Synthesis and Pharmacological Activities of Some New 2-[1-Heptyl-3-(4-methoxybenzyl)-5-oxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl]acetohydrazide Derivatives

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In the present investigation, the key intermediate acetohydrazide derivative **5** was synthesized starting from 3-(4-methoxybenzyl)-4-amino-4,5-dihydro-1,2,4-triazol-5-one (**1**) by a four-step reaction. Thiosemicarbazides **6a**–**f** and arylidenehydrazide derivatives **8a**–**d** were obtained from compound **5**. The cyclization of compounds **6a**–**f** in the presence of NaOH resulted in the formation of compounds **7a**–**f**. The compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy, elemental analysis and mass spectral studies. The compounds were tested for their anti-lipase, anti-α-glucosidase and anti-mycobacterial activities. Compounds **6b** and **8c** exhibited excellent anti-lipase activity, and compound **8d** showed excellent anti-α-glucosidase activity. Compounds **3** and **4** exhibited good anti-tuberculosis activity.

Key words: Acetohydrazide Derivatives, 1,2,4-Triazoles, 1,2,4-Triazole-5-thiones, Lipase and α-Glucosidase Inhibitor Activities, Anti-mycobacterial Activity

Introduction

A recent publication of the World Health Organization (WHO) has shown that worldwide obesity, calculated as body mass index (BMI) by dividing the weight by the square of the height, has inreased drastically [1]. In fact, obesity has more than doubled since 1980 [2]. Obesity is a result of the energy imbalance between energy intake and expenditure, the consumption of unhealty foods and lack of exercise [3]. In 2012, obesity WAs the fifth leading risk of deaths, with at least 2.8 million adulthood deaths [4]. There are now over 1.4 billion adults overweight with women outnumbering men by a ratio 3 to 2 [5]. Obesity can cause many diseases such as hypertension, stroke, sleep apne, non insulin dependent hyperlipidemia, and diabetes mellitus, and also coronary heart diseases and certain types of cancer are attributed to overweight and obesity [6, 7].

Pancreatic lipase is the main lipid-digesting enzyme that catalyzes the hydrolysis of ester bonds of triacylglycerols to produce free fatty acids, diglycerides, monoglycerides and glycerol [8]. Inhibition of pancreatic lipase is an attractive target for the treatment of obesity [9, 10]. α-Glucosidase is a key enzyme involved in the digestion of dietary carbohydrates in humans [11]. This enzyme hydrolyzes polysaccharides into monosaccharides in the small intestine [12]. Inhibition of this enzyme decreases blood glucose levels by delaying or preventing the digestion and hence absorption [13]. Therefore, α-glucosidase inhibitors are widely used in the treatment of patients with type 2 diabetes and obesity [14].

According to the WHO reports, another leading health problem around the world is tuberculosis (TB) [15]. Tuberculosis is one of the deadly infectious

diseases caused by *Mycobacterium tuberculosis*, and approximately 2 million people die from this disease each year [16].

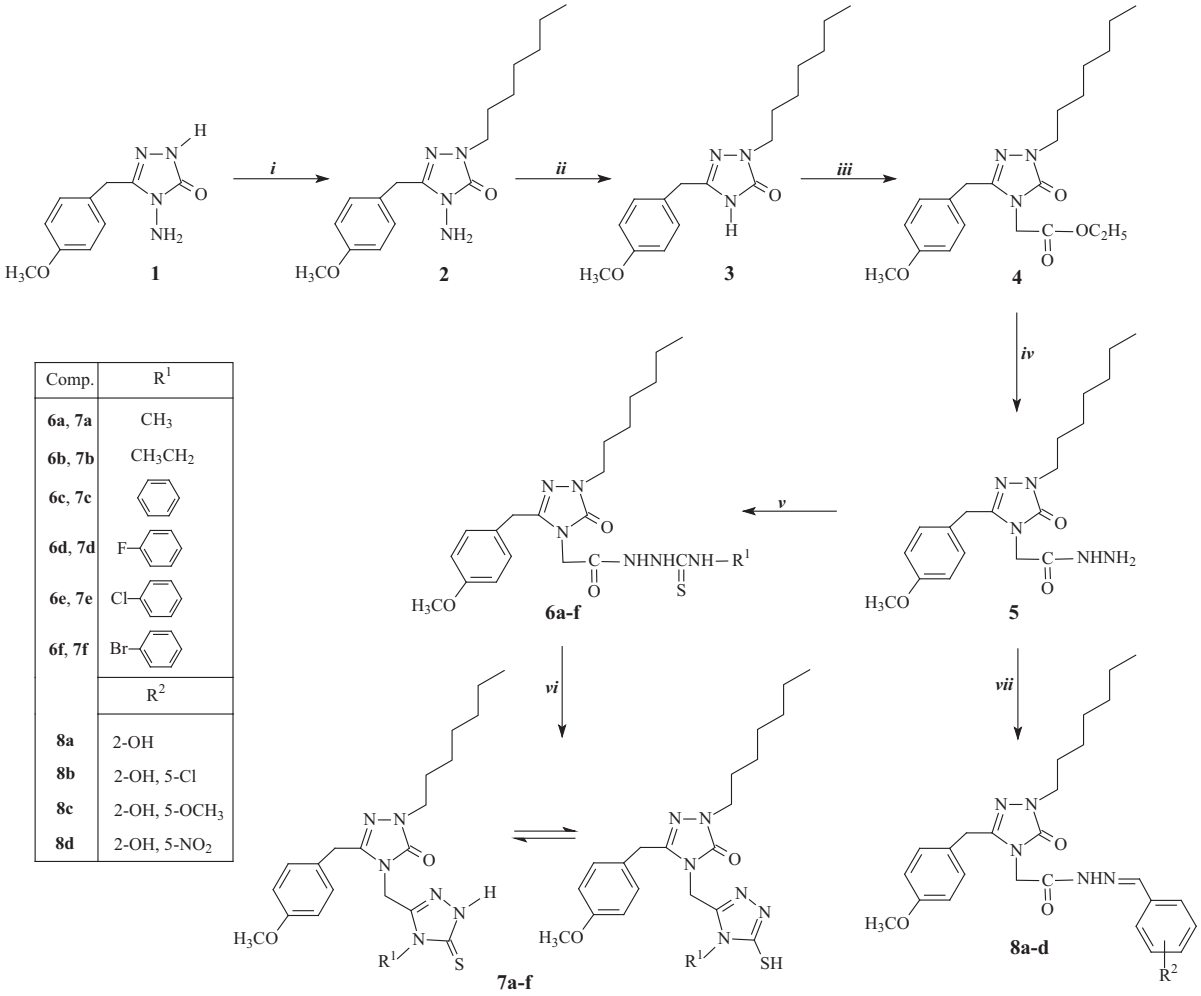
1,2,4-Triazoles and their derivatives are an important class of compounds with a wide spectrum of biological activities including antimicrobial [17], antifungal [18], antitubercular [19], anti-inflammatory [20], anticancer [21], antihypertensive [22], antiviral [23], antidiabetic [24], anticonvulsant [25], antidepressant [26], hypoglycemic [27], enzyme inhibitory [28], and antioxidant activity [29]. In addition to these, various compounds containing a 1,2,4-triazole ring are well known drugs such as anastrozole, letrozole, vorozole (antineoplastics, nonsteroidal competitive aromatase inhibitors), fluconazole, itraconazole, terconazole (antifungal agents), ribavirin (antiviral agent), alprazolam (anxiolytic agent, tranquilizer), estazolam (hypnotic, sedative, tranquilizer), etoperidone (antidepressant), benatradin (diuretic), rizatriptan (antimigraine agent), trapidil (hypotensive), trazodone (antidepressant, anxiolytic, selectively inhibiting central serotonin uptake), triazolam (sedative and hypnotic), rilmazafon (hypnotic, anxiolytic, used in the case of neurotic insomnia), and nefazodone (antidepressant, 5-HT2 A-antagonist) [30 – 37]. Similarly, acetohydrazide derivatives have shown significant pharmaceutical potential, possessing antimicrobial, antitumor, anticonvulsant, analgesic, antioxidant, anti-inflammatory, antimalarial, antiparasitic, antihypertensive, and antituberculosis activities [38 – 43]. Some present day drugs such as isoniazide and isocarboxazide (antituberculosis), nifuroxazide (intestinal antiseptic), ftivazide (antibacterial), and iproniazide (antidepressant) are examples of potent bioactive molecules possessing hydrazide-hydrazone moieties [44 – 47]. Moreover, hydrazide derivatives can be considered as useful intermediates leading to the formation of a wide variety of heterocyclic compounds such as pyrroles, pyrazoles, imidazoles, oxadiazoles, thiadiazoles, and triazoles [48]. On the other hand, 1,2,4-triazoles bearing open-chain thiosemicarbazide and mercapto-1,2,4-triazole moities are also more potent biologically active compounds [49 – 51]. In view of these findings, we report the synthesis, characterization, lipase and α-glucosidase inhibitory properties, and anti-mycobacterial activities of some new 2-heptyl-5-(4-methoxybenzyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one derivatives.

Results and Discussion

Chemistry

The synthetic route to compounds **1**–**8** is outlined in Scheme 1. In the present work, 3-(4-methoxybenzyl)-4-amino-4,5-dihydro-1,2,4-triazol-5-one (**1**) was prepared according to the literature [52]. The reaction of compound **1** with 1-bromoheptane in the presence of sodium ethoxide produced compound **2**. The preparation of compound **3** was achieved in good yield by deamination of compound **2** in the presence of hypophosphorous acid (50 % aqueous solution) and sodium nitrite according to the literature [53]. Compound **3** was transformed into the ethyl acetate derivative **4** by reacting it with ethyl bromoacetate in the presence of sodium ethoxide. The key intermediate in our study has been the acetohydrazide derivative **5**, which was prepared by the reaction of **4** and hydrazine hydrate in butanol. The condensation of the acid hydrazide **5** with alkyl/aryl isothiocyanates resulted in the formation of thiosemicarbazide derivatives **6a**–**f**. The FT-IR spectra exhibited characteristic absorption bands at 3213 – 3275 and 1671 – 1678 cm^{-1} due to three NH and thiosemicarbazide C=O vibrations, respectively. The ^{1}H NMR signals of the protons linked to N1–N2 and N3 nitrogens appeared at δ = 7.44 – 9.82 and 9.80 – 10.41 ppm, respectively. The characteristic carbon signals were observed at around δ = 166 (thiosemicarbazide C=O) and 180 ppm (thiosemicarbazide C=S). The synthesized thiosemicarbazides **6a**–**f** were cyclized with 2 M sodium hydroxide in the presence of ethanol to obtain the corresponding derivatives **7a**–**f**. Compounds **7a**–**f** can exist in thiole and thione tautomeric forms [54]. Spectral analysis (IR and ^{1}H NMR) has shown that these compounds have the thione structure. In the IR spectra, the SH vibration bands (2500 – 2600 cm^{-1}) were absent and the C=S vibration bands were observed in the region 1314 – 1351 cm^{-1}. Also, the presence of NH absorption bands in the region 3100 – 3374 cm^{-1} and signals at δ = 13.52 – 13.85 ppm in the ^{1}H NMR spectrum are supporting proofs for the formation of the thione tautomeric form [54 – 56].

Compound **5** was condensed with various aromatic aldehydes in ethanol to give the corresponding arylidene hydrazides (**8a**–**d**). In the FT-IR spectra of **8a**–**d**, we observed bands at around 3210, 3175 and 1689 cm^{-1} due to OH, (CO)NH and hydrazide C=O



Comp.	R^1
6a, **7a**	CH_3
6b, **7b**	CH_3CH_2
6c, **7c**	
6d, **7d**	F–
6e, **7e**	Cl–
6f, **7f**	Br–
	R^2
8a	2-OH
8b	2-OH, 5-Cl
8c	2-OH, 5-OCH_3
8d	2-OH, 5-NO_2

Scheme 1. Reagents and conditions: *i*: absolute ethanol, NaOEt/$CH_3(CH_2)_6$-Br, reflux; *ii*: H_3PO_2 (50% aqueous solution), $NaNO_2$, room temperature; *iii*: absolute ethanol, NaOEt/$BrCH_2CO_2Et$, reflux; *iv*: butanol, $NH_2NH_2 \cdot H_2O$, reflux; *v*: absolute ethanol, RNCS, reflux; *vi*: 2 N NaOH, reflux; *vii*: ethanol, ArCHO, reflux.

stretching vibrations, respectively. The signals belonging to benzyl CH_2, NCH_2 C=O, N=CH, OH, and NH groups in the ^{1}H NMR spectra and to triazole C-3, triazole C=O and N=CH in the ^{13}C NMR spectra of **8a**–**d** were observed as double singlets. According to the literature, arylidene hydrazide derivatives may exist as *E*/*Z* geometrical isomers with respect to the C=N double bonds and as *cis*/*trans* amide conformers at the N–C(O) bond [57, 58]. It is known that, when arylidene hydrazide derivatives are dissolved in polar solvents such as dimethyl [D_6] sulfoxide, the geometrical *E* isomers of these compounds undergo a rapid *trans*/*cis* amide equilibration, in which the *trans* conformer predominates [21, 59]. The *E* isomers and the *trans*/*cis* conformer ratios can be calculated from ^{1}H NMR data [57 – 59]. In this study, we determined the percentage ratios of *trans*/*cis* in the mixture of the conformers of compounds **8a**–**d**. The ratios of *trans*/*cis* conformers are 63.3 : 36.7 for **8a**, 68.8 : 31.2 for **8b**, 63.8 : 36.2 for **8c**, and 66.2 : 33.8 for **8d**. The signals belonging to benzyl CH_2, N–CH_2–CO, N=CH, OH and NH protons were seen at around δ = 3.78 (*trans*)/3.82 (*cis*), 4.27 (*cis*)/4.67 (*trans*), 8.29 (*trans*)/8.35 (*cis*), 10.39 (*trans*)/11.17 (*cis*), and 11.67 (*trans*)/ 11.90 (*cis*) ppm, respectively. In contrast, the NCH_2 proton signals of the *trans* conformers are found

downfield compared to that of the *cis* conformers, because of steric hindrance [57 – 59]. In the ^{13}C NMR spectra of **8a–d**, two signals each belonging to the N=CH, triazole C-3 and triazole C=O units were observed at δ = 141.68 (*trans*)/161.20 (*cis*), 146.35 (*trans*)/153.64 (*cis*), and 155.80 (*trans*)/157.84 (*cis*) ppm.

Pharmacology

Anti-lipase activity

All compounds were evaluated with regard to pancreatic lipase activity and **6a–6c**, **6e**, **8a–8c** showed anti-lipase activities at various concentrations (Table 1). No significant inhibitory effect was detected for the other compounds. Among the tested compounds, **8c** and **6b** showed the best anti-lipase activity. These compounds inhibited pancreatic lipase activity by 98.3 % and 91.5 % at a concentration of 9.375 μM, respectively (Table 1). Orlistat, a known pancreatic lipase inhibitor used as an antiobesity drug, showed an inhibitory effect of 95.3 % at a concentration of 312 nM. IC_{50} values for compounds **8c** and **6b** were calculated as 0.04 ± 0.00 and 0.63 ± 0.1 μM, respectively. The IC_{50} value of **8b** was determined as 1.13 ± 0.2 μM. Orlistat is the only approved antiobesity medication [60], but it has some side effects, such as fecal incontinence, flatulence, and steatorrhea [61, 62]. The synthesized compounds **8c** and **6b** have a significant potential to become alternatives of Orlistat.

α-Glucosidase inhibitory activity

All compounds were evaluated with regard to their α-glucosidase activity, and **6a–c**, **7f** and**8a–d** showed anti-α-glucosidase activity at various concentrations.

Table 1. Inhibitory effects of selected compounds (at a final concentration of 9.375 μM). Orlistat was used as positive control.

Compound	Inhibition (%)	IC_{50} (μM)
6a	94.4 ± 5.2	2.34 ± 1.30
6b	91.5 ± 14.2	0.63 ± 0.10
6c	82.6 ± 4.0	3.75 ± 0.20
6e	92.8 ± 3.6	2.95 ± 0.40
8a	92.8 ± 0.9	2.82 ± 0.40
8b	97.1 ± 2.5	1.13 ± 0.20
8c	98.3 ± 4.1	0.04 ± 0.00
Orlistat (312 nM)	95.3 ± 0.0	$9.88 \times 10^{-3} \pm 2.30 \times 10^{-3}$

Table 2. Inhibition of α-glucosidase by selected compounds. All compounds were assayed at a concentration of 100 μM.

Compound	Inhibition (%)	$IC_{50} \pm$ SD (μM)
6a	95.4 ± 4.1	35.15 ± 3.96
6b	100.0 ± 8.6	39.21 ± 11.51
6c	100.0 ± 12.5	19.15 ± 2.86
7f	100.0 ± 1.6	19.01 ± 5.29
8a	100.0 ± 6.1	17.55 ± 2.77
8b	100.0 ± 6.0	11.42 ± 2.13
8c	100.0 ± 2.0	4.85 ± 0.09
8d	100.0 ± 0.2	0.59 ± 0.02
Acarbose	55.4 ± 3.0	69.16 ± 5.20

These compounds exhibited a larger inhibitory effect than Acarbose, a known α-glucosidase inhibitor used as an antidiabetic drug (Table 2). No significant inhibitory effect was detected for other compounds. Among the tested compounds, **8d** showed the best anti-α-glucosidase activity. The compound inhibited α-glucosidase activity by 100 ± 0.2 % at a concentration of 100 μM. Acarbose showed an inhibitory effect by 55.4 ± 3.0 % at the same concentration. IC_{50} values of Acarbose and compound **8d** were calculated as 69.16 ± 5.2 and 0.59 ± 0.02 μM, respectively (Table 2).

Anti-mycobacterial activity

The anti-mycobacterial activity results of the newly synthesized compounds are presented in Table 3. The compounds not mentioned in Table 3 were found to be ineffective. Compounds **3** and **4** were effective against *M. smegmatis* (17 and 18 mm inhibition zone, respectively). Besides, compounds **2**, **6f** and **7d** showed a moderate effect against *M. smegmatis*. The other

Table 3. Anti-mycobacterial activity results. Fifty microliters of compound solutions at 20 mM concentration were delivered into the wells.

Compound	Inhibition Zone (mm)
2	12
3	17
4	18
6f	13
7a	9
7b	7
7c	7
7d	11
7e	8
7f	9
Strep.	30
DMSO	–

compounds exhibited only weak effects (7 – 9 mm inhibition zone).

Conclusion

One of the current antiobesity strategies is the inhibition of the digestive enzymes lipase and glycosidase with the use of inhibitors orlistat and acarbose, respectively. However, these and other drugs available in the market have limitations and produce serious side effects [60 – 63]. *Mycobacterium tuberculosis* is the cause of tuberculosis, and currently the antibiotics including isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin are used as antituberculosis agents. The effectiveness of these drugs is severely compromised because extensive drug-resistant tuberculosis (MDR-TB and XDR-TB) has emerged [64 – 66].

As the current antiobesity and antituberculosis drugs have limitations and side-effects, new drugs or leads are required to combat pathologies and infections. Thus, new acetohydrazide (**5**), open-chain thiosemicarbazides (**6a–f**), 1,2,4-triazole-5-thiones (**7a–f**), and benzylidene hydrazides (**8a–d**) bearing a 2-heptyl-5-(4-methoxybenzyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one ring have been synthesized.

Among the tested compounds, **8c** ($0.04 \pm 0.00\,\mu$M) and **6b** ($0.63 \pm 0.1\,\mu$M) showed a high anti-lipase activity, **8d** ($0.59 \pm 0.02\,\mu$M) showed a high anti-α-glucosidase activity, and compounds **3** and **4** were effective against *M. smegmatis* (17 and 18 mm inhibition zones, respectively). In addition, compounds **2**, **6f** and **7d** showed moderate effects against *M. smegmatis*. The structures of the active compounds are clearly unrelated with those currently in clinical use, and deserve further investigations.

Experimental Section

Chemistry

All melting points were determined on a Gallenkamp Electrothermal digital melting point apparatus. Infrared (IR) spectra were recorded with a Perkin-Elmer Frontier FT-IR spectrophotometer using attenuated total reflection (ATR) accessory. ^{1}H and ^{13}C NMR spectra were recorded in [D$_6$]DMSO on a Varian Mercury 400 MHz spectrometer using TMS as internal standard. The elemental analyses were performed on a Costech Elemental Combustion System CHNS-O elemental analyzer. Mass spectra were measured on a Quattro LC-MS (70 eV) 4.0 micromass spectrometer. The reactions were monitored by thin layer chromatography (TLC) using 0.2 mm precoated plates of silica gel G60 F254. Compound **1** was synthesized by the method reported earlier [52].

*General method for the synthesis of compounds **2** and **4***

The corresponding compound **1** (10 mmol) was refluxed with 1 equivalent of sodium in absolute ethanol for 2 h. Then, 1-bromoheptane-ethyl bromoacetate (10 mmol) was added, and the mixture was refluxed for additional 8 h. After evaporation of the solvent under reduced pressure, a solid appeared, which was recrystallized from ethanol-water (1 : 2) to afford the desired products.

*4-Amino-2-heptyl-5-(4-methoxybenzyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**2**)*

M. p. 98 – 99 °C. Yield 87 %. – IR (KBr): ν = 3298, 3206 (NH_2), 2998, 2836 (aliphatic CH), 1703 (triazole C=O), 1648 (C=N) cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): δ = 0.83 (t, 3H, J = 6.8 Hz, CH_3), 1.21 – 1.23 (m, 8H, 4CH_2), 1.54 – 1.58 (m, 2H, NCH_2*CH_2*), 3.58 (t, 2H, J = 6.8 Hz, N*CH_2*CH_2), 3.70 (s, 3H, OCH_3), 3.78 (s, 2H, benzyl CH_2), 5.22 (s, 2H, NH_2); Ar-H: 6.83 (d, 2H, J = 8.4 Hz), 7.16 (d, 2H, J = 8.4 Hz) ppm. – ^{13}C NMR ([D$_6$]DMSO): δ = 14.37 (N-$(CH_2)_6$*CH_3*), 22.42 (N-$(CH_2)_5$-*CH_2*-CH_3), 26.27 (N-$(CH_2)_2$-*CH_2*-$(CH_2)_3CH_3$), 28.60 (N-$(CH_2)_3$-*CH_2*-$(CH_2)_2CH_3$), 28.61 (N-CH_2-CH_2-$(CH_2)_4$-CH_3), 30.70 (N-$(CH_2)_4$-*CH_2*-CH_2CH_3), 31.60 (benzyl CH_2), 45.03 (N-*CH_2*-$(CH_2)_5$-CH_3), 55.46 (OCH_3); Ar-C: 114.25 (2CH), 128.38, 130.15 (2CH), 158.45; 147.16 (triazole C-5), 153.28 (triazole C=O) ppm. – Anal. for $C_{17}H_{26}N_4O_2$ (318.42): calcd. C 64.13, H 8.23, N 17.60; found C 64.28, H 8.08, N. 17.65. – MS ((+)-ES, 70 eV): m/z(%) = 341.45 (100) [M+Na]$^+$, 319.43 (73) [M+H]$^+$, 219.25 (70), 221.13 (32), 182.20 (25), 174.15 (23), 149.18 (28), 132.20 (75), 114.28 (44).

*Ethyl 2-[1-hepthyl-3-(4-methoxybenzyl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl] acetate (**4**)*

M. p. 46 – 47 °C. Yield 74 %. – IR (KBr): ν = 2952, 2852 (aliphatic CH), 1757 (ester C=O), 1696 (triazole C=O), 1611 (C=N) cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): δ = 0.85 (3H, t, J = 6.8 Hz, CH_3), 1.09 (3H, t, J = 7.2 Hz, OCH_2*CH_3*), 1.22 – 1.26 (8H, m, 4CH_2), 1.58 – 1.62 (2H, m, NCH_2*CH_2*), 3.63 (2H, t, J = 6.8 Hz, N*CH_2*CH_2), 3.70 (3H, s, OCH_3), 3.81 (2H, s, benzyl CH_2), 3.95 (2H, q, J = 7.2 Hz, OCH_2), 4.34 (2H, s, N-CH_2- C=O); Ar-H: 6.84 (2H, d, J = 8.8 Hz), 7.12 (2H, d, J = 8.8 Hz) ppm. – ^{13}C NMR ([D$_6$]DMSO): δ = 14.21 (N-$(CH_2)_6$*CH_3*), 14.33 (OCH_2*CH_3*), 22.43 (N-$(CH_2)_5$-*CH_2*-CH_3), 26.17 (N-$(CH_2)_2$-CH_2-$(CH_2)_3CH_3$), 28.56 (N-$(CH_2)_3$-*CH_2*-$(CH_2)_2CH_3$), 28.59 (N-CH_2-*CH_2*-$(CH_2)_4$-CH_3), 30.70 (N-$(CH_2)_4$-*CH_2*-CH_2CH_3),

31.60 (benzyl CH_2), 42.42 (N-*CH_2*-C=O), 44.70 (N-*CH_2*-$(CH_2)_5$-CH_3), 55.44 (OCH_3), 61.61 (OCH_2CH_3); Ar-C:114.34 (2CH), 116.90, 130.20 (2CH), 158.68; 145.68 (triazole C-3), 153.52 (triazole C=O), 167.60 (ester C=O) ppm. – Anal. for $C_{21}H_{31}N_3O_4$ (389.49): calcd. C 64.76, H 8.02, N 10.79; found C 64.87, H 8.00, N. 10.83. – MS ((+)-ES, 70 eV): $m/z(\%) = 428.42$ (30) $[M+K]^+$, 412.47 (100) $[M+Na]^+$, 390.51 (55) $[M+H]^+$, 234.32 (53), 196.17 (36), 182.28 (42), 149.05 (53), 132.22 (37), 119.15 (17).

*Synthesis of 2-heptyl-5-(4-methoxybenzyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**3**)*

To a mixture of compound **2** (0.01 mol) with an aqueous solution of 50 % hypophosphorous acid (30 mL), an aqueous solution of sodium nitrite (0.05 mol in 10 mL of water) was added slowly. Vigorous nitrogen evolution was observed during this addition, and the mixture was stirred at room temperature for 1 h. The precipitate formed was filtred, washed with water and recrystallized from ethanol-water (1 : 1).

M. p. 71 – 72 °C. Yield 90 %. – IR (KBr): $\nu = 3192$ (NH), 2955, 2871 (aliphatic CH), 1682 (triazole C=O), 1644 (C=N) cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 0.83$ (t, 3H, CH_3, $J = 6.80$ Hz), 1.20 – 1.25 (m, 8H, $4CH_2$), 1.54 – 1.58 (m, 2H, NCH_2CH_2), 3.53 (t, 2H, NCH_2CH_2, $J = 6.8$ Hz), 3.65 (s, 2H, benzyl CH_2), 3.70 (s, 3H, OCH_3); Ar-H: 6.85 (d, 2H, $J = 8.8$ Hz), 7.14 (d, 2H, $J = 8.8$ Hz); 11.37 (s, 1H, NH) ppm. – ^{13}C NMR ([D$_6$]DMSO): $\delta = 14.35$ (N-$(CH_2)_6CH_3$), 22.42 (N-$(CH_2)_5$-CH_2-CH_3), 26.31 (N-$(CH_2)_2$-CH_2-$(CH_2)_3CH_3$), 28.58 (N-$(CH_2)_3$-CH_2-$(CH_2)_2CH_3$), 28.69 (N-CH_2-CH_2-$(CH_2)_4$-CH_3), 32.00 (N-$(CH_2)_4$-CH_2-CH_2CH_3), 31.59 (benzyl CH_2), 43.94 (N-*CH_2*-$(CH_2)_5$-CH_3), 55.48 (OCH_3); Ar-C: 114.36 (2CH), 128.41, 130.01 (2CH), 158.61; 145.43 (triazole C-5), 154.62 (triazole C=O) ppm. – Anal. for $C_{17}H_{25}N_3O_2$ (303.40): calcd. C 67.30, H 8.31, N 13.85; found C 67.43, H 8.15, N. 13.92. – MS ((+)-ES, 70 eV): $m/z(\%) = 326.48$ (60) $[M+Na]^+$, 304.47 (100) $[M+H]^+$, 256.42 (28), 219.31 (47), 206.29 (21), 135.22 (36), 132.26 (62), 114.28 (38).

*Synthesis of 2-[1-heptyl-3-(4-methoxybenzyl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl] acetohydrazide (**5**)*

Compound **4** (0.01 mol) and hydrazine hydrate (0.025 mol) in *n*-butanol (25 mL) were refluxed for 6 h. After cooling to room temperature, a colorless solid appeared. The solid mass that separated was filtered, dried and recrystallized from ethanol to get the desired product as a solid. M. p. 96 – 97 °C. Yield 78 %. – IR (KBr): $\nu = 3273$, 3204 (NH_2), 3177 (NH), 2957, 2856 (aliphatic CH), 1696 (triazole C=O), 1658 (hydrazide C=O), 1635 (C=N) cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 0.85$ (t, 3H, CH_3, $J = 6.8$ Hz), 1.21 – 1.23 (m, 8H, $4CH_2$), 1.57 – 1.59 (m, 2H, NCH_2CH_2), 3.59 (s, 2H, NCH_2CH_2, $J = 6.8$ Hz), 3.70 (s, 3H, OCH_3), 3.77 (s, 2H, benzyl CH_2), 4.03 (s, 2H, N-*CH_2*-C=O), 4.24 (s, 2H, NH_2); Ar-H: 6.85 (d, 2H, $J = 8.8$ Hz), 7.11 (d, 2H, $J = 8.8$ Hz); 9.25 (s, 1H, NH) ppm. – ^{13}C NMR ([D$_6$]DMSO): $\delta = 14.37$ (N-$(CH_2)_6CH_3$), 22.43 (N-$(CH_2)_5$-CH_2-CH_3), 26.25 (N-$(CH_2)_2$-CH_2-$(CH_2)_3CH_3$), 28.60 (2C, N-$(CH_2)_3$-CH_2-$(CH_2)_2CH_3$ + N-CH_2-CH_2-$(CH_2)_4$-CH_3), 30.96 (N-$(CH_2)_4$-CH_2-CH_2CH_3), 31.60 (benzyl CH_2), 41.96 (N-*CH_2*-C=O), 44.72 (N-*CH_2*-$(CH_2)_5$-CH_3), 55.48 (OCH_3); Ar-C: 114.43 (2CH), 127.12, 130.21 (2CH), 158.60; 146.26 (triazole C-3), 153.58 (triazole C=O), 166.17 (hydrazide C=O) ppm. – Anal. for $C_{19}H_{29}N_5O_3$ (375.47): calcd. C 60.78, H 7.78, N 18.65; found C 60.87, H 7.70, N. 18.78. – MS ((+)-ES, 70 eV): $m/z(\%) = 398.46$ (100) $[M+Na]^+$, 376.49 (15) $[M+H]^+$, 344.40 (39), 316.31 (40), 230.21 (12).

*General method for the synthesis of compounds **6a–f***

A mixture of an acid hydrazide **5** (0.01 mol) and an alkyl/aryl isothiocynate (0.01 mol) was refluxed in absolute ethanol for 3 – 5 h. The solution was cooled and a colorless solid appeared. This was filtered and recrystallized from ethanol.

*2-{[1-Heptyl-3-(4-methoxybenzyl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]acetyl}-4-methylthiosemicarbazide (**6a**)*

M. p. 201 – 202 °C. Yield 95 %. – IR (KBr): $\nu = 3274$, 3236 (3NH), 2958, 2857 (*aliphatic CH*), 1712 (triazole C=O), 1677 (thiosemicarbazide C=O), 1612 (C=N), 1291 (C=S) cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 0.85$ (t, 3H, CH_3, $J = 6.8$ Hz), 1.21 – 1.22 (m, 8H, $4CH_2$), 1.56 – 1.61 (m, 2H, NCH_2CH_2), 2.86 (s, 3H, $NHCH_3$), 3.62 (t, 2H, NCH_2CH_2, $J = 6.8$ Hz), 3.70 (s, 3H, OCH_3), 3.75 (s, 2H, benzyl CH_2), 4.22 (s, 2H, N-*CH_2*-C=O); Ar-H: 6.87 (d, 2H, $J = 8.4$ Hz), 7.13 (d, 2H, $J = 8.4$ Hz); 8.01 (s, 1H, NH), 9.30 (s, 1H, NH), 10.12 (s, 1H, NH) ppm. – ^{13}C NMR ([D$_6$]DMSO): $\delta = 14.37$ (N-$(CH_2)_6CH_3$), 22.43 (N-$(CH_2)_5$-CH_2-CH_3), 26.22 (N-$(CH_2)_2$-CH_2-$(CH_2)_3CH_3$), 28.60 (N-$(CH_2)_3$-CH_2-$(CH_2)_2CH_3$), 30.84 (NH-CH_3), 31.29 (N-CH_2-CH_2-$(CH_2)_4$-CH_3), 30.59 (N-$(CH_2)_4$-CH_2-CH_2CH_3 + benzyl CH_2), 42.24 (N-*CH_2*-C=O), 44.79 (N-*CH_2*-$(CH_2)_5$-CH_3), 55.49 (OCH_3); Ar-C: 114.44 (2CH), 128.11, 130.26 (2CH), 158.61; 146.27 (triazole C-3), 153.60 (triazole C=O), 166.78 (thiosemicarbazide C=O), 181.64 (thiosemicarbazide C=S) ppm. – Anal. for $C_{21}H_{32}N_6O_3S$ (448.58): calcd. C 56.23, H 7.19, N 18.73; found C 56.46, H 7.01, N. 18.82. – MS ((+)-ES, 70 eV): $m/z(\%) = 487.50$ (43) $[M+K]^+$, 471.54 (100) $[M+Na]^+$, 449.52 (42) $[M+H]^+$, 438.51 (41), 416.61 (26), 376.50 (12), 344.53 (20), 219.38 (21), 132.35 (32), 114.33 (31).

*2-{[1-Heptyl-3-(4-methoxybenzyl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]acetyl}-4-ethylthiosemicarbazide (**6b**)*

M. p. 188 – 189 °C. Yield 95 %. – IR (KBr): ν = 3275, 3234 (3NH), 2958, 2857 (*aliphatic CH*), 1711 (triazole C=O), 1678 (thiosemicarbazide C=O), 1612 (C=N), 1292 (C=S) cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): δ = 0.83 (t, 3H, CH_3, J = 6.8 Hz), 1.09 (t, 3H, NH-CH_2-CH_3, J = 6.8 Hz), 1.21 – 1.25 (m, 8H, 4CH_2), 1.56 – 1.59 (m, 2H, NCH_2-CH_2), 3.45 (m, 2H, CH_2-CH_3), 3.61 (t, 2H, NH-CH_2-CH_2, J = 6.8 Hz), 3.71 (s, 3H, OCH_3), 3.72 (s, 2H, benzyl CH_2), 4.22 (s, 2H, N-CH_2-C=O); Ar-H: 6.87 (d, 2H, J = 8.8 Hz), 7.14 (d, 2H, J = 8.8 Hz); 7.99 (s, 1H, NH), 9.24 (s, 1H, NH), 10.12 (s, 1H, NH) ppm. – ^{13}C NMR ([D$_6$]DMSO): δ = 14.38 (N-$(CH_2)_6$-CH_3), 14.80 (NH-CH_2-CH_3), 22.43 (N-$(CH_2)_5$-CH_2-CH_3), 26.24 (N-$(CH_2)_2$-CH_2-$(CH_2)_3CH_3$), 28.59 (N-$(CH_2)_3$-CH_2-$(CH_2)_2CH_3$), 30.84 (NH-CH_2-CH_3), 31.30 (N-CH_2-CH_2-$(CH_2)_4$-CH_3), 30.59 (N-$(CH_2)_4$-CH_2-CH_2CH_3 + benzyl CH_2), 42.52 (N-CH_2-C=O), 44.97 (N-CH_2-$(CH_2)_5$-CH_3), 55.49 (OCH_3); Ar-C: 114.43 (2CH), 128.12, 130.27 (2CH), 158.60; 146.28 (triazole C-3), 153.62 (triazole C=O), 166.79 (thiosemicarbazide C=O), 181.65 (thiosemicarbazide C=S) ppm. – Anal. for $C_{22}H_{34}N_6O_3S$ (462.61): calcd. C 57.12, H 7.41, N 18.17; found C 57.33, H 7.37, N. 18.23. – MS ((+)-ES, 70 eV): m/z(%) = 485.50 (26) [M+Na]$^+$, 463.66 (8) [M+H]$^+$, 240.35 (22), 224.33 (100), 192.35 (32), 182.34 (56), 174.33 (74), 149.24 (98), 135.23 (42), 114.33 (59).

*2-{[1-Heptyl-3-(4-methoxybenzyl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]acetyl}-4-phenylthiosemicarbazide (**6c**)*

M. p. 145 – 146 °C. Yield 95 %. – IR (KBr): ν = 3219 (3NH), 2953, 2855 (aliphatic CH), 1721 (triazole C=O), 1671 (thiosemicarbazide C=O), 1612 (C=N), 1278 (C=S) cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): δ = 0.83 (t, 3H, CH_3, J = 6.8 Hz), 1.21 – 1.32 (m, 8H, 4CH_2), 1.56 – 1.59 (m, 2H, NCH_2-CH_2), 3.61 (t, 2H, NCH_2-CH_2, J = 6.8 Hz), 3.71 (s, 3H, OCH_3), 3.80 (s, 2H, benzyl CH_2), 4.28 (s, 2H, N-CH_2-C=O); Ar-H: 6.86 (d, 2H, J = 8.4 Hz), 7.10 – 7.16 (m, 3H), 7.30 – 7.35 (m, 2H), 7.44 (d, 2H, J = 8.0 Hz); 9.69 (s, 2H, NH), 10.39 (s, 1H, NH) ppm. – ^{13}C NMR ([D$_6$]DMSO): δ = 14.37 (N-$(CH_2)_6$-CH_3), 22.43 (N-$(CH_2)_5$-CH_2-CH_3), 26.24 (N-$(CH_2)_2$-CH_2-$(CH_2)_3CH_3$), 28.60 (N-$(CH_2)_3$-CH_2-$(CH_2)_2CH_3$ + N-CH_2-CH_2-$(CH_2)_4$-CH_3), 30.86 (N-$(CH_2)_4$-CH_2-CH_2CH_3), 31.57 (benzyl CH_2), 42.53 (N-CH_2-C=O), 44.82 (N-CH_2-$(CH_2)_5$-CH_3), 55.48 (OCH_3); Ar-C: 114.44 (2CH), 126.87 (2CH), 127.12, 129.58 (2CH), 130.25 (2CH), 133.35, 136.27, 158.60; 146.27 (triazole C-3), 153.72 (triazole C=O), 166.84 (thiosemicarbazide C=O), 181.68 (thiosemicarbazide C=S) ppm. – Anal. for $C_{26}H_{34}N_6O_3S$ (510.65): calcd. C 61.15, H 6.71, N 16.46; found C 61.27, H 6.68, N. 16.61. – MS ((+)-ES, 70 eV): m/z(%) = 549.51 (20) [M+K]$^+$, 533.49 (100) [M+Na]$^+$, 511.53 (19) [M+H]$^+$, 499.64 (18), 440.51 (7), 398.52 (8), 219.45 (58), 132.41 (18).

*2-{[1-Heptyl-3-(4-methoxybenzyl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]acetyl}-4-(4-fluorophenyl)-thiosemicarbazide (**6d**)*

M. p. 167 – 168 °C. Yield 83 %. – IR (KBr): ν = 3213 (3NH), 2957, 2857 (aliphatic CH), 1720 (triazole C=O), 1672 (thiosemicarbazide C=O), 1611 (C=N), 1291 (C=S) cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): δ = 0.83 (t, 3H, CH_3, J = 6.8 Hz), 1.21 – 1.22 (m, 8H, 4CH_2), 1.60 – 1.61 (m, 2H, NCH_2-CH_2), 3.61 (t, 2H, NCH_2-CH_2, J = 6.8 Hz), 3.71 (s, 3H, OCH_3), 3.79 (s, 2H, benzyl CH_2), 4.28 (s, 2H, N-CH_2-C=O); Ar-H: 6.86 (d, 2H, J = 8.4 Hz), 7.14 – 7.19 (m, 4H), 7.40 – 7.44 (m, 2H); 9.74 (s, 2H, NH), 10.39 (s, 1H, NH) ppm. – ^{13}C NMR ([D$_6$]DMSO): δ = 14.37 (N-$(CH_2)_6$-CH_3), 22.43 (N-$(CH_2)_5$-CH_2-CH_3), 26.23 (N-$(CH_2)_2$-CH_2-$(CH_2)_3CH_3$), 28.59 (N-$(CH_2)_3$-CH_2-$(CH_2)_2CH_3$ + N-CH_2-CH_2-$(CH_2)_4$-CH_3), 30.86 (N-$(CH_2)_4$-CH_2-CH_2CH_3), 31.59 (benzyl CH_2), 42.51 (N-CH_2-C=O), 44.82 (N-CH_2-$(CH_2)_5$-CH_3), 55.48 (OCH_3); Ar-C: 114.39 (2CH), 116.28 (2CH, J_{C-F} = 22.0 Hz), 125.92, 127.11, 130.67 (2CH), 131.11 (2CH, J_{C-F} = 10.2 Hz), 158.62, 164.24 (C, J_{C-F} = 250.5 Hz); 146.23 (triazole C-3), 153.69 (triazole C=O), 166.85 (thiosemicarbazide C=O), 181.69 (thiosemicarbazide C=S) ppm. – Anal. for $C_{26}H_{33}FN_6O_3S$ (528.64): calcd. C 59.07, H 6.29, N 15.90; found C 59.21, H 6.10, N. 16.00. – MS ((+)-ES, 70 eV): m/z(%) = 567.46 (44) [M+K]$^+$, 551.57 (100) [M+Na]$^+$, 529.48 (94) [M+H]$^+$, 517.47 (31), 511.46 (30), 414.98 (31), 399.52 (31), 344.53 (22), 316.49 (30), 256.43 (62).

*2-{[1-Heptyl-3-(4-methoxybenzyl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]acetyl}-4-(4-chlorophenyl)-thiosemicarbazide (**6e**)*

M. p. 124 – 125 °C. Yield 87 %. – IR (KBr): ν = 3222 (3NH), 2957, 2856 (aliphatic CH), 1720 (triazole C=O), 1673 (thiosemicarbazide C=O), 1612 (C=N), 1291 (C=S) cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): δ = 0.83 (t, 3H, CH_3, J = 6.8 Hz), 1.21 – 1.23 (m, 8H, 4CH_2), 1.56 – 1.61 (m, 2H, NCH_2-CH_2), 3.61 (t, 2H, NCH_2-CH_2, J = 6.8 Hz), 3.75 (s, 3H, OCH_3), 3.79 (s, 2H, benzyl CH_2), 4.28 (s, 2H, N-CH_2-C=O); Ar-H: 6.88 (d, 2H, J = 8.8 Hz), 7.13 (d, 2H, J = 8.8 Hz), 7.37 (d, 2H, J = 8.4 Hz), 7.48 (d, 2H, J = 8.4 Hz); 9.68 (s, 1H, NH), 9.80 (s, 1H, NH), 10.41 (s, 1H, NH) ppm. – ^{13}C NMR ([D$_6$]DMSO): δ = 14.37 (N-$(CH_2)_6$-CH_3), 22.42 (N-$(CH_2)_5$-CH_2-CH_3), 26.22 (N-$(CH_2)_2$-CH_2-$(CH_2)_3CH_3$), 28.59 (N-$(CH_2)_3$-CH_2-$(CH_2)_2CH_3$ + N-CH_2-CH_2-$(CH_2)_4$-CH_3), 30.85 (N-$(CH_2)_4$-CH_2-CH_2CH_3), 31.58 (benzyl CH_2), 42.52 (N-CH_2-C=O), 44.81 (N-CH_2-$(CH_2)_5$-CH_3), 55.48 (OCH_3); Ar-C: 114.44 (2CH), 127.09 (2CH), 127.12,

130.08 (2CH), 130.25 (2CH), 132.53, 138.36, 158.62; 146.22 (triazole C-3), 153.67 (triazole C=O), 166.83 (thiosemicarbazide C=O), 181.70 (thiosemicarbazide C=S) ppm. – Anal. for $C_{26}H_{33}ClN_6O_3S$ (545.10): calcd. C 57.29, H 6.10, N 15.42; found C 57.43, H 6.07, N. 15.57. – MS ((+)-ES, 70 eV): $m/z(\%) = 567.28$ (30) $[M+Na]^+$, 545.56 (62) $[M]^+$, 537.55 (52), 536.62 (40), 511.46 (30), 447.64 (36), 429.43 (38), 421.61 (25), 398.59 (100).

*2-{[1-Heptyl-3-(4-methoxybenzyl)-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]acetyl}-4-(4-bromophenyl)-thiosemicarbazide (**6f**)*

M. p. 174 – 175 °C. Yield 85 %. – IR (KBr): $\nu = 3223$ (3NH), 2960, 2857 (aliphatic CH), 1724 (triazole C=O), 1673 (thiosemicarbazide C=O), 1611 (C=N) cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 0.83$ (t, 3H, CH_3, $J = 6.8$ Hz), 1.21 – 1.22 (m, 8H, $4CH_2$), 1.56 – 1.61 (m, 2H, NCH_2CH_2), 3.61 (t, 2H, NCH_2CH_2, $J = 6.8$ Hz), 3.71 (s, 3H, OCH_3), 3.79 (s, 2H, benzyl CH_2), 4.28 (s, 2H, N-CH_2-C=O); Ar-H: 6.86 (d, 2H, $J = 8.8$ Hz), 7.15 (d, 2H, $J = 8.8$ Hz), 7.44 (d, 2H, $J = 8.4$ Hz), 7.50 (d, 2H, $J = 8.4$ Hz); 9.82 (s, 2H, NH), 10.41 (s, 1H, NH) ppm. – ^{13}C NMR ([D$_6$]DMSO): $\delta = 14.38$ (N-$(CH_2)_6CH_3$), 22.44 (N-$(CH_2)_5$-CH_2-CH_3), 26.23 (N-$(CH_2)_2$-CH_2-$(CH_2)_3CH_3$), 28.60 (N-$(CH_2)_3$-CH_2-$(CH_2)_2CH_3$ + N-CH_2-CH_2-$(CH_2)_4$-CH_3), 30.86 (N-$(CH_2)_4$-CH_2-CH_2CH_3), 31.59 (benzyl CH_2), 42.54 (N-CH_2-C=O), 44.84 (N-CH_2-$(CH_2)_5$-CH_3), 55.49 (OCH_3); Ar-C: 114.45 (2CH), 127.08, 130.26 (2CH), 130.98 (2CH), 131.45 (2CH), 132.15, 138.87, 158.61; 146.22 (triazole C-3), 153.68 (triazole C=O), 166.82 (thiosemicarbazide C=O), 181.68 (thiosemicarbazide C=S) ppm. – Anal. for $C_{26}H_{33}BrN_6O_3S$ (589.55): calcd. C 52.97, H 5.64, N 14.25; found C 53.12, H 5.60, N. 14.33. – MS ((+)-ES, 70 eV): $m/z(\%) = 613.41$ (30) $[M+H+Na]^+$, 589.72 (11) $[M]^+$, 523.56 (100), 504.36 (51), 464.22 (30), 447.73 (36), 417.46 (54).

*General method for the synthesis of compounds **7a–f***

A 20 mL ethanolic solution of a thiosemicarbazide **6a–f** (0.01 mol) was refluxed in aqueous NaOH solution (2 M, 50 mL). The reaction was monitored by TLC. After completion of the reaction (4 – 6 h), the reaction mixture was cooled and then acidified to pH = 3 – 4 with concentrated HCl. The precipitate formed was filtered, washed with cold water and recrystallized from ethanol-water (1:1).

*2-Heptyl-4-[(4-methyl-4,5-dihydro-5-thione-1H-1,2,4-triazol-3-yl)methyl]-5-(4-methoxybenzyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**7a**)*

M. p. 142 – 143 °C. Yield 87 %. – IR (KBr): $\nu = 3100$ (NH), 2960, 2857 (aliphatic CH), 1671 (triazole C=O), 1327 (C=S) cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 0.83$ (t, 3H, CH_3, $J = 6.8$ Hz), 1.22 – 1.23 (m, 8H, $4CH_2$), 1.58 – 1.62 (m, 2H, NCH_2CH_2), 3.35 (s, 3H, N-CH_3), 3.63 (t, 2H, NCH_2CH_2, $J = 6.8$ Hz), 3.70 (s, 3H, OCH_3), 3.83 (s, 2H, benzyl CH_2), 4.85 (s, 2H, N-CH_2-C=O); Ar-H: 6.79 (d, 2H, $J = 8.8$ Hz), 7.06 (d, 2H, $J = 8.8$ Hz); 13.52 (s, 1H, NH) ppm. – ^{13}C NMR ([D$_6$]DMSO): $\delta = 14.38$ (N-$(CH_2)_6CH_3$), 22.43 (N-$(CH_2)_5$-CH_2-CH_3), 26.22 (N-$(CH_2)_2$-CH_2-$(CH_2)_3CH_3$), 28.55 (2C, N-CH_2-CH_2-$(CH_2)_4$-CH_3 + N-$(CH_2)_3$-CH_2-$(CH_2)_2CH_3$), 30.32 (N-CH_3), 30.72 (N-$(CH_2)_4$-CH_2-CH_2CH_3), 31.60 (benzyl CH_2), 36.30 (N-CH_2-C=O), 44.82 (N-CH_2-$(CH_2)_5$-CH_3), 55.46 (OCH_3); Ar-C: 114.27 (2CH), 126.77, 129.99 (2CH), 158.62; 145.78 (triazole C-3′), 148.13 (triazole C-3), 153.37 (triazole C=O), 167.84 (triazole C=S) ppm. – Anal. for $C_{21}H_{30}N_6O_2S$ (430.57): calcd. C 58.58, H 7.02, N 19.52; found C 58.71, H 6.98, N. 19.60. – MS ((+)-ES, 70 eV): $m/z(\%) = 453.52$ (93) $[M+Na]^+$, 431.56 (58) $[M+H]^+$, 304.48 (12), 219.45 (100), 135.35 (52), 114.45 (21).

*2-Heptyl-4-[(4-ethyl-4,5-dihydro-5-thione-1H-1,2,4-triazol-3-yl)methyl]-5-(4-methoxybenzyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**7b**)*

M. p. 123 – 124 °C. Yield 85 %. – IR (KBr): $\nu = 3125$ (NH), 2926, 2859 (aliphatic CH), 1670 (triazole C=O), 1351 (C=S) cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 0.83$ (t, 3H, CH_3, $J = 6.8$ Hz), 1.06 (t, 3H, NCH_2CH_3, $J = 6.8$ Hz), 1.21 – 1.23 (m, 8H, $4CH_2$), 1.58 – 1.61 (m, 2H, NCH_2CH_2), 3.64 (t, 2H, NCH_2CH_2, $J = 6.8$ Hz), 3.70 (s, 3H, OCH_3), 3.84 (s, 2H, benzyl CH_2), 3.91 (q, 2H, NCH_2CH_3, $J = 6.8$ Hz), 4.87 (s, 2H, N-CH_2-C=O); Ar-H: 6.79 (d, 2H, $J = 8.8$ Hz), 7.05 (d, 2H, $J = 8.8$ Hz); 13.57 (s, 1H, NH) ppm. – ^{13}C NMR ([D$_6$]DMSO): $\delta = 13.48$ (N-CH_2CH_3), 14.38 (N-$(CH_2)_6CH_3$), 22.42 (N-$(CH_2)_5$-CH_2-CH_3), 26.22 (N-$(CH_2)_2$-CH_2-$(CH_2)_3CH_3$), 28.55 (2C, N-CH_2-CH_2-$(CH_2)_4$-CH_3 + N-$(CH_2)_3$-CH_2-$(CH_2)_2CH_3$), 30.75 (N-$(CH_2)_4$-CH_2-CH_2CH_3), 31.60 (benzyl CH_2), 36.17 (N-CH_2-C=O), 38.80 (N-CH_2CH_3), 44.87 (N-CH_2-$(CH_2)_5$-CH_3), 55.49 (OCH_3); Ar-C: 114.31 (2CH), 126.70, 130.05 (2CH), 158.64; 145.78 (triazole C-3′), 147.67 (triazole C-3), 153.29 (triazole C=O), 167.32 (triazole C=S) ppm. – Anal. for $C_{22}H_{32}N_6O_2S$ (444.60): calcd. C 59.43, H 7.25, N 18.90; found C 59.55, H 7.17, N. 19.07. – MS ((+)-ES, 70 eV): $m/z(\%) = 467.60$ (100) $[M+Na]^+$, 445.58 (58) $[M+H]^+$, 327.44 (20), 304.61 (10), 219.45 (55), 135.35 (58), 114.45 (29).

*2-Heptyl-4-[(4-phenyl-4,5-dihydro-5-thione-1H-1,2,4-triazol-3-yl)methyl]-5-(4-methoxybenzyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**7c**)*

M. p. 171 – 172 °C. Yield 80 %. – IR (KBr): $\nu = 3212$ (NH), 2956, 2856 (aliphatic CH), 1668 (triazole C=O),

1329 (C=S) cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 0.84$ (t, 3H, CH_3, $J = 6.8$ Hz), 1.18 – 1.25 (m, 8H, 4CH_2), 1.56 – 1.60 (m, 2H, NCH$_2$*CH*$_2$), 3.53 (t, 2H, N*CH*$_2$CH$_2$, $J = 6.8$ Hz), 3.71 (s, 5H, OCH_3 + benzyl CH_2), 4.58 (s, 2H, N-*CH*$_2$-C=O); Ar-H: 6.81 (d, 2H, $J = 8.4$ Hz), 7.02 (d, 2H, $J = 8.4$ Hz), 7.35 (d, 2H, $J = 7.6$ Hz), 7.52 (m, 3H); 13.81 (s, 1H, NH) ppm. – ^{13}C NMR ([D$_6$]DMSO): $\delta = 14.38$ (N-(CH$_2$)$_6$*CH*$_3$), 22.44 (N-(CH$_2$)$_5$-*CH*$_2$-CH$_3$), 26.22 (N-(CH$_2$)$_2$-*CH*$_2$-(CH$_2$)$_3$CH$_3$), 28.52 (N-(CH$_2$)$_3$-*CH*$_2$-(CH$_2$)$_2$CH$_3$), 28.56 (N-CH$_2$-*CH*$_2$-(CH$_2$)$_4$-CH$_3$), 30.64 (N-(CH$_2$)$_4$-*CH*$_2$-CH$_2$CH$_3$), 31.59 (benzyl CH_2), 36.85 (N-*CH*$_2$-C=O), 44.73 (N-*CH*$_2$-(CH$_2$)$_5$-CH$_3$), 55.51 (OCH_3); Ar-C: 114.35 (2CH), 126.73, 128.25 (2CH), 129.91 (CH), 130.05 (2CH), 130.11 (2CH), 133.22, 158.64; 145.39 (triazole C-3′), 147.51 (triazole C-3), 152.99 (triazole C=O), 168.26 (triazole C=S) ppm. – Anal. for $C_{26}H_{32}N_6O_2S$ (492.64): calcd. C 63.39, H 6.55, N 17.06; found C 63.51, H 6.49, N. 17.14. – MS ((+)-ES, 70 eV): $m/z(\%) = 515.24$ (10) [M+Na]$^+$, 493.67 (18) [M+H]$^+$, 461.25 (93), 389.59 (27), 368.46 (100), 355.42 (34), 338.43 (48), 317.43 (31).

*2-Heptyl-4-{[4-(4-fluorophenyl)-4,5-dihydro-5-thione-1H-1,2,4-triazol-3-yl]methyl}-5-(4-methoxybenzyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**7d**)*

M. p. 154 – 155 °C. Yield 78 %. – IR (KBr): $\nu = 3374$ (NH), 2928, 2855 (aliphatic CH), 1693 (triazole C=O), 1325 (C=S) cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 0.84$ (t, 3H, CH_3, $J = 6.8$ Hz), 1.17 – 1.25 (m, 8H, 4CH_2), 1.51 – 1.55 (m, 2H, NCH$_2$*CH*$_2$), 3.53 (t, 2H, N*CH*$_2$CH$_2$, $J = 6.8$ Hz), 3.71 (s, 3H, OCH_3), 3.73 (s, 2H, benzyl CH_2), 4.61 (s, 2H, N-*CH*$_2$-C=O); Ar-H: 6.81 (d, 2H, $J = 8.4$ Hz), 7.02 (d, 2H, $J = 8.4$ Hz), 7.35 – 7.40 (m, 4H); 13.83 (s, 1H, NH) ppm. – ^{13}C NMR ([D$_6$]DMSO): $\delta = 14.38$ (N-(CH$_2$)$_6$*CH*$_3$), 22.44 (N-(CH$_2$)$_5$-*CH*$_2$-CH$_3$), 26.21 (N-(CH$_2$)$_2$-*CH*$_2$-(CH$_2$)$_3$CH$_3$), 28.51 (N-(CH$_2$)$_3$-*CH*$_2$-(CH$_2$)$_2$CH$_3$), 28.56 (N-CH$_2$-*CH*$_2$-(CH$_2$)$_4$-CH$_3$), 30.65 (N-(CH$_2$)$_4$-*CH*$_2$-CH$_2$CH$_3$), 31.57 (benzyl CH_2), 36.75 (N-*CH*$_2$-C=O), 44.75 (N-*CH*$_2$-(CH$_2$)$_5$-CH$_3$), 55.51 (OCH_3); Ar-C: 114.35 (2CH), 116.81 (2CH, $J_{C-F} = 22.9$ Hz), 126.68, 129.45, 130.02 (2CH), 130.71 (2CH, $J_{C-F} = 9.3$ Hz), 158.64, 162.72 (C, $J_{C-F} = 245.5$ Hz); 145.36 (triazole C-3′), 147.54 (triazole C-3), 152.93 (triazole C=O), 168.98 (triazole C=S) ppm. – Anal. for $C_{26}H_{31}FN_6O_2S$ (510.63): calcd. C 61.16, H 6.12, N 16.46; found C 61.33, H 5.97, N. 16.52. – MS ((+)-ES, 70 eV): $m/z(\%) = 533.68$ (30) [M+Na]$^+$, 516.72 (100), 511.46 (20) [M+H]$^+$, 491.35 (18), 390.5 (23).

*2-Heptyl-4-{[4-(4-chlorophenyl)-4,5-dihydro-5-thione-1H-1,2,4-triazol-3-yl]methyl}-5-(4-methoxybenzyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**7e**)*

M. p. 168 – 169 °C. Yield 87 %. – IR (KBr): $\nu = 3200$ (NH), 2928, 2855 (aliphatic CH), 1707 (triazole C=O), 1315 (C=S) cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 0.84$ (t, 3H, CH_3, $J = 6.8$ Hz), 1.18 – 1.22 (m, 8H, 4CH_2), 1.51 – 1.54 (m, 2H, NCH$_2$*CH*$_2$), 3.52 (t, 2H, N*CH*$_2$CH$_2$, $J = 6.8$ Hz), 3.71 (s, 3H, OCH_3), 3.73 (s, 2H, benzyl CH_2), 4.63 (s, 2H, N-*CH*$_2$-C=O); Ar-H: 6.81 (d, 2H, $J = 8.8$ Hz), 7.00 (d, 2H, $J = 8.8$ Hz), 7.30 (d, 2H, $J = 8.4$ Hz), 7.70 (d, 2H, $J = 8.4$ Hz); 13.84 (s, 1H, NH) ppm. – ^{13}C NMR ([D$_6$]DMSO): $\delta = 14.38$ (N-(CH$_2$)$_6$*CH*$_3$), 22.45 (N-(CH$_2$)$_5$-*CH*$_2$-CH$_3$), 26.22 (N-(CH$_2$)$_2$-*CH*$_2$-(CH$_2$)$_3$CH$_3$), 28.50 (N-(CH$_2$)$_3$-*CH*$_2$-(CH$_2$)$_2$CH$_3$), 28.57 (N-CH$_2$-*CH*$_2$-(CH$_2$)$_4$-CH$_3$), 30.65 (N-(CH$_2$)$_4$-*CH*$_2$-CH$_2$CH$_3$), 31.59 (benzyl CH_2), 36.73 (N-*CH*$_2$-C=O), 44.76 (N-*CH*$_2$-(CH$_2$)$_5$-CH$_3$), 55.51 (OCH_3); Ar-C: 114.35 (2CH), 126.65, 129.93 (2CH), 130.02 (2CH), 130.21 (2CH), 132.06, 134.76, 158.65; 145.34 (triazole C-3′), 147.43 (triazole C-3), 152.90 (triazole C=O), 168.81 (triazole C=S) ppm. – Anal. for $C_{26}H_{31}ClN_6O_2S$ (527.08): calcd. C 59.25, H 5.93, N 15.94; found C 59.33, H 6.01, N. 16.10. – MS ((+)-ES, 70 eV): $m/z(\%) = 565.46$ (25) [M+K]$^+$, 549.51 (78) [M+Na]$^+$, 527.48 (61) [M]$^+$, 78.49 (100), 400.59 (23), 219.45 (42), 132.29 (56), 114.33 (42).

*2-Heptyl-4-{[4-(4-bromophenyl)-4,5-dihydro-5-thione-1H-1,2,4-triazol-3-yl]methyl}-5-(4-methoxybenzyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**7f**)*

M. p. 152 – 153 °C. Yield 85 %. – IR (KBr): $\nu = 3195$ (NH), 2929, 2854 (aliphatic CH), 1708 (triazole C=O), 1314 (C=S) cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): $\delta = 0.83$ (t, 3H, CH_3, $J = 6.8$ Hz), 1.18 – 1.25 (m, 8H, 4CH_2), 1.51 – 1.55 (m, 2H, NCH$_2$*CH*$_2$), 3.53 (t, 2H, N*CH*$_2$CH$_2$, $J = 6.8$ Hz), 3.71 (s, 5H, OCH_3 + benzyl CH_2), 4.63 (s, 2H, N-*CH*$_2$-C=O); Ar-H: 6.81 (d, 2H, $J = 8.8$ Hz), 7.00 (d, 2H, $J = 8.8$ Hz), 7.37 (d, 2H, $J = 8.4$ Hz), 7.54 (d, 2H, $J = 8.4$ Hz); 13.85 (s, 1H, NH) ppm. – ^{13}C NMR ([D$_6$]DMSO): $\delta = 14.40$ (N-(CH$_2$)$_6$*CH*$_3$), 22.45 (N-(CH$_2$)$_5$-*CH*$_2$-CH$_3$), 26.23 (N-(CH$_2$)$_2$-*CH*$_2$-(CH$_2$)$_3$CH$_3$), 28.51 (N-(CH$_2$)$_3$-*CH*$_2$-(CH$_2$)$_2$CH$_3$), 28.57 (N-CH$_2$-*CH*$_2$-(CH$_2$)$_4$-CH$_3$), 30.65 (N-(CH$_2$)$_4$-*CH*$_2$-CH$_2$CH$_3$), 31.60 (benzyl CH_2), 36.73 (N-*CH*$_2$-C=O), 44.76 (N-*CH*$_2$-(CH$_2$)$_5$-CH$_3$), 55.51 (OCH_3); Ar-C: 114.35 (2CH), 123.41, 126.63, 130.03 (2CH), 130.48 (2CH), 132.50, 132.87 (2CH), 158.65; 145.34 (triazole C-3′), 147.38 (triazole C-3), 152.90 (triazole C=O), 168.75 (triazole C=S) ppm. – Anal. for $C_{26}H_{31}BrN_6O_2S$ (571.54): calcd. C 54.64, H 5.47, N 14.70; found C 54.72, H 5.50, N. 14.81. – MS ((+)-ES, 70 eV): $m/z(\%) = 595.38$ (38) [M+Na]$^+$, 571.42 (35) [M]$^+$, 481.56 (22), 437.45 (30), 393.52 (48), 349.47 (50), 305.24 (28), 169.02 (50), 149.12(73), 135.10 (100), 119.15 (48).

*General method for the synthesis of compounds **8a–f***

A solution of the acetohydrazide derivative (**5**) (0.01 mol) in ethanol (50 mL) was refluxed with the appropriate alde-

hyde (0.01 mol) for 2 h. After 1 h, the crude product precipitated from the reaction medium. It was recrystallized from ethanol.

*2-[3-(4-Methoxybenzyl)-1-heptyl-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]-N′-[(2-hydroxyphenyl)methylidene]-acetohydrazide (**8a**)*

M. p. 206 – 207 °C. Yield 90 %. – IR (KBr): ν = 3210 (OH), 3178 (NH), 1710 (triazole C=O), 1690 (hydrazide C=O) cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): δ = 0.84 (t, 3H, CH_3, J = 6.8 Hz), 1.19 – 1.24 (m, 8H, 4CH_2), 1.58 – 1.60 (m, 2H, NCH$_2$*CH*$_2$), 3.63 (t, 2H, N*CH*$_2$CH$_2$, J = 6.8 Hz), 3.68 (s, 3H, OCH_3), 3.79 and 3.83 (s, 2H, benzyl CH_2, *trans* and *cis* conformers), 4.27 and 4.63 (s, 2H, N-*CH*$_2$- C=O, *cis* and *trans* conformers); Ar-H: 6.80 – 6.91 (m, 4H), 7.11 – 7.22 (m, 3H), 7.64 – 7.66 (m, 1H); 8.29 and 8.37 (s, 1H, N=CH, *trans* and *cis* conformers), 10.00 and 10.88 (s, 1H, OH, *trans* and *cis* conformers), 11.61 and 11.69 (s, 1H, NH, *trans* and *cis* conformers) ppm. – ^{13}C NMR ([D$_6$]DMSO): δ = 14.38 (N-(CH$_2$)$_6$*CH*$_3$), 22.43 (N-(CH$_2$)$_5$-*CH*$_2$-CH$_3$), 26.24 (N-(CH$_2$)$_2$-*CH*$_2$-(CH$_2$)$_3$CH$_3$), 28.62 (N-(CH$_2$)$_3$-*CH*$_2$-(CH$_2$)$_2$CH$_3$), 28.68 (N-CH$_2$-*CH*$_2$-(CH$_2$)$_4$-CH$_3$), 30.91 (N-(CH$_2$)$_4$-*CH*$_2$-CH$_2$CH$_3$), 31.62 (benzyl CH_2), 42.23 (N-*CH*$_2$- C=O), 44.72 (N-*CH*$_2$-(CH$_2$)$_5$-CH$_3$), 55.39 (OCH_3); Ar-C: 114.35 (2CH), 116.58 (CH), 116.80, 119.81 (CH), 126.58, 130.25 (2CH), 131.76 (CH), 131.99 (CH), 158.68, 163.14; 141.96 and 146.24 (N=CH, *trans* and *cis* conformers), 145.38 and 153.64 (triazole C-3, *trans* and *cis* conformers), 156.87 and 157.74 (triazole C-5, *trans* and *cis* conformers), 167.60 (C=O) ppm. The ratio of *trans*/*cis* conformers: 63.3 : 36.7. – Anal. for $C_{26}H_{33}N_5O_4$ (479.58): calcd. C 65.12, H 6.94, N 14.60; found C 65.31, H 6.90, N. 14.67. – MS ((+)-ES, 70 eV): m/z(%) = 502.45 (15) [M+Na]$^+$, 480.37 (41) [M+H]$^+$, 468.30 (31), 355.35 (22), 338.46 (27), 313 (48), 281. 08 (68), 277.20 (75), 270.25 (100), 253.05 (78).

*2-[3-(4-Methoxybenzyl)-1-heptyl-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]-N′-[(5-chloro-2-hydroxyphenyl)-methylidene]acetohydrazide (**8b**)*

M. p. 214 – 215 °C. Yield 92 %. – IR (KBr): ν = 3209 (OH), 3177 (NH), 1713 (triazole C=O), 1689 (hydrazide C=O) cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): δ = 0.83 (t, 3H, CH_3, J = 6.8 Hz), 1.21 – 1.26 (m, 8H, 4CH_2), 1.58 – 1.63 (m, 2H, NCH$_2$*CH*$_2$), 3.61 (t, 2H, N*CH*$_2$CH$_2$, J = 6.8 Hz), 3.67 (s, 3H, OCH_3), 3.78 and 3.82 (s, 2H, benzyl CH_2, *trans* and *cis* conformers), 4.27 and 4.67 (s, 2H, N-*CH*$_2$- C=O , *cis* and *trans* conformers); Ar-H: 6.81 – 6.99 (m, 3H), 7.12 – 7.39 (m, 2H), 7.61 – 7.76 (m, 1H), 8.93 (s, 1H); 8.23 and 8.34 (s, 1H, N=CH, *trans* and *cis* conformers), 10.33 and 11.17 (s, 1H, OH, *trans* and *cis* conformers), 11.67 and 11.93 (s, 1H, NH, *trans* and *cis* conformers) ppm. – ^{13}C NMR ([D$_6$]DMSO): δ = 14.38 (N-(CH$_2$)$_6$*CH*$_3$), 22.43 (N-(CH$_2$)$_5$-*CH*$_2$-CH$_3$), 26.23 (N-(CH$_2$)$_2$-*CH*$_2$-(CH$_2$)$_3$CH$_3$), 28.62 (N-(CH$_2$)$_3$-*CH*$_2$-(CH$_2$)$_2$CH$_3$), 28.68 (N-CH$_2$-*CH*$_2$-(CH$_2$)$_4$-CH$_3$), 30.90 (N-(CH$_2$)$_4$-*CH*$_2$-CH$_2$CH$_3$), 31.61 (benzyl CH_2), 42.34 (N-*CH*$_2$- C=O), 44.73 (N-*CH*$_2$-(CH$_2$)$_5$-CH$_3$), 55.40 (OCH_3); Ar-C: 114.32 (2CH), 118.50 (CH), 122.36, 123.74, 127.12, 130.25 (2CH), 131.14 (CH), 133.14 (CH), 158.61 (2C); 139.99 and 161.32 (N=CH, *trans* and *cis* conformers), 146.35 and 153.81 (triazole C-3, *trans* and *cis* conformers), 155.62 and 157.73 (triazole C-5, *trans* and *cis* conformers), 168.00 (C=O) ppm. The ratio of *trans*/*cis* conformers: 68.8 : 31.2 – Anal. for $C_{26}H_{32}ClN_5O_4$ (514.02): calcd. C 60.75, H 6.27, N 13.62; found C 60.87, H 6.15, N. 13.71. – MS ((+)-ES, 70 eV): m/z(%) = 536.20 (26) [M+Na]$^+$, 514.24 (8) [M]$^+$, 429.36 (12), 390.40 (17), 368.25 (33), 338.43 (46), 316.40 (72), 309.10 (100).

*2-[3-(4-Methoxybenzyl)-1-heptyl-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]-N′-[(2-hydroxy-5-methoxyphenyl)-methylidene]acetohydrazide (**8c**)*

M. p. 172 – 173 °C. Yield 95 %. – IR (KBr): ν = 3203 (OH), 3175 (NH), 1709 (triazole C=O), 1691 (hydrazide C=O) cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): δ = 0.83 (t, 3H, CH_3, J = 6.8 Hz), 1.21 – 1.25 (m, 8H, 4CH_2), 1.57 – 1.61 (m, 2H, NCH$_2$*CH*$_2$), 3.62 (t, 2H, N*CH*$_2$CH$_2$, J = 6.8 Hz), 3.68 (s, 3H, OCH_3), 3.77 and 3.83 (s, 2H, benzyl CH_2, *trans* and *cis* conformers), 4.27 and 4.65 (s, 2H, N-CH_2, *cis* and *trans* conformers); Ar-H: 6.80 – 6.84 (m, 3H), 6.88 – 6.91 (m, 2H), 6.99 – 7.17 (m, 1H), 7.25 – 7.26 (m, 1H); 8.27 and 8.35 (s, 1H, N=CH, *trans* and *cis* conformers), 10.39 and 11.07 (s, 1H, OH, *trans* and *cis* conformers), 11.62 and 12.01 (s, 1H, NH, *trans* and *cis* conformers) ppm. – ^{13}C NMR ([D$_6$]DMSO): δ = 14.37 (N-(CH$_2$)$_6$*CH*$_3$), 22.44 (N-(CH$_2$)$_5$-*CH*$_2$-CH$_3$), 26.25 (N-(CH$_2$)$_2$-*CH*$_2$-(CH$_2$)$_3$CH$_3$), 28.62 (N-(CH$_2$)$_3$-*CH*$_2$-(CH$_2$)$_2$CH$_3$), 28.67 (N-CH$_2$-*CH*$_2$-(CH$_2$)$_4$-CH$_3$), 30.92 (N-(CH$_2$)$_4$-*CH*$_2$-CH$_2$CH$_3$), 31.61 (benzyl CH_2), 42.32 (N-*CH*$_2$- C=O), 44.73 (N-*CH*$_2$-(CH$_2$)$_5$-CH$_3$), 55.38 (OCH_3); Ar-C: 113.49 (CH), 114.33 (2CH), 117.62 (CH), 118.75, 120.71, 127.11, 130.27 (2CH), 158.61, 163.22; 141.68 and 162.48 (N=CH, *trans* and *cis* conformers), 146.38 and 153.80 (triazole C-3, *trans* and *cis* conformers), 152.58 and 152.71 (triazole C-5, *trans* and *cis* conformers), 167.81 (C=O) ppm. The ratio of *trans*/*cis* conformers: 63.8 : 36.2. – Anal. for $C_{27}H_{35}N_5O_5$ (509.61): calcd. C 63.64, H 6.92, N 13.74; found C 63.79, H 7.05, N 13.78. – MS ((+)-ES, 70 eV): m/z(%) = 532.55 (42) [M+Na]$^+$, 510.52 (10) [M+H]$^+$, 438.51 (5), 240.35 (20), 224.33 (39), 196.36 (98), 182.34 (82), 135.23 (86), 132.29 (100), 119.21 (53).

*2-[3-(4-Methoxybenzyl)-1-heptyl-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]-N′-[(2-hydroxy-5-nitrophenyl)-methylidene]acetohydrazide (**8d**)*

M. p. 286 – 287 °C. Yield 87 %. IR (KBr, ν, cm^{-1}), 3270 (OH), 3184 (NH), 1715 (triazole C=O), 1687 (hydrazide C=O) cm^{-1}. – ^{1}H NMR ([D$_6$]DMSO): δ = 0.83 (bs, 3H, CH_3), 1.22 (bs, 8H, $4CH_2$), 1.59 (bs, 2H, NCH_2CH_2), 3.63 (bs, 2H, NCH_2CH_2), 3.66 (s, 3H, OCH_3), 3.79 and 3.82 (s, 2H, benzyl CH_2, *trans* and *cis* conformers), 4.28 and 4.69 (s, 2H, N-CH_2- C=O, *cis* and *trans* conformers); Ar-H: 6.80 – 6.85 (m, 2H), 7.06 – 7.13 (m, 2H), 8.11 – 8.14 (m, 1H), 8.25 – 8.27 (s, 1H), 9.06 (s, 1H); 8.47 and 8.53 (s, 1H, N=CH, *trans* and *cis* conformers), 11.67 and 11.79 (s, 1H, OH, *trans* and *cis* conformers), 11.93 and 12.00 (s, 1H, NH, *trans* and *cis* conformers). – ^{13}C NMR ([D$_6$]DMSO): δ = 14.37 (N-$(CH_2)_6CH_3$), 22.43 (N-$(CH_2)_5$-CH_2-CH_3), 26.23 (N-$(CH_2)_2$-CH_2-$(CH_2)_3CH_3$), 28.61 (2C, N-$(CH_2)_3$-CH_2-$(CH_2)_2CH_3$ + N-CH_2-CH_2-$(CH_2)_4$-CH_3), 30.91 (N-$(CH_2)_4$-CH_2-CH_2CH_3), 31.61 (benzyl CH_2), 42.33 (N-CH_2- C=O), 44.71 (N-CH_2-$(CH_2)_5$-CH_3), 55.36 (OCH_3); Ar-C: 114.32 (2CH), 116.93 (CH), 117.92, 121.77 (CH), 125.47 (CH), 127.09, 130.29 (2CH), 140.40, 158.60, 164.14; 139.18 and 161.24 (N=CH, *trans* and *cis* conformers), 146.36 and 154.01 (triazole C-3, *trans* and *cis* conformers),155.80 and 157.84 (triazole C-5, *trans* and *cis* conformers),168.10 (C=O) ppm. The ratio of *trans*/*cis* conformers: 66.2 : 33.8. – Anal. for $C_{26}H_{32}N_6O_6$ (524.58): calcd. C 59.53, H 6.15, N 16.02; found C 59.64, H 6.08, N. 16.27. – MS ((+)-ES, 70 eV): m/z(%) = 563.46 (34) $[M+K]^+$, 547.63 (100) $[M+Na]^+$, 525.54 (31) $[M+H]^+$, 495.44 (10), 449.52 (10), 323.44 (15).

Pharmacology

Anti-lipase activity assay

The inhibitory effects of the compounds were evaluated against Porcine Pancreatic Lipase (obtained from Applichem, Germany) (15 ng mL^{-1}). Lipase activity assays were performed according to Kurihara et al. [67]. The lipase activity was measured using 4-methylumbelliferyl oleate (4-MU oleate) as a substrate. Briefly, compounds were mixed with PPL 1 : 3 (v/v) and incubated for 30 min. The microtiter plates containing 50 μL 0.1 mM 4-MU oleate, 25 μL diluted compound-lipase solution, 25 μL H_2O and assay buffer (13 mM Tris–HCl, 150 mM NaCl, and 1.3 mM $CaCl_2$, pH = 8.0) were incubated at 37 °C for 20 min. After incubation, in order to stop the reaction, 0.1 mL 0.1 M citrate buffer was added to the reaction mixture. The amount of 4-methylumbelliferone released by the lipase was measured by using a spectrofluorometer (SpectraMax M5, Molecular Devices) at an excitation wavelength of 355 nm and an emission wavelength of 460 nm. The inhibitory activity of these compounds and Orlistat (Xenical, Hoffman, La Roche, Segrate, Italy), an inhibitor control of pancreatic lipase, were measured at various concentration. Residual activities were calculated by comparing to a control without inhibitor. The assays were done in triplicate. The IC_{50} values were determined as the concentration of a compound that gave 50 % inhibition of maximal activity.

α-Glucosidase inhibition assay

The α-glucosidase inhibition assay was performed spectrophotometrically. α-Glucosidase from *Saccharomyces cerevisiae* (Sigma-Aldrich) was dissolved in phosphate buffer (pH = 6.8, 50 mM). The test compounds were dissolved in 80 % methanol. In 96-well microtiter plates, 20 μL of the test sample, 20 μL of the enzyme (200 mU mL^{-1}) and 135 μL of the buffer were added and incubated for 15 min at 37 °C. After incubation, 25 μL of *p*-nitrophenyl-α-D-glucopyranoside (2 mM, Sigma-Aldrich) was added, and the change in absorbance was monitored for 30 min at 400 nm. The test compound was replaced by 80 % methanol (7.5 % final concentration) as control. Acarbose (Sigma-Aldrich) was used as a standard inhibitor [68].

Anti-mycobacterial activity assay

Mycobacterium smegmatis ATCC 607 was obtained from the Hifzissihha Institute of Refik Saydam (Ankara, Turkey). All compounds were weighed and dissolved in dimethyl sulfoxide (DMSO) to prepare an extract stock solution of 20 mM. The anti-mycobacterial assay was performed in Brain Heart Infusion broth (BHI) (Difco, Detriot, MI). Streptomycin (10 μg) was used as standard anti-mycobacterial drug. DMSO was used as solvent control. Five-millimeter diameter wells were cut from the agar using a sterile cork-borer, and 50 μL of the compound was delivered into the wells. The petri dishes were incubated for 48 – 72 h at 35 °C [69]. Anti-mycobacterial activity was evaluated by measuring the inhibition zone against the test organism. The test was done in duplicate.

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