analyzer.

General procedure for the formation of 5a-l

The stoichiometric mixtures of dimedone **1** (1.0 mmol, 0.140 g) with 3-amino-1,2,4-triazole **2** (1.0 mmol, 0.084 g) were melted at 120 °C for 15–20 min. Then the reaction mixture was cooled to room temperature and chloroform (5 mL) was added, and the solution was stirred for 10 min at room temperature. Next, benzaldehyde **3** (1.0 mmol) and cyanoacetohydrazide **4** (1.0 mmol, 0.099 g) were added, respectively, and the solution was stirred at room temperature for the time given in Fig. 2. The progress of the reaction was monitored by TLC using ethyl acetate/n-hexane (1:1). After completion of the reaction, the precipitated product was filtered off and washed on the filter funnel with a small amount of chloroform to give pure products **5a-l**.

2-Amino-7,7-dimethyl-5-oxo-4-phenyl-1-(4H-1,2,4-triazol-3-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbohydrazide (5a)

Yellow solid, m.p.: 201–203 °C, yield 0.322 g (82%); IR (KBr) (ν_{max} /cm^{-1}): 3279, 3048 (NH, NH_2), 2867 (C–H), 1694 (C=O), 1588, 1536 (C=C), 1391 (C–N), 1198 (C–O), 753 (Ar). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.98 (6H, s, $2CH_3$), 2.03 (2H, s, CH_2), 2.48 (2H, s, CH_2), 3.80 (1H, s, CH), 4.19 (2H, s, N–NH_2), 7.40–7.43 (3H, m, ArH), 7.66–7.70 (2H, m, ArH), 7.96 (1H, s,=CH), 9.55 (1H, s, O=C–NH), 11.79 (2H, s, NH_2), 13.65 (1H, br s, NH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 24.8 (C), 28.4 ($2CH_3$), 32.8 (CH), 41.9 (CH_2), 50.5 (CH_2), 79.7 (**C**=C–NH_2), 102.7 (O=C–**C**=C), 116.6, 127.7, 129.3, 130.8 (Ar), 134.2 (O=C–C=**C**), 144.8 (C-NH_2), 157.0 (N=CH), 159.4 (N–C=N), 165.3 (NH–C=O), 197.3 (C=O). Anal. Calcd for $C_{20}H_{23}N_7O_2$ (393.19): C, 61.05; H, 5.89; N, 24.92. Found C, 61.84; H, 6.09; N, 25.23.

2-Amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-1-(4H-1,2,4-triazol-3-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbohydrazide (5b)

Yellow solid, m.p.: 203–204 °C, yield 0.380 g (90%); IR (KBr) (ν_{max} /cm^{-1}): 3279, 3215, 3075 (NH, NH_2), 2876 (C–H), 1678 (C=O), 1591, 1533 (C=C), 1380, 1258 (C–N), 1185 (C–O), 691 (Ar). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.98 (6H, s, $2CH_3$), 2.03 (2H, s, CH_2), 2.34 (2H, s, CH_2), 3.77 (3H, s, OCH_3), 3.80 (1H, s, CH), 4.20 (2H, s, N–NH_2), 6.96 (2H, d, $^{3}J_{HH}$ = 8.4 Hz, ArH), 7.61 (2H, d, $^{3}J_{HH}$ = 8.4 Hz, ArH), 7.93 (1H, s, =CH), 9.55 (1H, s, O=C–NH), 11.66 (2H, s, NH_2), 13.66 (1H, br s, NH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 24.8 (C), 28.4 ($2CH_3$), 32.8 (CH), 41.9 (CH_2), 50.5 (CH_2), 55.8 (OCH_3), 79.6 (**C**=C–NH_2), 102.7 (O=C–**C**=C), 114.8, 116.6, 126.8, 129.3 (Ar), 144.7 (O=C–C=**C**), 156.9 (C–NH_2), 159.1 (N=CH), 161.3 (N–C=N), 165.0 (NH–C=O), 197.2 (C=O). MS (EI, 70 eV): *m*/z (%) = 423 (0.1) $[M]^+$, 217 (28), 133 (100), 77 (15), 51 (9).

2-amino-4-(3-methoxyphenyl)-7,7-dimethyl-5-oxo-1-(4H-1,2,4-triazol-3-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbohydrazide (5c)

Yellow solid, m.p.: 204–205 °C, yield 0.342 g (81%); IR (KBr) (ν_{max} /cm^{-1}): 3280, 3213, 3049 (NH, NH_2), 2873 (C–H), 1689 (C=O), 1589, 1536 (C=C), 1369, 1270 (C–N), 1188 (C–O), 731 (Ar). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.98 (6H, s, $2CH_3$), 2.03 (2H, s, CH_2), 2.37 (2H, s, CH_2), 3.77 (3H, s, OCH_3), 3.80 (1H, s, CH), 4.20 (2H, s, N-NH_2), 6.97 (2H, d, $^{3}J_{HH}$ = 7.5 Hz, ArH), 7.25 (1H, s,

ArH), 7.24–7.34 (2H, m, ArH), 7.95 (1H, s,=CH), 9.55 (1H, s, O=C–NH), 11.80 (2H, s, NH_2), 13.65 (1H, br s, NH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 24.8 (C), 28.4 ($2CH_3$), 32.8 (CH), 41.9 (CH_2), 50.5 (CH_2), 55.6 (OCH3), 79.7 (**C**=C–NH_2), 102.7 (O=C–**C**=C), 112.0, 116.6, 120.3, 120.5, 130.35 (Ar), 135.7 (O=C–C=**C**), 144.6 (C–NH_2), 156.9 (N=CH), 160.0 (N–C=N), 165.4 (NH–C=O), 197.3 (C=O). MS (EI, 70 eV): *m*/z (%) = 423 (0.05) $[M]^+$, 217 (39), 133 (100), 103 (15), 77 (17).

2-Amino-4-(2-chlorophenyl)-7,7-dimethyl-5-oxo-1-(4H-1,2,4-triazol-3-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbohydrazide (5d)

Yellow Solid, m.p.: 205–206 °C, yield 0.362 g (85%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.97 (6H, s, $2CH_3$), 2.02 (2H, s, CH_2), 2.37 (2H, s, CH_2), 3.83 (1H, s, CH), 4.22 (2H, s, N–NH_2), 7.40–7.47 (3H, s, ArH), 7.97 (1H, d, $^3J_{HH}$ = 7.5 Hz, ArH), 8.37 (1H, s,=CH), 9.56 (1H, s, O=C–NH), 11.96 (2H, s, NH_2), 13.66 (1H, br s, NH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 24.9 (C), 28.4 ($2CH_3$), 32.8 (CH), 41.9 (CH_2), 50.5 (CH_2), 79.6 (**C**=C–NH_2), 102.7 (O=C–**C**=C), 116.5, 127.5, 128.0, 130.4, 131.5, 132.0 (Ar), 140.8 (O=C–C=**C**), 144.1 (C-NH_2), 156.9 (N=CH), 159.6 (N–C=N), 165.5 (NH–C=O), 197.3 (C=O). MS (EI, 70 eV): *m*/z (%) = 429 (0.1) $[M+2]^+$, 427 (0.3) $[M]^+$, 293 (100), 191 (56), 150 (81), 122 (99), 84 (45).

2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-1-(4H-1,2,4-triazol-3-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbohydrazide (5e)

Yellow solid, m.p.: 200–202 °C, yield 0.311 g (73%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.98 (6H, s, $2CH_3$), 2.03 (2H, s, CH_2), 2.39 (2H, s, CH_2), 3.80 (1H, s, CH), 4.20 (2H, s, N–NH_2, D_2O exchangeable), 7.49 (2H, d, $^3J_{HH}$ = 8.4 Hz, ArH), 7.70 (2H, d, $^3J_{HH}$ = 8.7 Hz, ArH), 7.98 (1H, s,=CH), 9.56 (1H, s, O=C–NH, D_2O exchangeable), 11.79 (2H, s, NH_2, D_2O exchangeable), 13.65 (1H, br s, NH, D_2O exchangeable). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 24.8 (C), 28.4 ($2CH_3$), 32.8 (CH), 41.9 (CH_2), 50.5 (CH_2), 102.7 (O=C–**C**=C), 116.5, 129.1, 129.3, 133.2 (Ar), 135.1 (O=C–C=**C**), 143.5 (C–NH_2), 156.4 (N–C=N), 165.4 (NH–C=O), 197.2 (C=O). MS (EI, 70 eV): *m*/z (%) = 428 (1) $[M+1]^+$, 427 (3) $[M]^+$, 216 (27), 165 (34), 104 (74), 86 (100), 75 (40), 45 (59).

2-Amino-4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-1-(4H-1,2,4-triazol-3-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbohydrazide (5f)

Yellow solid, m.p.: 196–200 °C, yield 0.265 g (65%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.97 (6H, s, $2CH_3$), 2.03 (2H, s, CH_2), 2.38 (2H, s, CH_2), 3.76 (1H, s, CH), 4.13 (2H, s, N–NH_2), 6.80 (2H, d, $^3J_{HH}$ = 8.4 Hz, ArH), 7.49 (2H, d, $^3J_{HH}$ = 8.1 Hz, ArH), 7.88 (1H, s,=CH), 9.56 (1H, s, O=C–NH), 9.95 (1H, br s, OH), 11.59 (2H, s, NH_2), 13.67 (1H, br s, NH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 24.8 (C), 28.7 ($2CH_3$), 32.8 (CH), 41.9 (CH_2), 50.5 (CH_2), 102.7 (O=C–**C**=C), 116.2, 125.2, 129.5, 143.2 (Ar), 145.1 (O=C–C=**C**), 148.5 (C-NH_2), 156.9 (N=CH), 159.1 (N–C=N), 164.8 (NH–C=O), 197.3 (C=O). MS (EI, 70 eV): *m*/z (%) = 409 (0.5) $[M]^+$, 328 (14), 247 (75), 191 (25), 163 (100), 122 (34).

2-Amino-4-(3-fluorophenyl)-7,7-dimethyl-5-oxo-1-(4H-1,2,4-triazol-3-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbohydrazide (5 g)

Yellow solid, m.p.: 208–209 °C, yield 0.246 g (60%); IR (KBr) (ν_{max} /cm^{-1}): 3280, 3213, 3045 (NH, NH_2), 2871 (C–H), 1634 (C=O), 1586, 1537 (C=C), 1385, 1248 (C–N), 1147 (C–O), 785 (Ar). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.97 (6H, s, $2CH_3$), 2.03 (2H, s, CH_2), 2.39 (2H, s, CH_2), 3.76 (1H, s, CH), 4.22 (2H, s, N–NH_2), 7.23 (1H, d, $^3J_{HH}$ = 7.5 Hz, ArH), 7.51 (1H, s, ArH), 7.41–7.57 (2H, m, ArH), 8.00 (1H, s,=CH), 9.55 (1H, s, O=C–NH), 11.90 (2H, s, NH_2), 13.66 (1H, br s, NH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 24.8 (C), 28.4 ($2CH_3$), 32.8 (CH), 41.9 (CH_2), 50.5 (CH_2), 102.7 (O=C–**C**=C), 113.1, 113.4 (Ar, d, $^2J_{CF}$ = 22.5 Hz), 116.6 (Ar),117.2, 117.5 (Ar, d, $^2J_{CF}$ = 21.7 Hz), 124.1, 131.2 (Ar), 136.8 (O=C–C=**C**), 143.4 (C–NH_2), 156.9 (N=CH), 159.6 (N–C=N), 161.2, 164.5 (Ar, d, $^1J_{CF}$ = 243 Hz), 165.5 (NH–C=O), 197.3 (C=O).

2-Amino-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-1-(4H-1,2,4-triazol-3-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbohydrazide (5 h)

Yellow solid, m.p.: 207–209 °C, yield 0.254 g (62%); IR (KBr) (ν_{max} /cm^{-1}): 3222, 3083 (NH, NH_2), 2873 (C-H), 1682 (C=O), 1599, 1532 (C=C), 1278 (C–N), 1152 (C–O), 691 (Ar). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.97 (6H, s, $2CH_3$), 2.02 (2H, s, CH_2), 2.36 (2H, s, CH_2), 3.80 (1H, s, CH), 4.19 (2H, s, N–NH_2), 7.25 (2H, t, ArH), 7.74 (2H, t, ArH), 7.98 (1H, s,=CH), 9.56 (1H, s, O=C–NH), 11.80 (2H, s, NH_2), 13.67 (1H, br s, NH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 24.8 (C), 28.4 ($2CH_3$), 32.8 (CH), 41.9 (CH_2), 50.5 (CH_2), 102.7 (O=C–**C**=C), 116.2, 116.5 (Ar, d, $^2J_{CF}$ = 22.5 Hz),

129.7, 129.8, 130.9 (Ar), 143.7 (O=C–C=**C**), 147.1 (C-NH_2), 156.9 (N–C=N), 159.4, 162.46 (Ar, d, $^1J_{CF}$ = 227 Hz), 165.3 (NH–C=O), 197.3 (C=O).

2-Amino-4-(3,4-dimethoxyphenyl)-7,7-dimethyl-5-oxo-1-(4H-1,2,4-triazol-3-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbohydrazide (5i)

Yellow solid, m.p.: 196–200 °C, yield 0.403 g (89%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.97 (6H, s, $2CH_3$), 2.03 (2H, s, CH_2), 2.48 (2H, s, CH_2), 3.76 (6H, s, OCH_3), 3.80 (1H, s, CH), 4.19 (2H, s, N-NH_2), 6.96 (1H, d, $^3J_{HH}$ = 8.4 Hz, ArH), 7.14 (1H, d, $^3J_{HH}$ = 8.4 Hz, ArH), 7.31 (1H, s, Ar), 7.90 (1H, s,= CH), 9.56 (1H, s, O=C–NH), 11.67 (2H, s, NH_2), 13.66 (1H, br s, NH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 24.8 (C), 28.4 ($2CH_3$), 32.8 (CH), 41.9 (CH_2), 50.5 (CH_2), 55.9 (OCH3), 79.6 (**C**=C–NH_2), 102.7 (O=C–**C**=C), 109.1, 111.9, 116.3, 122.0, 126.9 (Ar), 144.9 (O=C–C=**C**), 148.4 (C-NH_2), 151.2 (Ar), 156.9 (N=CH), 159.1 (N–C=N), 165.0 (NH-C = O), 197.3 (C=O). MS (EI, 70 eV): *m*/z (%) = 453 (0.5) $[M]^+$, 203 (23), 150 (30), 119 (100), 95 (13).

2-Amino-4-(3-chlorophenyl)-7,7-dimethyl-5-oxo-1-(4H-1,2,4-triazol-3-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbohydrazide (5j)

Yellow solid, m.p.: 205–207 °C, yield 0.350 g (82%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.98 (6H, s, $2CH_3$), 2.03 (2H, s, CH_2), 2.37 (2H, s, CH_2), 3.81 (1H, s, CH), 4.24 (2H, s, N-NH_2), 7.43 (1H, s, ArH), 7.50–7.79 (3H, m, ArH), 7.97 (1H, s,=CH), 9.56 (1H, s, O=C–NH), 11.90 (2H, s, NH_2), 13.66 (1H, br s, NH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 24.9 (C), 28.4 ($2CH_3$), 32.8 (CH), 41.9 (CH_2), 50.5 (CH_2), 80.0 (**C**=C–NH_2), 102.7 (O=C–**C**=C), 116.5, 126.5, 126.6, 130.2, 131.1, 134.1 (Ar), 136.5 (O=C–C=**C**), 143.2 (C-NH_2), 156.9 (N–C=N), 165.6 (NH–C=O), 197.2 (C=O). MS (EI, 70 eV): *m*/z (%) = 427 (0.5) $[M]^+$, 206 (56), 191 (57), 150 (83), 122 (100), 95 (35).

2-Amino-4-(5-bromo-2-hydroxyphenyl)-7,7-dimethyl-5-oxo-1-(4H-1,2,4-triazol-3-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbohydrazide (5 k)

Yellow solid, m.p.: 204–206 °C, yield 0.355 g (73%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.98 (6H, s, $2CH_3$), 2.03 (2H, s, CH_2), 2.37 (2H, s, CH_2), 3.81 (1H, s, CH), 4.22 (2H, s, N-NH_2), 6.86 (1H, d, $^3J_{HH}$ = 6.9 Hz, ArH), 7.36 (1H, d, $^3J_{HH}$ = 6.9 Hz, ArH), 7.74 (1H, s, Ar), 8.30 (1H, s,=CH), 9.55 (1H, s, O=C–NH), 10.40 (OH), 11.77 (2H, s, NH_2), 13.66 (1H, br s, NH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 24.9 (C), 28.4 ($2CH_3$), 32.8 (CH), 41.9 (CH_2), 50.5 (CH_2), 102.7 (O=C–**C**=C), 11.3, 116.6, 118.8, 119.1, 122.8, 128.3, 134.1 (Ar), 140.0 (O=C–C=**C**), 145.4 (C-NH_2), 156.1 (N=CH), 159.0 (N–C=N), 165.3 (NH–C=O), 197.3 (C=O).

2-Amino-4-(2-hydroxy-3-methoxyphenyl)-7,7-dimethyl-5-oxo-1-(4H-1,2,4-triazol-3-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbohydrazide (5 l)

Yellow solid, m.p.: 207–209 °C, yield 0.351 g (80%); ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.97 (6H, s, $2CH_3$), 2.03 (2H, s, CH_2), 2.37 (2H, s, CH_2), 3.76 (3H, s, OCH_3), 3.82 (1H, s, CH), 4.16 (2H, s, N-NH_2), 6.78–6.84 (1H, m, ArH), 6.96 (1H, d, $^3J_{HH}$ = 8.4 Hz, ArH), 7.30 (1H, d, $^3J_{HH}$ = 7.8 Hz, ArH), 8.35 (1H, s,=CH), 9.31 (1H, br s, OH), 9.56 (1H, s, O=C–NH), 11.72 (2H, s, NH_2), 13.68 (1H, br s, NH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 24.8 (C), 28.4 ($2CH_3$), 32.8 (CH), 41.9 (CH_2), 50.5 (CH_2), 56.3 (OCH3), 102.7 (O=C–**C**=C), 113.5, 116.1, 118.0, 119.3, 120.6, 142.0, (Ar), 146.5 (O=C–C=**C**), 148.4 (C-NH_2), 157.0 (N=CH), 159.3 (N–C=N), 165.0 (NH–C=O), 197.3 (C=O).

3-((1H-1,2,4-triazol-5-yl)amino)-5,5-dimethylcyclohex-2-en-1-one (6)

White solid, ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.98 (6H, s, $2CH_3$), 2.03 (2H, s, CH_2), 2.40 (2H, s, CH_2), 6.24 (1H, s=CH), 8.38 (1H, s, N=CH), 9.56 (1H, br s, NH), 13.65 (1H, br s, NH).

(E)-3-(4-chlorophenyl)-2-cyanoacrylohydrazide (7)

Light yellow solid, ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.31 (2H, s, NH_2), 7.47 (2H, d, $^3J_{HH}$ = 7.2 Hz, ArH), 7.71 (2H, d, $^3J_{HH}$ = 7.5 Hz, ArH), 7.97 (1H, s=CH), 11.83 (1H, s, NH).

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11030-022-10592-5.

Acknowledgements Financial support of this research from Imam Khomeini International University, Iran is gratefully acknowledged.

Declarations

Conflict of interest The authors declare no competing financial interests.

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