ANTIOXIDANT PROPERTIES OF 1,2,4-TRIAZOLES

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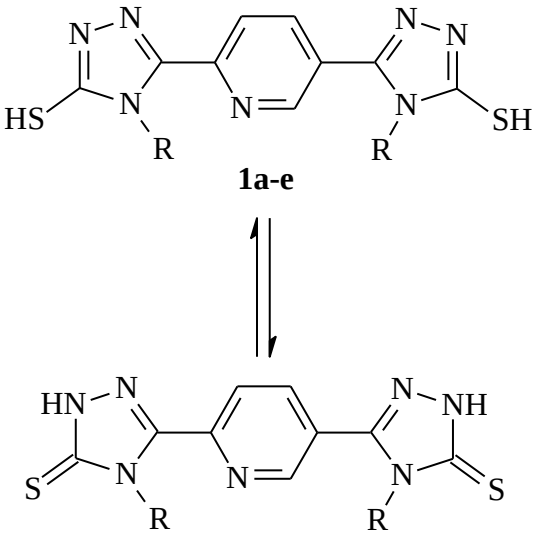
In recent years, interest in endogenous and exogenous antioxidants that delay or prevent the oxidation of biomolecules has been increasing. The production of synthetic antioxidants that do not harm the organism and their effects on oxidant-antioxidant balance in biological systems are being investigated (Hussain et al., 2003). Endogenous chemicals formed from exogenous and metabolic reactions can form highly reactive free radicals. Oxygen-origin radicals can oxidize biomolecules to cause cell damage and cell death. Oxidative stress plays an essential role in the pathology of diseases. Excessive production of reactive oxygen species (ROS) and insufficient antioxidant capacity cause various physio-pathological events in organisms such as inflammation, diabetes, genotoxicity, and cancer (McClements & Decker, 2000). Moreover, there are claims that oxidative stress plays a crucial role in tissue damage related to various diseases such as cancer, rheumatoid arthritis, osteoporosis, polycystic ovarian syndrome, Alzheimer's, and Parkinson's (Harmankaya et al., 2021; Phaniendra et al., 2015). Many natural or synthetic antioxidants, known as exogenous, are believed to affect health and disease prevention positively (Harmankaya & Harmankaya, 2022).

Considering that 1,2,4-triazole fused heterocycles have antioxidant properties besides some other biological activities, in this section different 1,2,4-triazole derivatives are discussed in terms of their antioxidant abilities.

Bulut et al. synthesized a novel 1,2,4-triazole-3-thiol series (Figure 1) and evaluated them for *in vitro* antioxidant activity. Among the synthesized compounds, the derivative 1a substituted with the aromatic phenyl group showed the highest DPPH$^{\cdot}$ scavenging activity, while bulk substituted 1e showed the least activity (Bulut et al., 2018).

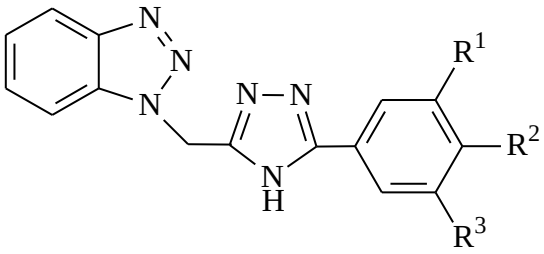


1a-e

a: R=phenyl
b: R=ethyl
c: R=3-methoxyphenyl
d: R=1-naphtyl
e: R=3-(4-morpholino)propyl

Figure 1. 5,5′-pyridine-2,5-diylbis (4-substituted 4*H*-1,2,4-triazole-3-thiol) series (Bulut et al., 2018).

Some new 1-(((aryl)-3-yl)-4*H*-(1,2,4)-triazol-5-ylmethyl)-1*H*-benzotriazoles have been synthesized and then evaluated for their antimicrobial and antioxidant activities. The study reported that the presence of the -*OH* group at the *para* positions in 2a and 2b (Figure 2) made these compounds good antioxidants due to possible extended conjugation after hydrogen radical abstraction (Chand et al., 2018).



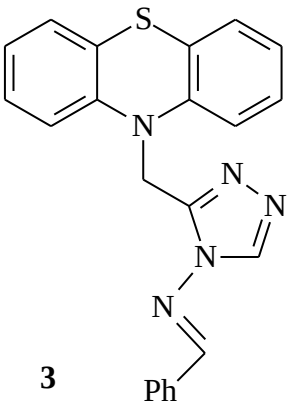
2

2a R^1=H, R^2=OH, R^3=OCH_3
2b R^1=R^3=H, R^2=OH

Figure 2. 1-Substitue-4*H*-(1,2,4)-triazol-5-ylmethyl)-1*H*-benzotriazoles (Chand et al., 2018).

A series of novel 5-((10*H*-phenothiazin-10yl)methyl)-4-(substitutedbenzylidene-amino)-4*H*-1,2,4-triazole-3-thiol derivatives (3a-i) synthesized. All the novel compounds (Figure 3) were screened for their *in vitro* antioxidant activity by using nitric oxide, hydrogen peroxide, and

DPPH· scavenging assays. Compounds 3d, 3e and 3i showed potent antioxidant activity (Maddila et al., 2015).



3

a: Ph=4-Br
b: Ph=4-Cl
c: Ph=4-F
d:Ph=4-MeO
e: Ph=4-OH
f: Ph=2,4-Cl
g: Ph=2,5-Br
h: Ph=3,5-F
i: Ph=3,5-MeO

Figure 3. 5-((10*H*-Phenothiazin-10yl)methyl)-4-(substitutedbenzylideneamino)-4*H*-1,2,4-triazole-3-thiol compounds (Maddila et al., 2015).

Ünver et al. prepared novel tiophene-1,2,4-triazole-5(3)-ones (Figure 4) and evaluated their antioxidant capacity by ferric reducing antioxidant power (FRAP) assay and DPPH radical scavenging assay. The results revealed that all the compounds were active in FRAP assay, while thiosemicarbazide derivatives (4a-d) were very active and triazole-thiol derivatives (5a-d) and Schiff bases 6d and 7d showed low activity in DPPH· scavenging assay (Ünver et al., 2014).

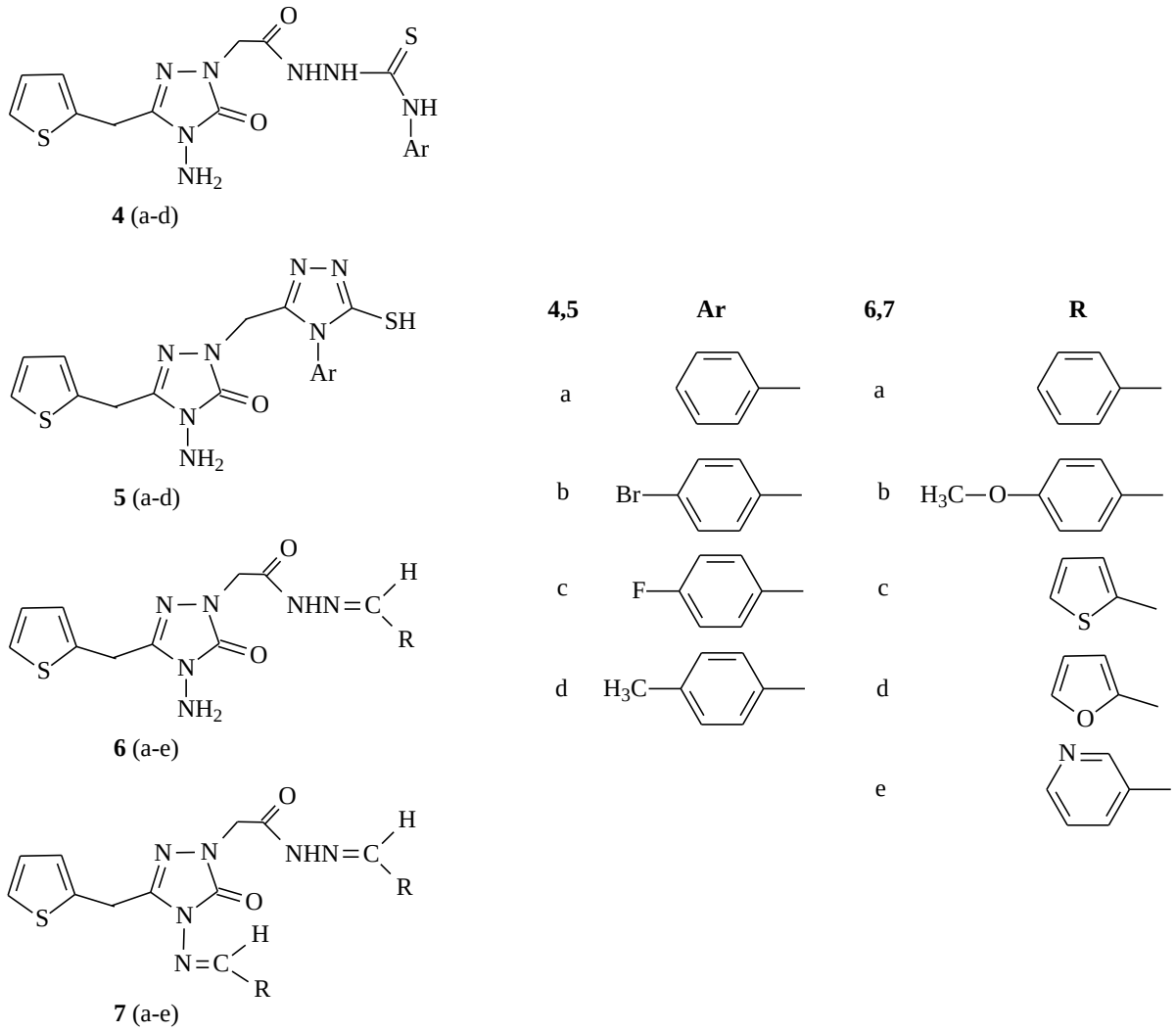


Figure 4. Structures of compounds 4, 5, 6 and 7 (Ünver et al., 2014).

Cetin and Gecibesler synthesized a series of 1,2,4-triazole derivative compounds (Figure 5) substituted with groups of phenol and pyridine and screened their antioxidant properties by various antioxidant assays to determine the effect of substituted functional groups to 1,2,4-triazole rings. The present study demonstrated that phenol and pyridine substituted 1,2,4-triazole compounds would be a better perspective in developing antioxidant agents (Cetin & Gecibesler, 2015).

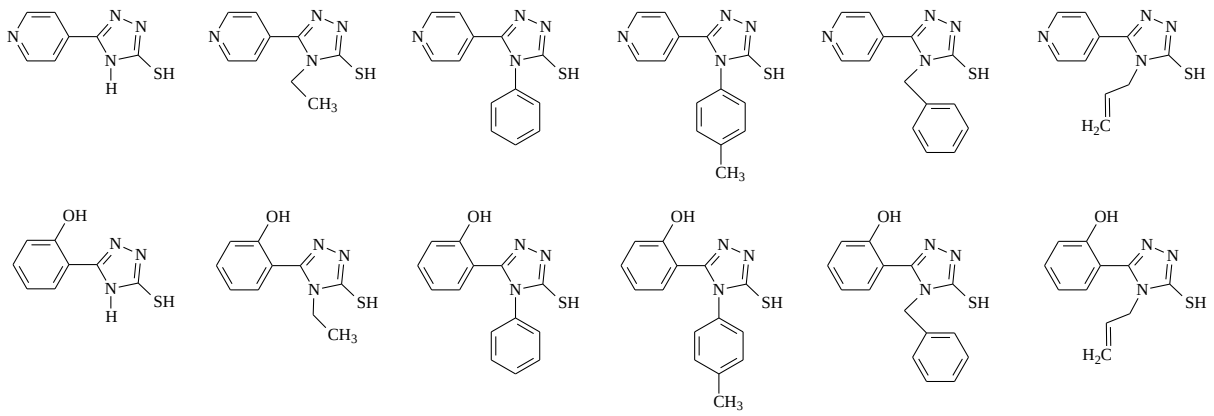


Figure 5. Structures of 1,2,4-triazole derivatives (Cetin & Gecibesler, 2015).

Yehye et al. synthesized new derivatives of the antioxidant butylated hydroxytoluene (BHT), which are Schiff base-1,2,4-triazoles as a new multipotent antioxidant series (Figure 6). The synthesized compounds were screened by DPPH radical scavenging bioassay to determine their antioxidant activities. The synthesized compounds inhibited stable DPPH free radicals at a level 10^{-4} M higher than the standard antioxidant BHT (Yehye et al., 2016).

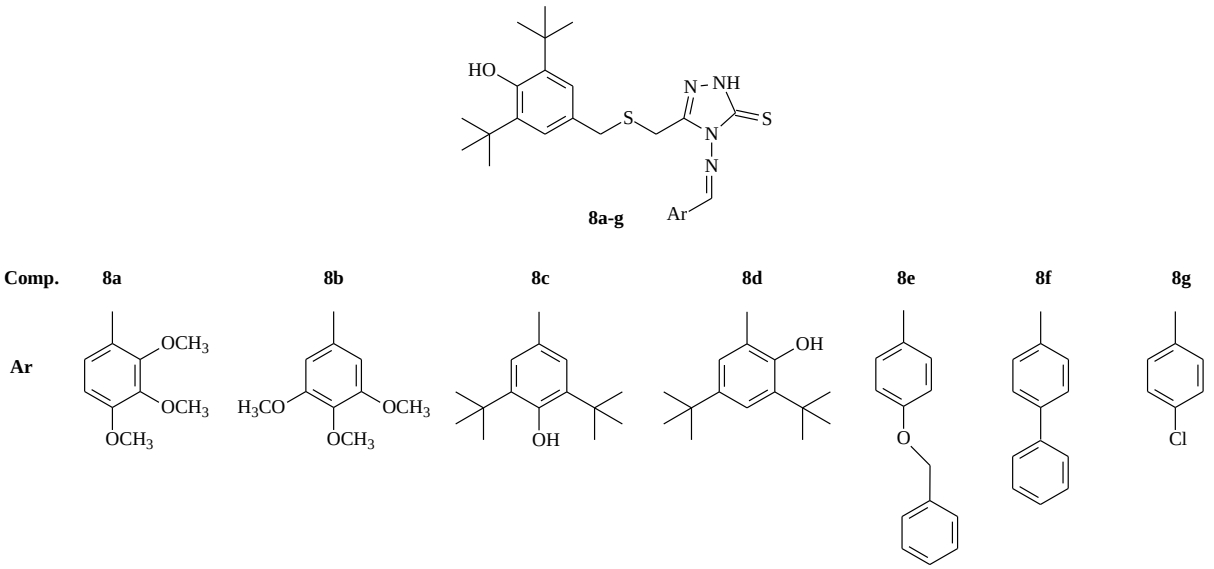
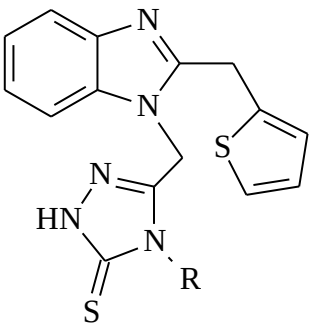


Figure 6. A novel series of 4-(Substituted benzylideneamino)-3-(3,5-di-tert-butyl-4-hydroxybenzyl thio)methyl)-1*H*-1,2,4-triazole-5(4H)-thiones (Yehye et al., 2016).

A series of 4-substitute-5-{[2-(thiophen-2-ylmethyl)-1*H*-benzimidazol-1-yl]methyl}-4*H*-1,2,4-triazole-3-thiones (Figure 7) were synthesized and their antioxidant activities were determined with Cupric Reducing Antioxidant Capacity (CUPRAC), ABTS (2,2-azinobis(3-ethylbenzothiazoline-6-sulfonic acid)/persulfate, and DPPH (1,1-diphenyl-2-picrylhydrazyl)

assays. Compound 9f demonstrated very good antioxidant capacity in the CUPRAC method. Compounds 9a-d and 9f showed very good ABTS scavenging activity (Menteşe et al., 2015).



9

R= **a**: CH_3, **b**: CH_2CH_3, **c**: C_6H_5, **d**: *p*-C_6H_4-F, **e**: *p*-C_6H_4-Br, **f**: *m*-C_6H_4-I, **g**: *p*-C_6H_4-CH_3, **h**: *p*-C_6H_4-NO_2

Figure 7. A novel series of 4*H*-1,2,4-triazole-3-thione derivatives (Menteşe et al., 2015).

In 2014, novel triazole-thiol derivatives obtained, and their antioxidant properties was screened by DPPH· scavenging method. 4,4'-(Butane-1,4-diyl/Hexane-1,6-diyl)-bis(2-((4-(4-halogenophenyl)-5-mercapto-4*H*-1,2,4-triazole-3-yl)methyl)-5-methyl-2*H*-1,2,4-triazole-3(4*H*)-one compounds 10a / 10b / 11a / 11b (Figure 8) showed moderate activity with IC50 value of 40 ± 2.7 / 40 ± 0.9 / 36 ± 0.9 / 10 ± 0.7, respectively. BHT was used as a positive control with IC50 value of 19.8 ± 0.5 (Düğdü et al., 2014).

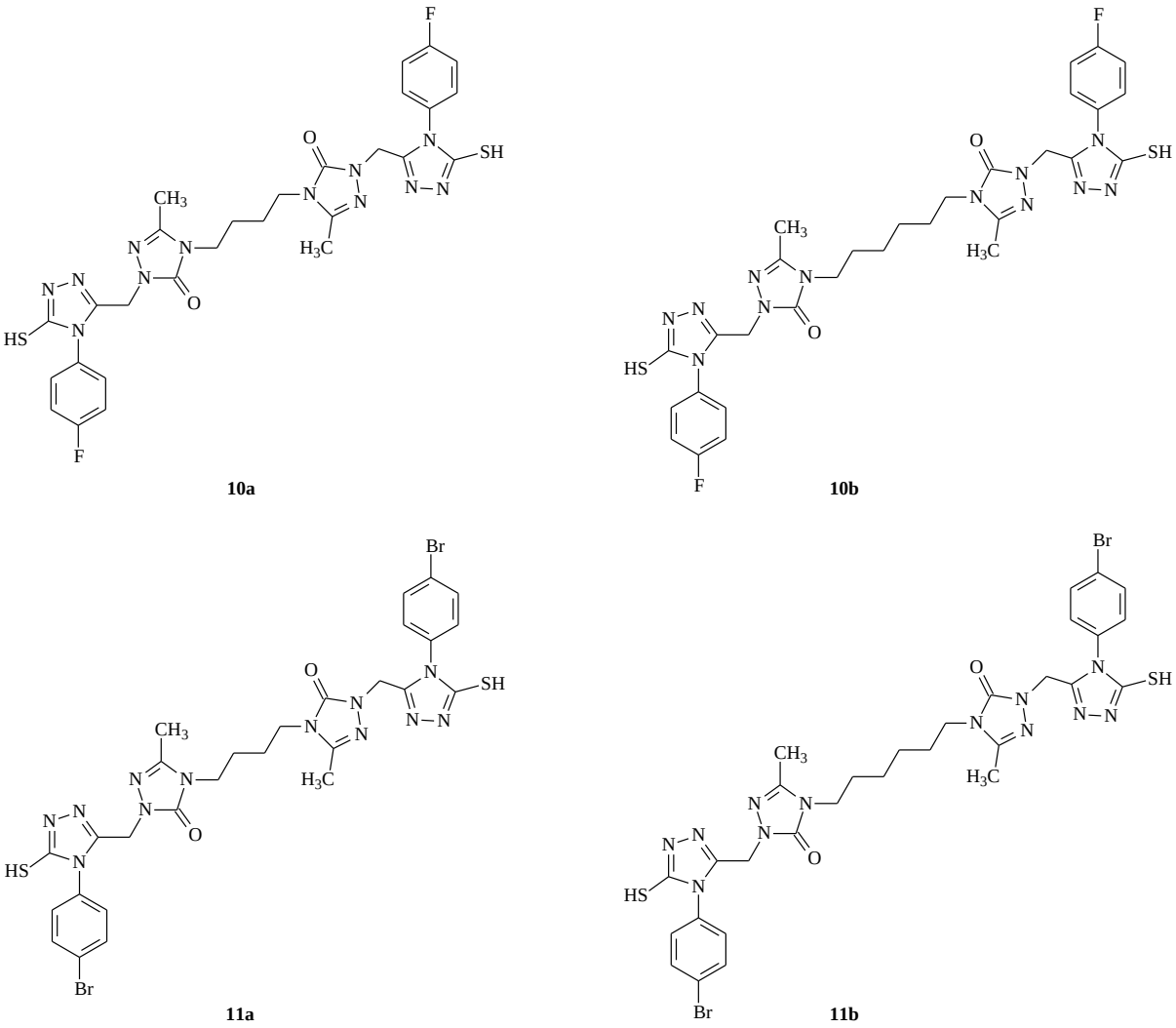


Figure 8. Structures of compounds 10a, 10b, 11a and 11b (Düğdü et al., 2014).

Barbuceanu et al. prepared a novel series of 1,2,4-triazole-3-thiones (12-14) and S-alkylated 1,2,4-triazoles (15–20) (Figure 9). The free radical scavenging activity of the compounds was carried out by DPPH· assay using ascorbic acid, *tert*-butyl-4-hydroxyanisole (BHA) and BHT antioxidant agents as the positive control. The inhibitory effect of 1,2,4-triazole-3-thiones was good, but S-alkylated 1,2,4-triazoles had a weak effect at the same concentration (Barbuceanu et al., 2014).

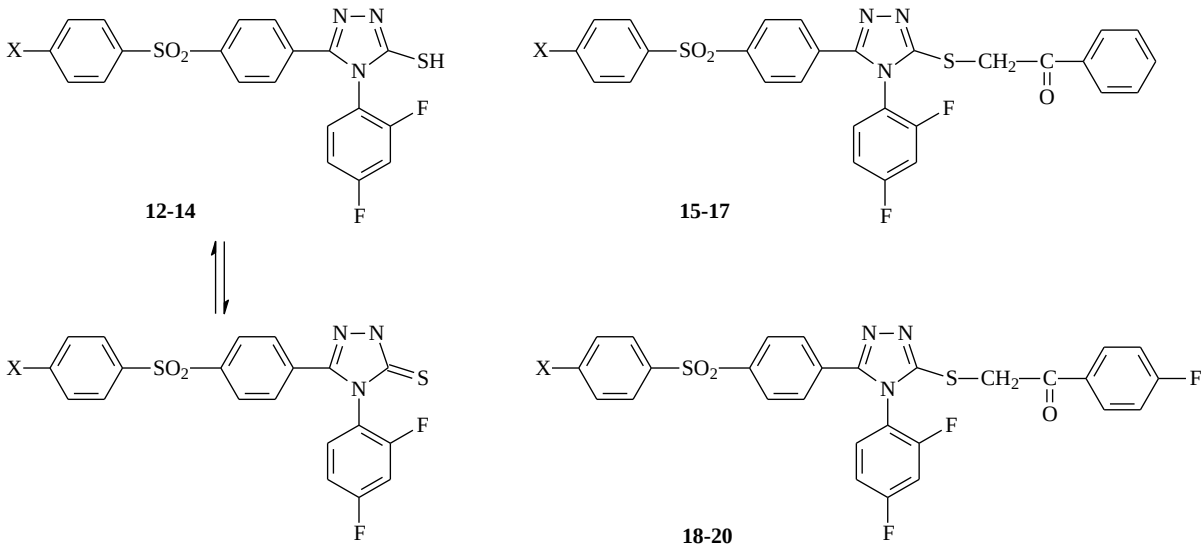


Figure 9. Novel series of 1,2,4-triazole-3-thiones (12-14) and S-alkylated 1,2,4-triazoles. X=H: 12, 15, 18; X=Cl: 13, 16, 19; X=Br: 14, 17, 20 (Barbuceanu et al., 2014).

4-Amino-3-(4-(((4-hydroxy-3,5-dimethoxybenzyl)-oxy)-methyl)-phenyl)-1,2,4-triazole-5-thione (21) and a series of its new Schiff Bases, 4-((arylidine)amino)-3-(4-(((4-hydroxy-3,5-dimethoxybenzyl)-oxy)-methyl)-phenyl)-1,2,4-triazole-5-thiones (22a-f), synthesized. Then the compounds (Figure 10) were tested for antioxidant activity by DPPH· and FRAP assays. All the compounds showed high antioxidant ability in both assays, especially compound 21. Within the Schiff bases, compound 22e exhibited higher antioxidant ability in both assays. The study was revealed that the type substituted in hydroxybenzylidene played a significant role in enhancing antioxidant ability (Hussain, 2016).

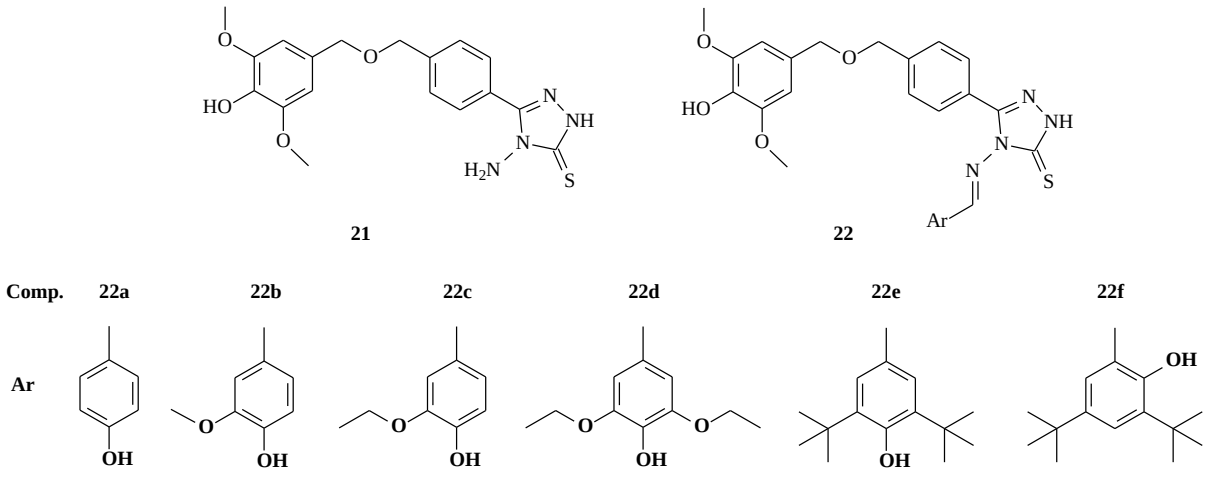
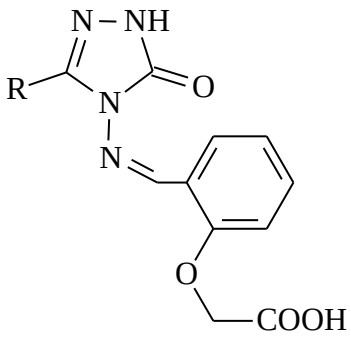


Figure 10. Structures of compounds 21, 22 (Hussain, 2016).

Çiftçi et al. synthesized a novel series of 2-[3-alkyl(aryl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl] phenoxyacetic acids (Figure 11) which were analyzed for their *in vitro* antioxidant and antibacterial properties. The compounds were also tested in the comet assay. Reducing power, free radical scavenging and metal chelating activity was used to determine the antioxidant activity. 2-(3-*p*-Methoxybenzyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-phenoxyacetic acid (23f) and 2-(3-*m*-chlorobenzyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-phenoxyacetic acid (23h) compounds demonstrated significant activity in the metal chelating activity, antimicrobial and comet assay tests (Çiftçi et al., 2018).

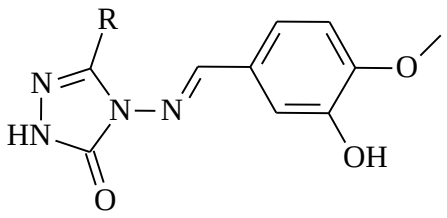


23

R= **a**: CH_3, b: CH_2CH_3, **c**: $CH_2CH_2CH_3$, **d**: $CH_2C_6H_5$, **e**: $CH_2C_6H_4CH_3$ (*p*-), **f**: $CH_2C_6H_4OCH_3$ (*p*-), **g**: $CH_2C_6H_4$.Cl (*p*-), **h**: $CH_2C_6H_4$.Cl (*m*-), **i**: C_6H_5

Figure 11. 2-[3-alkyl(aryl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl] phenoxyacetic acids (Çiftçi et al., 2018).

A series of new 3-alkyl(aryl)-4-(3-hydroxy-4-methoxybenzylideneamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones were synthesized (Figure 12). The synthesized compounds were analyzed for their *in vitro* antioxidant activities using three methods. Compounds 24f and 24h showed significant activity for iron chelating and DPPH radical scavenging activity (Bahçeci et al., 2016).

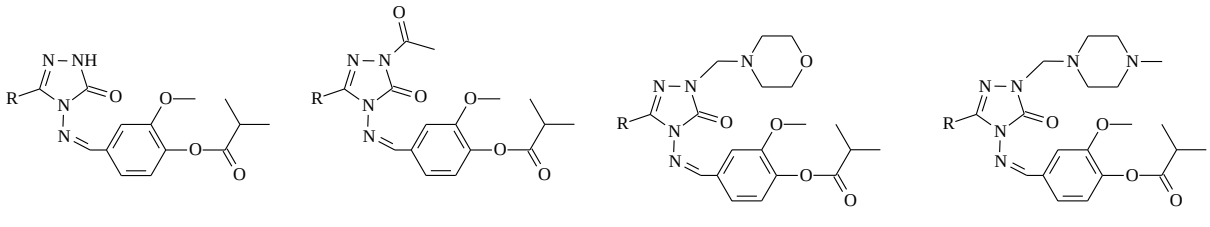


24

24	R
a	CH_3
b	CH_2CH_3
c	$CH_2CH_2CH_3$
d	$CH_2C_6H_5$
e	$CH_2C_6H_4.CH_3$ (*p*-)
f	$CH_2C_6H_4.OCH_3$ (*p*-)
g	$CH_2C_6H_4.Cl$ (*p*-)
h	$CH_2C_6H_4.Cl$ (*m*-)
i	C_6H_5
j	cyclopropyl

Figure 12. A series of new 3-alkyl(aryl)-4-(3-hydroxy-4-methoxybenzylideneamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (Bahçeci et al., 2016).

In 2020, some new Schiff bases and their Mannich bases (25-28) were synthesized, and *in vitro* antioxidant and antimicrobial properties of the new compounds were investigated (Figure 13). Three different methods were used for the determination of antioxidant activity. BHT, BHA, EDTA and α-tocopherol were used as the reference antioxidants. The results of some compounds were not considered as they were not significant. The scavenging effect of the compounds and references decreased in order of α-tocopherol > BHA > BHT > 28a > 25c > 25e > 27b > 25a > 25b > 25i > 28d, which were 74.9, 74.3, 65.8, 19.3, 16.0, 12.4, 9.6, 9.3, 8.2, 7.2, 5.3 (%), at the highest concentration, respectively. The compounds, except 25c-e, demonstrated a marked capacity for iron binding. Mannich bases were more active when compared to Schiff bases for all concentrations (Manap et al., 2020).

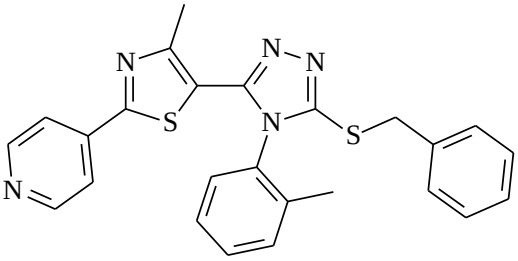


25 **26** **27** **28**

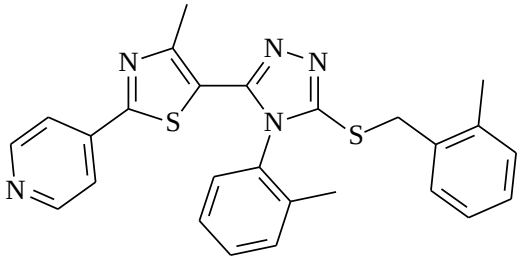
R= **a**: CH_3, b: CH_2CH_3, **c**: $CH_2CH_2CH_3$, **d**: $CH_2C_6H_5$, **e**: $CH_2C_6H_4CH_3$ (*p*-), **f**: $CH_2C_6H_4OCH_3$ (*p*-), **g**: $CH_2C_6H_4.Cl$ (*p*-), **h**: $CH_2C_6H_4.Cl$ (*m*-), **i**: C_6H_5

Figure 13. Structures of compounds 25-28 (Manap et al., 2020).

Tay et al. synthesized 63 different 5-[4-methyl-2-(pyridin-3/4-yl)thiazole-5-yl]-4-substituted-3-substitutedbenzylthio-4*H*-1,2,4-triazole derivatives and screened for their antibacterial, antifungal, and antioxidant properties. The compounds possessing 4-pyridyl moiety displayed marked antioxidant activity, especially compounds 29 and 30 (Figure 14) showed the highest antioxidant activity (Tay et al., 2022).



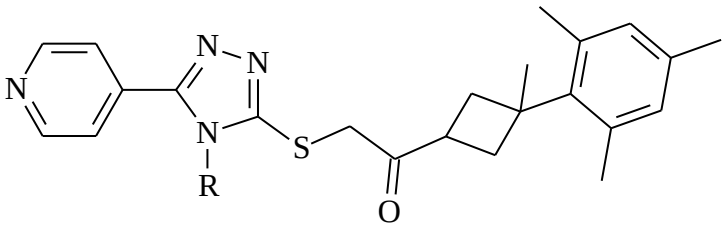
29



30

Figure 14. 5-[4-Methyl-2-(pyridin-4-yl)thiazole-5-yl]-4-(2-methylphenyl)-3-benzylthio-4*H*-1,2,4-triazole (29) and 5-[4-Methyl-2-(pyridin-4-yl)thiazole-5-yl]-4-(2-methylphenyl)-3-(2-methylbenzylthio)-4*H*-1,2,4-triazole (30) (Tay et al., 2022).

3,4,5-Trisubstituted 1,2,4-triazole sulfonyl compounds containing a cyclobutane ring (Figure 15) were synthesized and evaluated for their antioxidant, antimicrobial, and anti-cancer effects. Compounds 31c and 31e showed activity close to the reference antioxidant BHT. Compound 31d exhibited moderate activity, while compounds 31a and 31b showed the lowest activity (Koparir et al., 2022).

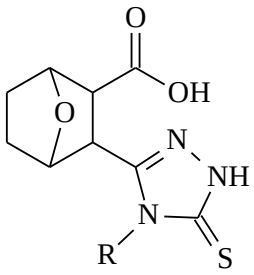


31

R= **a:** Ethyl, **b:** Allyl, **c:** Phenyl, **d:** Benzyl, **e:** *p*-Tolyl

Figure 15. Structures of compound 31 (Koparir et al., 2022).

In 2019, new norcantharidin analogs with the 1,2,4-triazole system (Figure 16) were obtained and screened for antioxidant activities. Promising activity with EC50=10.75 μg/ml presented compound 32f compared to the reference antioxidant Trolox (EC50=6.13 μg/ml) (Pachuta-Stec et al., 2019).



32

R= **a**: C_6H_5, **b**: C_6H_4.Cl (*o*-), **c**: C_6H_4.Cl (*p*-), **d**: C_6H_4.F (*p*-), **e**: $C_6H_4.CH_3$ (*o*-), **f**: CH_2CH_3, **g**: 2-(Morpholin-4-yl)ethyl

Figure 16. Norcantharidin analogs with the 1,2,4-triazole system (Pachuta-Stec et al., 2019).

Aouali et al. synthesized new imidazo[2,1-c][1,2,4]triazole derivatives and tested some of them (Figure 17) for their antibacterial, antifungal and antioxidant activities. The compounds were screened for *in vitro* antioxidant activity using DPPH· scavenging assay and exhibited significant effects compared to the reference antioxidants BHA and α-tocopherol. DPPH· scavenging capacities of the compounds were in the following order: 36 > 33 > 34 > 35. Compound 34 showed significant antifungal and antioxidant activity, suggesting a possible clinical significance (Aouali et al., 2015).

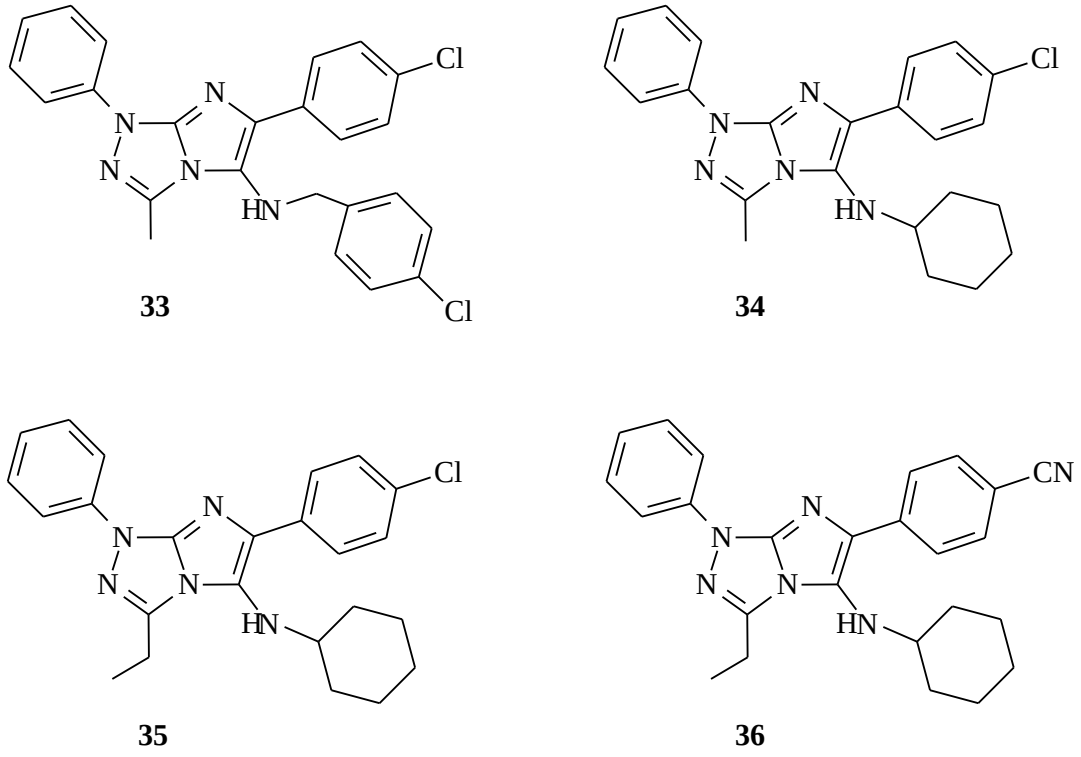


Figure 17. Structures of imidazo[2,1-c][1,2,4]triazole derivatives (Aouali et al., 2015).

Bekircan et al. obtained a series of 1,2,4-triazole derivatives containing fluorine (Figure 18) and screened them for potential antioxidant activity, and urease and xanthine oxidase inhibition activities. CUPRAC assay, 2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS), and DPPH methods were used to determine the synthesized compounds' antioxidant activities. Compounds 44a and 44b displayed the highest antioxidant capacity for the CUPRAC method and showed significant DPPH radical scavenging activity. Finally, according to the CUPRAC and ABTS methods; 38a, 38b, 40a, 40b, 41a, 41b, 43a, 43b, 44a, and 44b compounds showed good antioxidant activity (Bekircan et al., 2016).

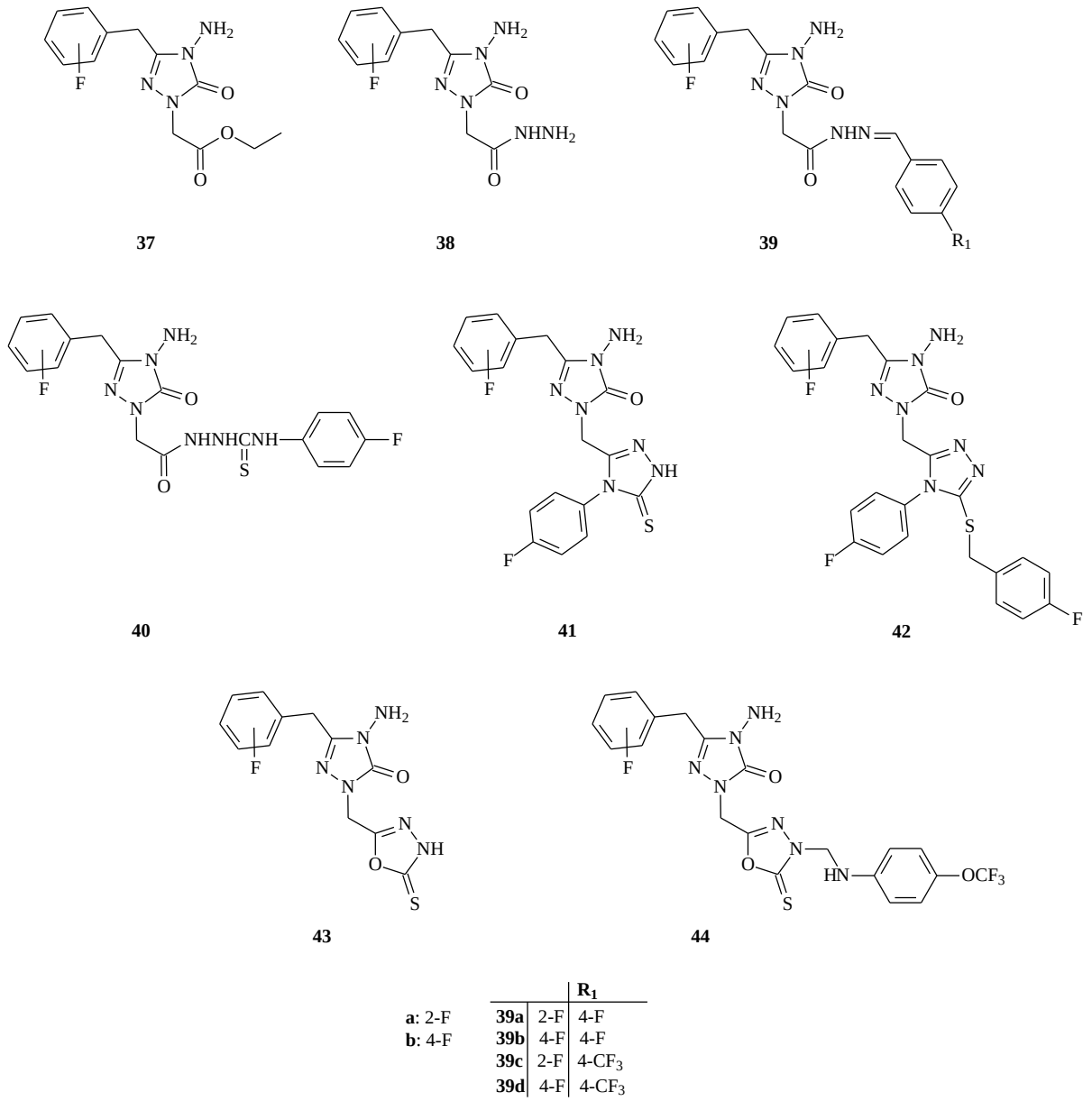


Figure 18. Structures of fluorine-containing 1,2,4-triazole derivatives (Bekircan et al., 2016).

New 1,2,4-triazole compounds (Figure 19) possessing Schiff and Mannich bases were synthesized and tested for their antioxidant and antimicrobial properties. DPPH radical scavenging and FRAP methods were carried out, and the newly synthesized compounds demonstrated antioxidant effect in both tests at various extends. Compound 46 (triazole-thiol) had the highest antioxidant activity in both assays. Moreover, as Schiff bases turned into Mannich bases, their antioxidant activities decreased, and it was determined that the type of substituent on the thiophene ring was effective on antioxidant property. The order of influence of the substituent type of the thiophene ring on the antioxidant activity was $–CH_3$ > $–NO_2$ > –Br > –H for both Schiff and Mannich bases (Ünver et al., 2016).

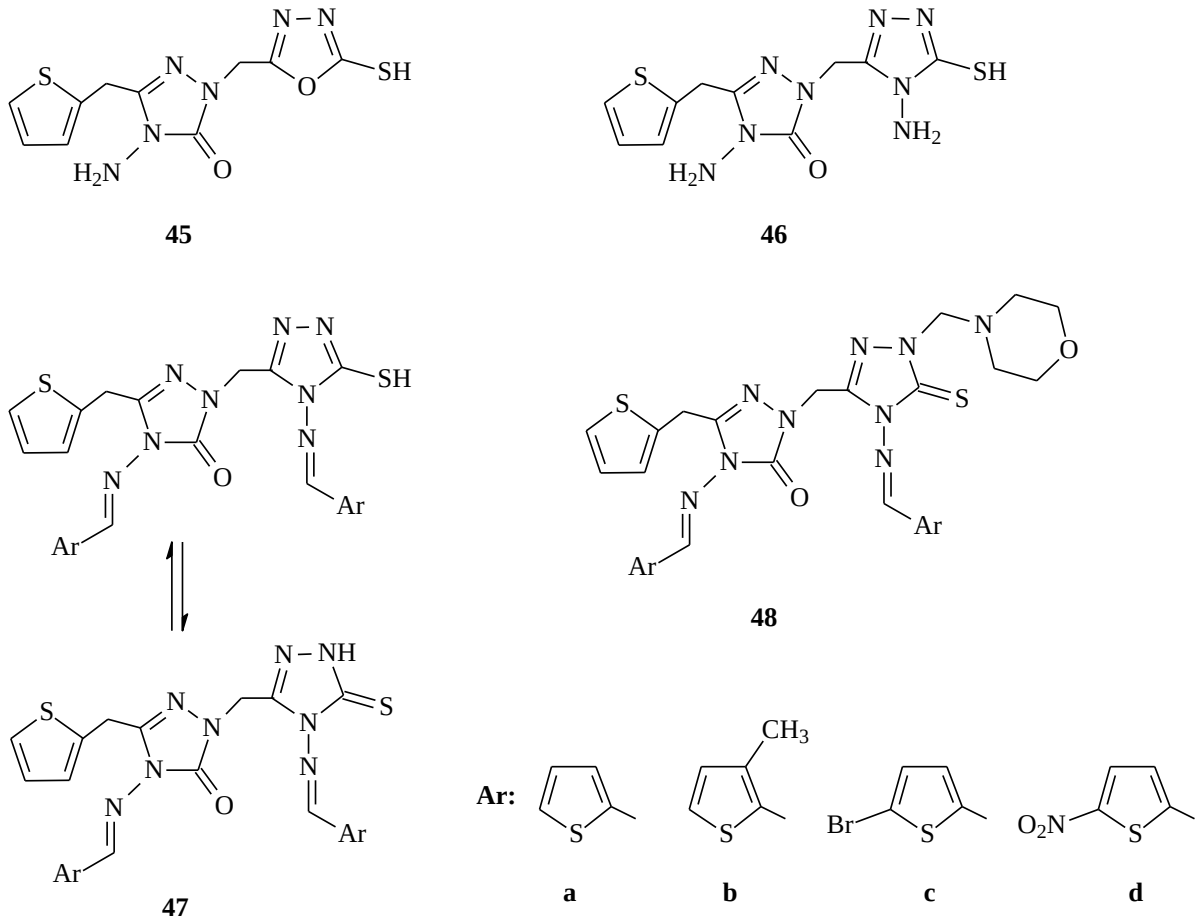
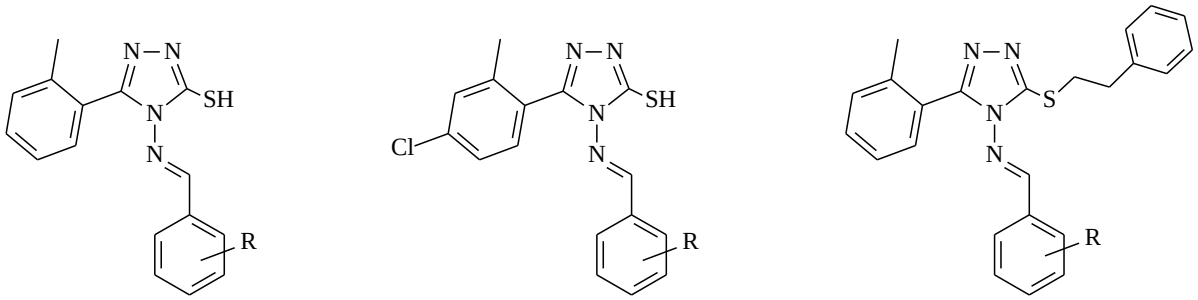


Figure 19. Structures of compounds 45-48 (Ünver et al., 2016).

A new series of 4-[(*E*)-benzylideneamino]-5-(2-methylphenyl)-4*H*-1,2,4-triazole-3-thiols (49a–h), 4-[(*E*)-benzylideneamino]-5-(4-chloro-2-methylphenyl)-4*H*-1,2,4-triazole-3-thiols (50a–i), and (*E*)-N-(benzylidene)-3-(phenethylthio)-5-*o*-tolyl-4*H*-1,2,4-triazole-4-amines (51a–h) (Figure 20) were obtained and screened for antioxidant activities by free-radical scavenging, anti-hemolytic activity, lipid peroxidation, and their protective effects against DNA oxidative damage. Compounds 50b, 50i, 51c, 51d, and 51h exhibited significant DPPH· scavenging effect with the level of inhibition between 86.8% and 94% when compared to BHT 90.4% (Aswathanarayanappa et al., 2013).

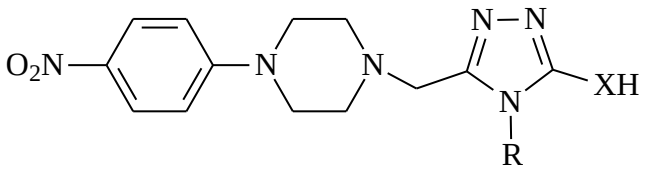


49a-h **50a-i** **51a-h**

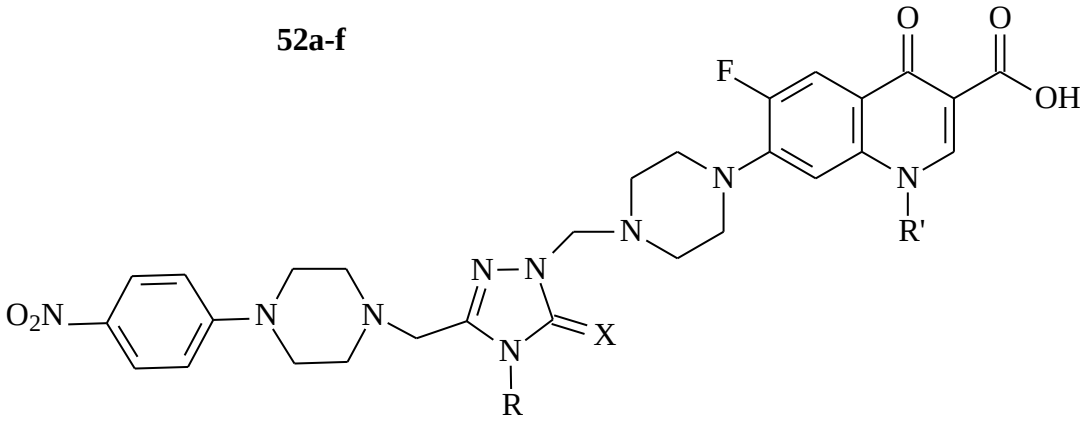
R			
49a, 50a, 51a	2,4-F	49f, 50f, 51f	3-F-4-CF_3
49b, 50b, 51b	2,5-OH	49g, 50g, 51g	4-OCH_3
49c, 50c, 51c	2-F	49h, 51h	4-$CH(CH_3)_2$
49d, 50d, 51d	3-F	50h	H
49e, 50e, 51e	5-Br-2-OH	50i	4-OH

Figure 20. New 1,2,4-triazole-based Schiff base heterocycles 49-51 (Aswathanarayanappa et al., 2013).

Menteşe et al. reported the synthesis, antimicrobial and antioxidant activity screening studies of novel hybrid molecules containing several heterocyclic pharmacophores: Fluoroquinolone, 1,2,4-triazole, 1,3,4-oxadiazole and, piperazine. DPPH·, FRAP, and CUPRAC assays were evaluated to determine the antioxidant capacity. Compounds 53j, 53d, and 53c for the DPPH· assay; 53c, 53j, and 53d for the CUPRAC assay, showed the highest antioxidant capacity values, while compounds 52b for DPPH and CUPRAC had the lowest values among the newly synthesized 1,2,4-triazole nucleus containing compounds (Figure 21) (Mentese et al., 2017).



52a-f



53a-f: R'= -C_2H_5; **53g-l**: R'= 

R, X	
52a, 53a, 53g: R= -$CH_2C_6H_5$, X=S	52d, 53d, 53j: R= -C_6H_5, X=S
52b, 53b, 53h: R= -$CH_2C_6H_5$, X=O	52e, 53e, 53k: R= -C_6H_5, X=O
52c, 53c, 53i: R= -CH_2CH_3, X=S	52f, 53f, 53l: R= -C_6H_4F(*p*-), X=S

Figure 21. Structures of compounds 52a-f, 53a-l (Mentese et al., 2017).

In 2013, 5,5'-butane-1,4-diylbis(4-ethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione and their Mannich bases (Figure 22) were synthesized and screened for their antioxidant, antifungal and antibacterial activities. Free radical scavenging activity of the synthesized compounds was determined by DPPH· assay. Compound 54 showed moderate antioxidant activity. From all the synthesized derivatives, compound 55b exhibited the lowest radical scavenging activities, while compound 55f showed the highest scavenging activities, which were better than the reference antioxidant compound. Moreover, compounds 55a, 55d, 55e, 55g, and 55h showed promising activities similar to the reference antioxidant compound (Koparır, 2013).

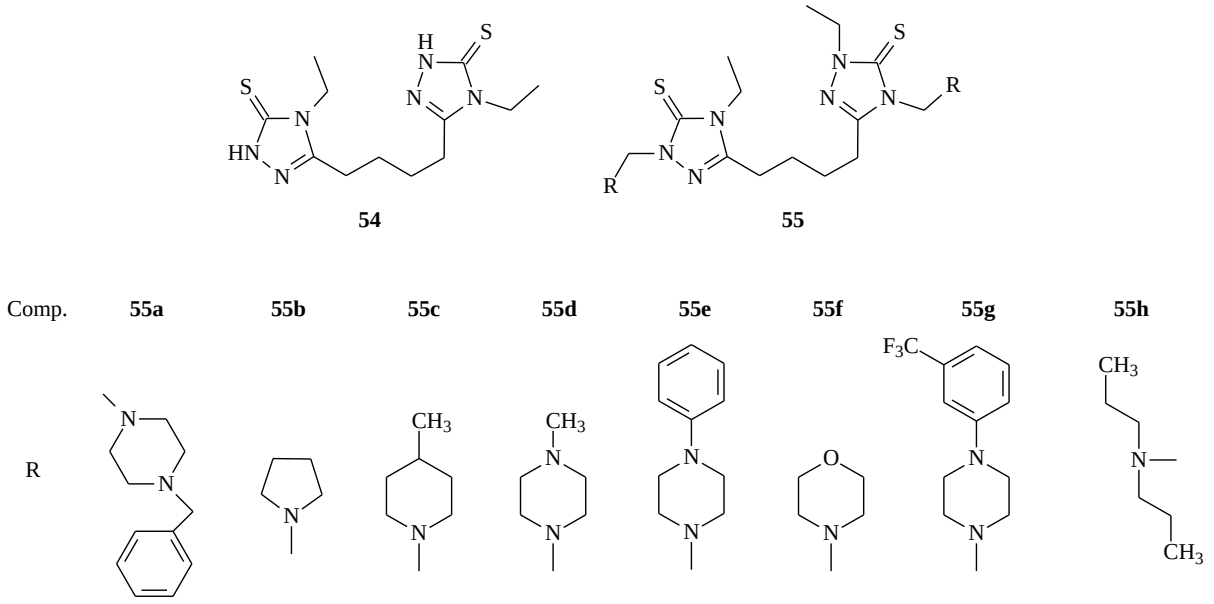


Figure 22. Structures of compounds 54 and 55 (Koparır, 2013).

In 2016, the effects of four selected 55 type compounds (Figure 22) on the levels of *in vivo* malondialdehyde (MDA) and antioxidant vitamins (A, E, C) were investigated in serum, livers, and kidneys of rats. The antioxidant effect was examined *in vitro* by determining the MDA levels in *Saccharomyces cerevisiae* cells. Moreover, the antitumor properties of the compounds were carried out against MCF-7 human breast cancer cells. 5,5'-Butane-1,4-diylbis{4-ethyl-2-((4-methylpiperidin-1-yl)methyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione} (55d), 5,5'-butane-1,4-diylbis(4-ethyl-2-({4-(3-(trifluoromethyl)phenyl)piperazin-1-yl}methyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione) (55g) and 5,5'-butane-1,4-diylbis{2-((dipropylamino)methyl)-4-ethyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione} (55h) compounds' substances demonstrated significant antitumor properties, which may be indicated by good antioxidant activity, can be an indication that these compounds showed remarkable pharmacological bioactivity. Although the antioxidant effect of 5,5'-butane-1,4-diylbis(4-ethyl-2-(pyrrolidin-1-ylmethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione) (55b) was low, it was effective against breast cancer (Parlak et al., 2016).

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To Cite This Chapter

Gürsoy Kol, Ö. & Alkan, M. (2022). Antioxidant Properties of 1,2,4-Triazoles. In H. Yüksek & M. Beytur (Eds.), *Chemistry of 1,2,4-Triazoles in Current Science*, (24-45). ISRES Publishing