ISSN Online: 2349-7777

Biological Activities of Various Triazolone Derivatives

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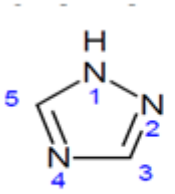
Received 27 October 2014; accepted in revised form 19 November 2014

Abstract: Triazolones are known as a class of 5-membered heterocyclic compounds comprising three nitrogen atoms on 1, 2 and 3-position of the ring along with one carbonyl group (C=O), either at 3-position or 5-position resulting in triazol-3-one and triazol-5- one respectively. Therapeutic potential of triazolones has attracted various researchers and has been explored extensively. Triazolones and their derivatives had shown a broad spectrum of biological activities such as antimicrobial, anticonvulsant, antioxidant, anticancer, analgesic, anti-nociceptive, and anti-inflammatory properties. In the present study, we have made an effort to compile various structural variations on triazolone nucleus and their reported pharmacological activities.

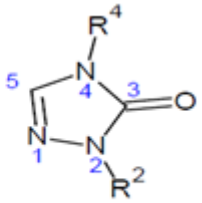
Key words: Triazolone ; Triazol-3-one, Triazol-5-one, Anticonvulsant, Antimicrobial, Antitumor.

Introduction

In the past years, synthesis of nitrogen containing heterocyclic systems has been attracted to many pharmaceutical and agrochemical industries. Triazole derivatives are commonly used for the treatment of local and systemic fungal infections. They are also frequently observed in immune-compromised patients suffering from AIDS or subjected to invasive surgery, anti-cancer therapy. 1,2,4-triazol ring with diverse pharmacological effects have been reported as therapeutic agents in medicinal chemistry. Compounds having triazole moieties such as vorozole, anastrozole, and letrozole appear to be very effective aromatase inhibitors very useful for preventing breast cancer. It has also been reported that the conversion of the amino group in the 4 position in the 1,2,4-triazole ring into an arylidene amino group causes antitumor activity. It is known that 1,2,4- triazole moieties are reported to interact strongly with the heme iron and aromatic substituents in the active site of aromatase enzyme. Triazol-3-ones are referred to as a class of 5-membered heterocyclic compounds containing three nitrogen atoms at 1, 2 and 4-position with one double bond along with carbonyl group at 3- and 5- position.



Triazole



Triazol-3-one

Triazolones and their derivatives showed a broad spectrum of biological activities such as antimicrobial, anticonvulsant, antioxidant, anticancer, analgesic, anti HIV, antinociceptive, and anti-inflammatory properties [1].

Triazolone derivatives as anticonvulsant agents

Quan *et al.,* designed and synthesized various

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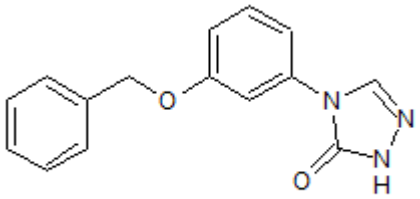
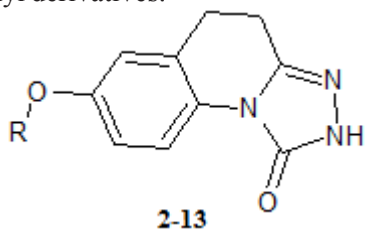
4-(3-alkoxy phenyl)-2, 4-dihydro - [1, 2, 4] triazol-3-one derivatives and screened them for anticonvulsant activity. Among various analogs synthesized ten compounds showed prominent anticonvulsant activity against maximal electroshock (MES) induced seizures at the low dose of 30 mg / kg. These compounds were then screened to determine their therapeutic dose (ED_{50}) and toxic dose (TD_{50}) in mice. Among these compounds, 4-(3-benzyloxy phenyl)-2,4- dihydro-[1, 2, 4] triazol-3-one (**1**) was found to be most promising compound with relatively high activity (ED_{50}: 30.5mg/kg) and lowest toxicity (TD_{50}: 568.1 mg/kg).



1

SAR studies suggested that the length of the alkyl chain in alkyloxy substituted derivatives has no direct impact on anticonvulsant activity. Among benzyloxy substituted derivatives, the position of the substituted group on phenyl ring appeared to greatly influence the anticonvulsant activity [2].

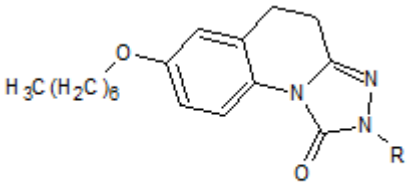
Quan *et al.,* also reported various 7-Alkoxy-4, 5-dihydro-[1, 2, 4] triazole [4, 3-a] quinoline-1 (2H)-ones and evaluated for anticonvulsant activity. All compounds exhibited good anticonvulsant activity against MES induced seizures. Among all synthesized compounds, butyl, pentyl, hexyl and heptyl derivatives were found most active with lowest toxicity than standard compound in pre clinical studies (Protective Index ranging from 2.9-44.7). SAR studies revealed that the length of alkyl chain appeared to have a direct impact on anticonvulsant activity of the 7-alkyloxyl derivatives.



2-13

R= nC_4H_9 **(2)**, nC_5H_{11} **(3),** nC_6H_{13} **(4),** nC_7H_{15} **(5),** nC_8H_{17} **(6),** $-CH_2C_6H_5$ **(7),** $-CH_2C_6H_4(o\text{-F})$ **(8),** $-CH_2C_6H_4(m\text{-F})$ **(9),** $-CH_2C_6H_4(p\text{-F})$ **(10),** $-CH_2C_6H_4(p\text{-}CH_3)$ **(11),** $-CH_2C_6H_4(p\text{-Cl})$ **(12),** $-CH_2C_6H_4(p\text{-}OCH_3)$ **(13)**

From compound **2-5,** as the alkyl chain length increased, ED_{50} gradually increased with compound **5** being the most active. The trend reversed when alkyl chain had more than seven carbon numbers as seen with compound **6**. Among 7- benzyloxy derivatives, the anticonvulsant potency of compounds containing substituted benzyloxy was lower than that of non-substituted benzyloxy (**i.e., 7**). The potency of order of three fluoro substituted derivatives was p-F > o-F > m-F. The p-F substituted derivative (**10**) exhibited the strongest anticonvulsant activity. Among compounds **11-13**, *p*-OCH_3 derivative (**13**) exhibited the weakest activity [3]. The same research group have also reported various 2-substituted-7-heptyloxy-4, 5- dihydro-[1, 2, 4]–triazole [4, 3-a] quinolin-1 (2H) -one derivatives and evaluated for anticonvulsant activity. To study the effect on anticonvulsant activity, contribution of different acyl and alkyl groups at position 2 of the 7-heptyloxy-4, 5-dihydro-[1, 2, 4]–triazole [4, 3-a] quinolin-1 (2H) -one were investigated.



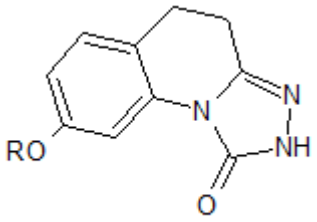
14-25

R=$-COCH_3$ (**14**), COC_2H_5 (**15**), COC_4H_9 (**16**), COC_5H_{11} (**17**), COC_6H_{13} (**18**), COPh (**19**), C_2H_5 (**20**), n-C_3H_7 (**21**), nC_4H_9 **(22),** nC_6H_{13} **(23),** nC_7H_{15} **(24),** $-CH_2C_6H_5$ **(25)**

As a result of preliminary screening, compound **14** ($COCH_3$), **15** (COC_2H_5), **19** (COPh) and **21** (n-C_3H_7) were subjected to pre-clinical trials for quantification of their anticonvulsant activity and neurotoxicity in mice. Compounds **14** and **15** displayed excellent anticonvulsant activity with ED_{50} value of 7.2 mg/kg and 8.2 mg/kg respectively with weak neurotoxicity. SAR studies revealed that the length of the acyl chain appeared to have direct impact on anticonvulsant activity

of the 2-acyl derivatives. From **14-18,** as the acyl chain length increased, ED_{50} gradually increased with compound **14** being the most active compound but had high neurotoxicity with TD_{50} = 88 mg/kg and protective index (PI) = 12.2, so compound **15** was considered potentially more useful and safe compound. When compound having R = H was acylated at the 2- position with big acyl group such as valeryl, hexanoyl and heptanoyl, the compounds exhibited markedly reduced activities. The 2-benzoyl derivative **19** showed lower anticonvulsant activity and neurotoxicity than compound having R = H. When compound with R = H was alkylated at the 2- position, no matter how big or small the alkyl group was; compounds showed markedly reduced activities. The 2- propyl derivative **21** showed lower anticonvulsant activity and high neurotoxicity [4].

Quan *et al.,* also screened a series of 8-Alkoxy-4, 5-dihydro-[1, 2, 4] triazole [4, 3-a] quinoline-1-ones for anticonvulsant activity in MES and subcutaneous pentylene tetrazole (scPTZ) methods and their neurotoxicity was measured by the rotarod test.

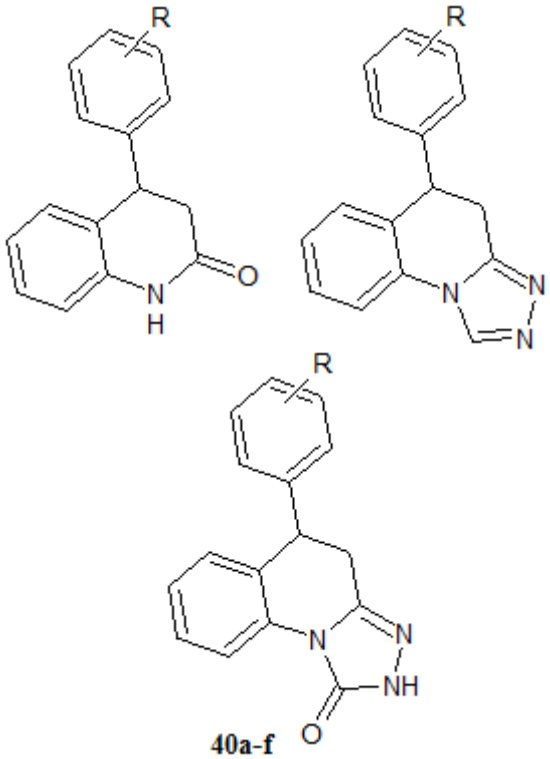


26-37

R= CH_3 (**26**), C_3H_7 (**27**), C_4H_9 (**28**), C_5H_{11} (**29**), C_6H_{13} (**30**), C_7H_{15} (**31**), C_8H_{17} (**32**), $CH_2C_6H_5$ (**33**), $CH_2C_6H_4$(p-F) (**34**),-$CH_2C_6H_4$(p-Cl) (**35**), $CH_2C_6H_4$(p-CH_3) (**36**), $CH_2C_6H_4$(o-F) (**37**)

The preliminary screening (phase I) indicated that compounds **30** (nC_6H_{13}), **31** (nC_7H_{15}), **32** (nC_8H_{17}) and **33** ($CH_2C_6H_5$) displayed anticonvulsant activity at 30 mg/kg, while others displayed anticonvulsant activity at 100 mg/kg. All the compounds exhibited no neurotoxicity at a dose of 300 mg/kg. After pre-clinical trial of compound **30**, **31**, **32** and **33,** it was concluded that the compound **30** and **31** were found to be most active having ED_{50} value of 17.7 mg/kg and 19.7 mg/kg in the MES test and ED_{50} value of 24.5 mg/kg and 21.2 mg/kg in the sc-PTZ tests, respectively [5].

Quan *et al.,* also reported a new series of 4-substituted-phenyl-3, 4-dihydro-2(1*H*)-quinolines, 5-substituted phenyl-4, 5-dihydro-1, 2, 4-triazolo [4, 3*a*] quinolines and 5-substituted-phenyl-4, 5-dihydro-1, 2, 4-triazolo-[4, 3-*a*] quinoline-1-(2*H*)-one derivatives for anticonvulsant activity. The anticonvulsant activity was evaluated by maximal electroshock (MES) test, subcutaneous pentylene tetrazole (scPTZ) test and their neurotoxicity was determined by the rotarod test.



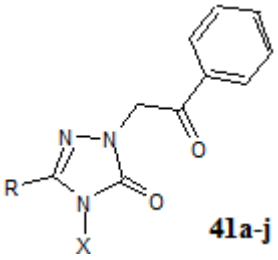
40a-f

38-40; a= H, **b=** *p*-Cl, **c=** *p*-OCH_3, **d=** *p*-CH_3, **e=** *p*-F, **f=** *m*-F

The compounds 4-substitued-phenyl- 3, 4-dihydro- 2(1*H*)-quinolines **(38a-f)** had increased anticonvulsant effects compared to the parental compounds. The compounds 5-substituted-phenyl -4, 5-dihydro-1, 2, 4-triazolo [4, 3-*a*] quinolines **(39a-f)** had significantly increased anticonvulsant activity compared to **38a-f**. However, the compounds 5-substituted-phenyl-4, 5-dihydro-1, 2, 4-triazolo [4, 3- *a*] quinoline-1(2*H*)-ones **(40a-f),** exhibited no anticonvulsant effects even under a high dose of 300 mg/kg [6].

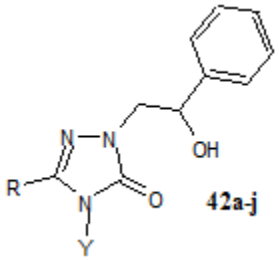
Triazolone derivatives as antimicrobial agents

Demirbas *et al.,* synthesized various 1, 2, 4-triazol-3-one derivatives and evaluated them for antimicrobial activity and among the compounds tested, **41c**, **41h** and **42j** exhibited good activities against *S. aureus* and *B. subtilis* with MIC values ranging from 1-4 µg/ml.



41a-j

a; R= CH_3, **X**= NH_2, **Y**= NH_2
b; **R**= $CH_2C_6H_5$, **X**= NH_2, **Y**= NH_2
c; **R**= CH_3, **X**= -$NCHC_6H_5$, **Y**= -$NHCH_2C_6H_5$
d; **R**= C_6H_5, **X**= -$NCHC_6H_5$, **Y**= $NHCH_2C_6H_5$
e; **R**= $CH_2C_6H_5$, **X**= -$NCHC_6H_3$(2,4-Cl), **Y**= $NHCH_2C_6H_3$(2,4-Cl)

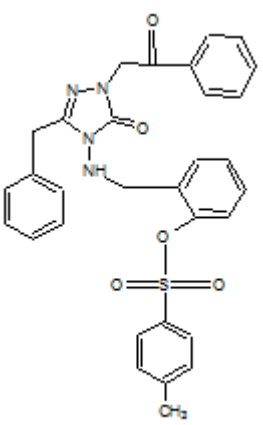


42a-j

f; **R**= $CH_2C_6H_4$ (p-Cl), **X**= -$NCHC_6H_3$(2,4-Cl), **Y**= $NHCH_2C_6H_3$(2,4-Cl
g; **R**= CH_3, **X**= -$NCHC_6H_4$(2-OH), **Y**= $NHCH_2C_6H_4$(2-OH)
h; R= C_2H_5, **X**= $NCHC_6H_4$(2-OH), **Y**= $NHCH_2C_6H_4$(2-OH)
i; R= C_3H_7, **X**= $NCHC_6H_4$(2-OH), **Y**= $NHCH_2C_6H_4$(2-OH)
j; R=$CH_2C_6H_5$, **X**=$NCHC_6H_4$(2-OH), **Y**=$NHCH_2C_6H_4$(2-OH)

An increased activity towards *S. aureus* was observed when **41j** was converted to **42j**. The tosylation of phenolic hydroxyl in **41j** and **42j** highly increased the antimicrobial effect of the resulting **43** *(*MIC: 0.5 µg/ml*)* and **44** *(*MIC: 8 µg/ml*)* towards *E. faecalis*, while decreasing the activity against *B. subtilis*. Compound **41b** manifested a good activity against *E. coli*. Decreased activities towards *E. coli, E. faecalis, S. aureus* and *B. subtilis* were observed for **45** [7].

Muhi-eldeen *et al.,* investigated a series of 4, 5-diaryl-2-[4-(t-amino)-2-butynyl]-2, 4-dihydro-3H-1, 2, 4-triazol-3-ones for antimicrobial activity against Gram-positive bacteria, Gram-negative bacteria and fungi. The MIC of the compounds synthesized indicated that compound **51** showed the maximum activity against Gram positive bacteria (MIC value of 6.25 µg/ml), Gram negative bacteria (MIC value of 6.25 µg/ml) with less activity against *P. aeruginosa* (MIC value of 25 µg/ml) and good activity activity against *Candida albicans* (MIC value of 12.5 µg/ml), compound **50** showed similar activity to **51** against Gram positive bacteria and *C. albicans*. Compound **49** was less active against Gram positive bacetria, Gram negative bacteria and fungi.



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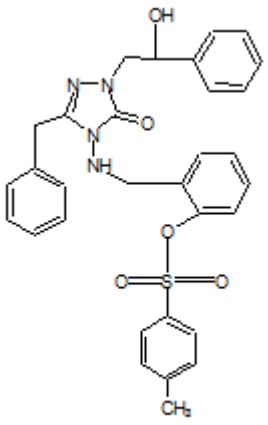

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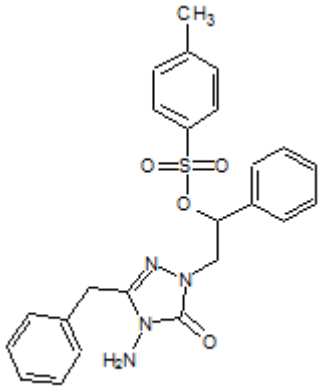
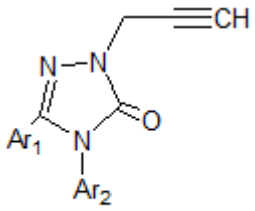


45

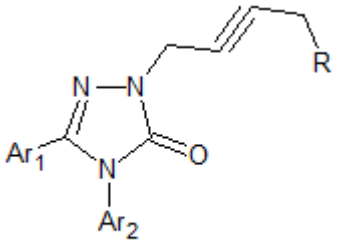


46-48

46; Ar_1= Ph, **Ar_2**= Ph, **47; Ar_1**= p-Cl-Ph, **Ar_2**= Ph, **48; Ar_1**= Ph, **Ar_2**= 1-naphthyl

Compounds **53** and **55** showed activity against Gram positive bacetria, Gram negative bacteria and fungi with less activity against *P. aeruginosa* relative to compound **51**. All others were active against Gram positive bacteria and fungi with the exception of compounds **56** and **61.** The structure activity relationship indicated that the more lipophilic nature of the basic amino groups in as in compounds **49**, **50** and **51** yielded the most active agents which may attributes to their penetration ability [8].

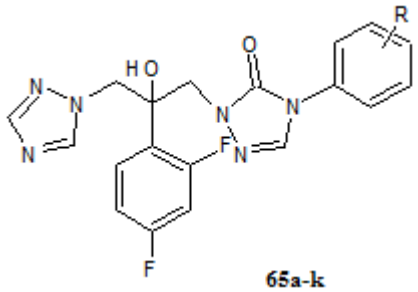
Qingyan *et al.,* evaluated a series of 1-(2-(2, 4-difluorophenyl)-2-hydroxy-3-(1H-1, 2, 4-triazol-1-yl) propyl)-1H-1, 2, 4-triazol-5(4H)-one of fluconazole derivatives for antifungal activity. The *in vitro* antifungal activities of the synthesized compounds were evaluated against eight human pathogenic fungi, *Candida albicans Y0109, Candida albicans SC5315, C. neoformans, C. parapsilosis, C. tropicalis, Trichophyton rubrum, C. keyfr & A. fumigatus*. All the compounds were found active against all fungi except *A. fumigates.* The activities of **65c, 65i, 66d, 67d, 67f** and **67i** were better than fluconazole *in vitro* against *C. albicans*. Compound **65i** also exhibited higher activity against *C. keyfr* than itraconazole and voriconazole with MIC_{80} value of 0.00024 µg/ml. Compound **66d** showed higher activity against *C. neoformans* than itraconazole and voriconazole with MIC_{80} value of 0.00024 µg/ml. SAR study revealed that among compounds **65a-65k,** compound **65g** which has p-methoxy group showed higher activity than compound **65f** which has a p-methyl group with MIC_{80} -value of 0.0625 µg/ml.



49-64

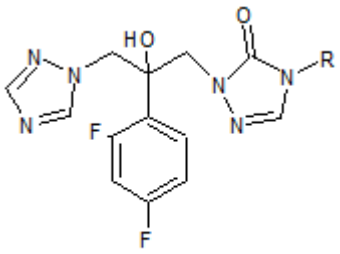
49; Ar1= Ph, Ar_2= Ph, R= 2, 6-dimethyl piperidino
50; Ar_1= Ph, Ar_2= Ph, R= perhydroazepino
51; Ar_1= Ph, Ar_2= Ph, R= perhydroazocin
52; Ar_1= Ph, Ar_2= Ph, R= 2-methyl piperidino
53; Ar_1= Ph, Ar_2= Ph, R= 3-methyl piperidino
54; Ar_1= Ph, Ar_2= Ph, R= pyrrolidino
55; Ar1= Ph, Ar_2= Ph, R= piperidino
56; Ar_1= Ph, Ar_2= 1-naphthyl, R= 2,6-dimethyl piperidino
57; Ar_1= Ph, Ar_2= 1-naphthyl, R= piperidino
58; Ar_1= Ph, Ar_2= 1-naphthyl, R= 2-methyl piperidino
59; Ar_1= Ph, Ar_2= 1-naphthyl, R= 3-methyl piperidino
60; Ar_1= Ph, Ar_2= 1-naphthyl, R= perhydroazepino
61; Ar_1= Ph, Ar_2= 1-naphthyl, R= perhydroazecino
62; Ar_1= *p*-chlorophenyl, Ar_2= phenyl, R= 2,6-dimethyl piperidino
63; Ar_1= *p*-chlorophenyl, Ar_2= phenyl, R= 2-methyl piperidino
64; Ar_1= *p*-chlorophenyl, Ar_2= phenyl, R= piperidino

Compound **65i** with m-cyano substituent showed excellent activity having MIC_{80} value of 0.00024 µg/ml, especially against *Candida* species. But compound **65h** which has a p-cyano group showed lower activity against *Candida* species than **65i**. Despite the different substitution position between the p-methoxy group in **65g** and m-cyano group in **65i**, both exhibited good antifungal activities against *Candida* species. Introduction of pyridine and phenyl thiazole group to replace phenyl group in the side chain obtained compounds **66a-66d.** Among them, compound **66d** exhibited excellent antifungal activity.

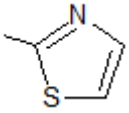


65a-k

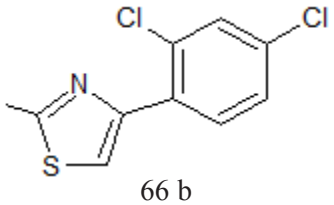
65a (R= H)**, b**(R= 4-F), **c**(R= 4-Cl), **d**(R= 2-Cl), **e**(R= 4-Br), **f**(R= 4-CH_3), **g**(R= 4-OCH_3), **h**(R= 4-CN), **i**(R= 3-CN), **j**(R= 3-Cl, 4-Cl), **k**(R= 4-NO_2)



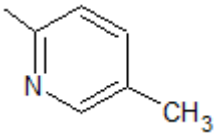
66 a-d



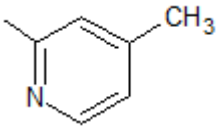
66 a



66 b

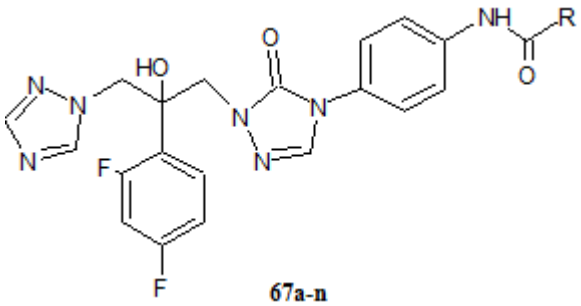


66 c



66 d

As for the alkyl side chain series, including compounds **67a-67g,** length of the alkyl side chain is essential for their antifungal activity. Among them, compounds **67d, 67e** and **67f** with a moderate length side chain presented higher activities.

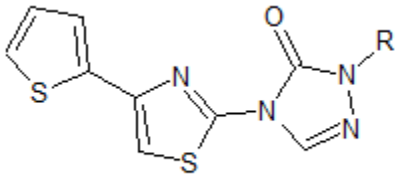


67a-n

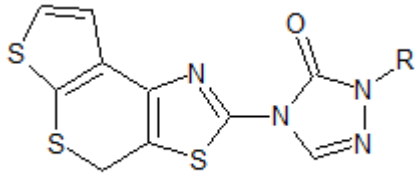
67a (R=CH_3), **67b** (R=C_2H_5), **67c** (R=C_3H_7), **67d**(R=C_4H_9), **67e** (R=C_5H_{11}), **67f** (R=C_6H_{13}), **67g** (R=C_7H_{15}), **67h** (R=CH_2CN), **67i** (R= cyclopropyl), **67j** (R=cyclohexyl), **67k** (R=3-pyridyl), **67l** (R=2-pyridyl), **67m** (R=furan), **67n** (R=thiophene)

However, compounds with longer or shorter alkyl side chain suffered a loss of activity. Besides, replacing the alkyl side chain with heterocyclic group yielded compounds **67i-67n,** but their activities were not delightful. It indicates that bulky substituent is not beneficial to the antifungal activity of such fluconazole analogs [9].

Bobade *et al.*, synthesized a new series of triazol-3-one derivatives bearing 4-methyl-4H-thieno [3', 2': 5, 6] thiopyrano[4, 3-d] [1, 3] thiazolyl and 4-(thiophene-3-yl) thiazolyl at 4-position and alkyl substitution at 2-position and screened for antifungal activity against *F. solani, A. niger* and *C. albicans* and antibacterial activity against Gram positive bacteria (*S. aureus, B. subtilis*) and Gram negative bacteria (*E. coli, K. pneumoniae*). From the antibacterial activity data, it was observed that compound **68a, 68e** and **69b** were the most active among the tested compounds against Gram positive bacteria with MIC value of 24 µg/ml and 14 µg/ml while other compounds showed less antibacterial activity compared to chloramphenicol.



68a-f



69a-f

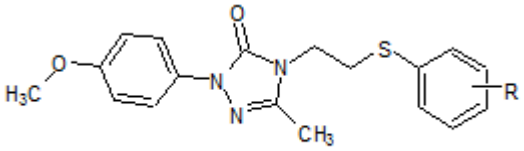
68a (R= CH_3), **68b** (R= C_2H_5), **68c** (R= $CHMe_2$), **68d** (R= $CH_2CH\text{-}Me_2$), **68e** (R= CH_2CN), **68f** (R= Me_3OCH_3)

69a (R= CH_3), **69b** (R= C_2H_5), **69c** (R= $CHMe_2$), **69d** (R= $CH_2CH\text{-}Me_2$), **69e** (R= CH_2CN), **69f** (R= Me_3OCH_3)

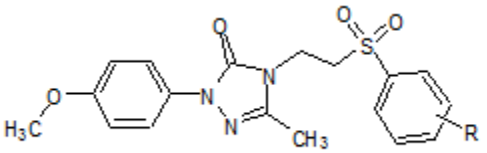
Based on the activity data for triazol-3-one derivatives, it was concluded that triazol-3-one bearing (thiophene-3-yl) thiazolyl moiety exhibits better antibacterial and antifungal activity than 4-methyl-4H-thieno [3′, 2′: 5, 6] thiopyrano [4, 3-d] [1, 3] thiazolyl moiety. Antibacterial activity

SAR revealed that for thiophene thiazolyl **68a-f**, N-CH_3 at 2-position increases the antibacterial activity while N-$CH(Me)_2$ reduces the activity compared to parent compound against Gram positive bacteria. In the case of other series thieno thiopyarano-thiazolyl **69a-69f**, N-C_2H_5 and N-$(CH_2)_3$-OCH_3 at 2-position of triazol-3-one increased the antibacterial activity while N-$CH(Me)_2$ reduces the activity against Gram positive bacterias. For both series, there was very little difference in activity of N-substituted derivatives (**68a-68f**) and (**69a-69f**) compared to their parent compounds against Gram negative bacteria *E. coli, K. pneumonia.* In the antifungal activity SAR; for the thiophene thiazolyl series, N-CH_3 increases antifungal activity while other substitution marginally reduced the activity compared to parent compound. Introduction of the N-$(CH_2)_3$-OCH_3 at 2-position of triazol-3-one in thieno thiopyrano thiazolyl series substantially increased the antifungal activity compared with unsubstituted parent compound. Introduction of isopropyl group, isobutyl group and cyanomethyl group reduced the antifungal activity whereas there was no effect of ethyl and methyl substitution compared with parent compound against all the tested pathogens [10].

Patil *et al.,* reported a series of 2-(4-methoxy-phenyl)-5-methyl-4-(2-arylsulfanyl-ethyl)-2, 4-dihydro-[1, 2, 4] triazol-3-ones and their corresponding sulfones with the objective of developing better antimicrobial agents. The synthesized compounds were screened for antimicrobial activity against *B. subtilis, S. aureus, S. epidermidis, E. coli* and *P. aeruginosa*. The results of antimicrobial screening revealed that both thioethers and their corresponding sulfones displayed better antibacterial activity compared with their antifungal activities. It was observed that the compound **70d** showed good inhibition against *S. aureus* and *E. coli* with MIC value of 9.75 µg/ml. The compound **71b** had moderate activity against *S. aureus* and *E. coli* with MIC value of 18.75 µg/ml and 9.375 µg/ml respectively. The compound with fluoro substitution **70a** exhibited significant activity against S. aureus, where as the compound with methoxy group **70f** showed moderate activity against *B. subtilis* and *E. coli*. Among all synthesized compounds, **70c, 70e, 70g, 70h, 70i, 71a** and **71c** showed poor activity. Almost all the newly synthesized compounds showed poor antifungal activity against all types of fungal strains [11].



70a-h



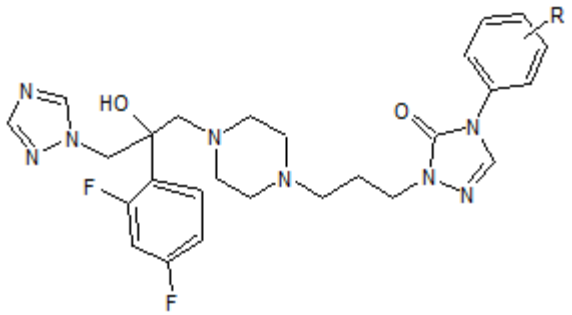
71a-e, 71h

70a (R= 2-F), **70b** (R= 3-F), **70c** (R= 4-F), **70d** (R= 3-CF_3), **70e** (R= 4-Br), **70f** (R= 3-OCH_3), **70g** (R= 4-NH_2), **70h** (R= H)

71a (R= 2-F), **71b** (R= 3-F), **71c** (R= 4-F), **71d** (R= 3-CF_3), **71e** (R= 4-Br), **71h** (R= H)

Yao and Zhang *et al.,* designed and synthesized 4- phenyl substituted derivatives of 1-(3-(4-(2-(2, 4-difluorophenyl)-2-hydroxy-3-(1H-1, 2, 4-triazol-1-yl) propyl) piperazine-1-yl) propyl) - 1H-1, 2, 4-triazol-5(4H)-ones and screened them for antifungal activities. *In vitro* antifungal activity of synthesized compounds was expressed as the minimum inhibitory concentration (MIC) that achieved 80 % inhibition of the tested fungal pathogens (*C. albicans, C. tropicalis, C. parapsilosis, C. krusei, C. neoformans* and *A. fumigatus*) using fluconazole as a reference drug. Most of the compounds showed good inhibitory activity against *Candida* species. Except compounds 5 and 19, the MIC range for C. albicans was 0.25 µg/ml to 0.0625 µg/ml indicated that the compounds were comparable or superior to fluconazole. Good activity was also observed for *C. Tropicalis* with MIC range of 0.25 to 1 µg/ml. On the *Candida parapsilosis* strain, nine compounds (**75, 77, 78, 79, 81, 82, 85, 87** and **88**) were most active than fluconazole with MIC value 0.25 µg/ml. Most of the compounds showed decreased activity against *C. krusei*. Most of the compounds including fluconazole only showed

moderate activity against *C. neoformans.* Among them, compounds **81, 87** and **88** were 16 folds more potent than fluconazole.

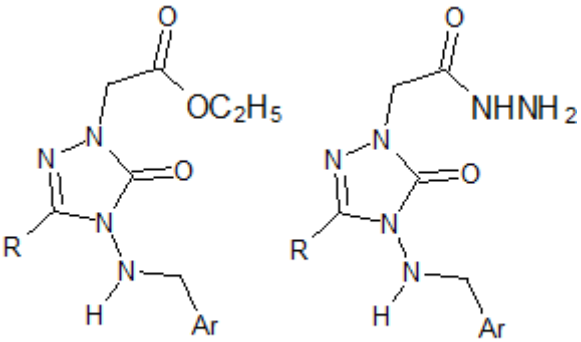


72-91

72 (R= 4-CH_3), **73** (R= 3-CH_3), **74** (R= H), **75** (R= 4-$C(CH_3)_3$), **76** (R= 2,4-2-CH_3), **77** (R= 3,4-2CH_3), **78** (R= 3,5-2CH_3), **79** (R= 3-Cl), **80** (R= 4-Cl), **81** (R= 3,4-2Cl), **82** (R= 4-Br), **83** (R= 2-F), **84** (R= 4-F), **85** (R= 4-I), **86** (R= 4-OEt), **87** (R= 3-Cl-4-CH_3), **88** (R= 3-Cl-4-F), **89** (R= 2,5-2CH_3), **90** (R= 2,6-2CH_3), **91**(R= 3-NO_2-4-CH_3)

SAR study revealed in general that the substitutions on the terminal phenyl group were important for the antifungal activities. The introduction of a chlorine substituent on *para*-position of terminal phenyl group (**76)** led to the improvement of the antifungal activity and spectrum. For compounds with other substitutions on position four (F, Br, I, methyl, ethoxy & *tert*-butyl), they showed the same activity against *C. albicans* as the non-substituted derivative **74,** but their antifungal spectrum was improved. If the chlorine atom of compound **76** was moved to position 3 (**79**), good activity was retained. Moreover, several di-halogen substituted derivatives (**80** and **88**) showed improved antifungal activity and spectrum. On the other hand, dimethyl substitution on the phenyl group (**76, 77, 78, 89** and **90**) had little effect on the antifungal activity. For 4-CH_3 derivative **72,** the addition of a chlorine atom on position 3 (**87**) led to increase of the antifungal activity, while adding a nitro group on position 3 did not show positive effect. From the above analysis, 4-Cl and 3, 4-dihalogen substitutions were found to be the most favorable for the antifungal activity. Generally, the more hydrophobic compounds were more active towards *A. fumigates*. For example, the most hydrophobic compounds **75, 81** and **87** showed the best anti- *A. fumigates* activities, whereas compounds with lowest logP values (**72, 83, 84** and **91**) were totally inactive [12].

Kahveci *et al.,* evaluated ethyl N'-(3-methyl-4-arylmethyleneamino-4, 5-dihydro-1H-1, 2, 4-triazolyl-5-one) acetates and N'-(3-methyl-4-arylmethyleneamino-4, 5-dihydro-1H-1, 2, 4-triazolyl-5-one) acetyl hydrazines for antimicrobial activity against some Gram positive, Gram negative bacteria and some fungi. The compounds showed antibacterial and antifungal activity against one or more of the test microorganisms. All compounds were found to be effective against both Gram positive and Gram negative bacteria. Only three compounds (**93a, 93b** and **93d**) were effective against yeast like fungi like *C. albicans* and *C. tropicalis.*



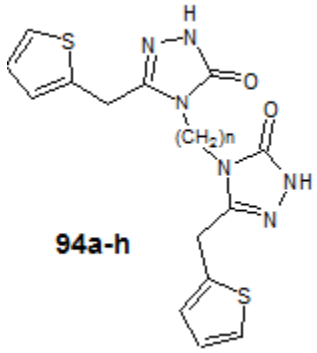
92a-d **93a-d**

92-93: a; (R=CH_3, Ar=Ph), **b;** (R=CH_2CH_3, Ar=Ph), **c;** (R=CH_2CH_3, Ar= *p*-CH_3Ph), **d;** (R= CH_3, Ar= *p*-CH_3Ph)

The most sensitive micro-organism was *B. subtilis* to **92a, 93a** and **93d** with MIC of 7, 31 and 250 µg/ml respectively. Among active compounds **92a, 92c, 93a** and **93c** inhibi-ted *S. aureus* with MIC 31 µg/ml [13].

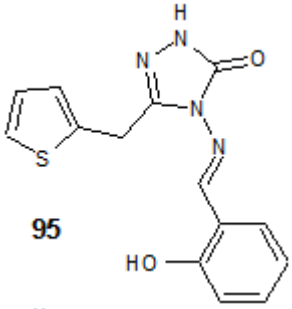
Ünver *et al,.* Reported a series of novel di-[3(thiophen-2-yl-methyl)-4, 5-dihydro-1*H*-[1, 2, 4] triazole-5-one-4yl] n-alkanes and their antimicrobial activities. Most of the compounds showed good antifungal activity only against yeast fungi, while few compound showed antimicrobial activity against the bacteria *Pseudomonas aeruginosa* ATCC10145, *Enterococcus faecalis*

ATCC29212 and the yeast fungi *Candida albicans* ATCC 60193 and *Candida tropicalis* ATCC 13803. Compounds **94f, 95, 96, 97, 99a,** and **100c** showed good antifungal activity only against yeast-like fungi, while compound **94d** showed antimicrobial activity against bacteria and yeast-like fungi.

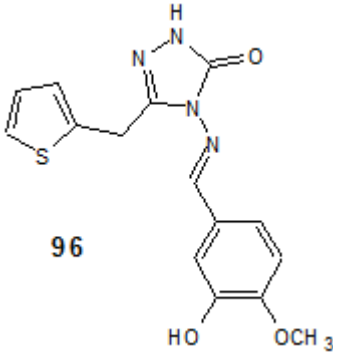


94a-h

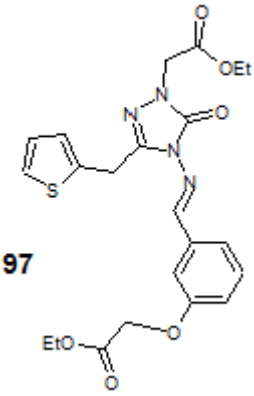
94a (n=3), **94b** (n=5), **94c** (n=6), **94d** (n=7), **94e** (n=8). **94f** (n=9). **94g** (n=10), **94h** (n=12)



95



96



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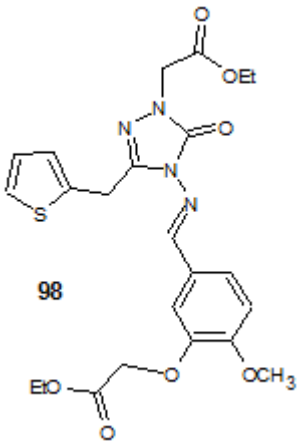

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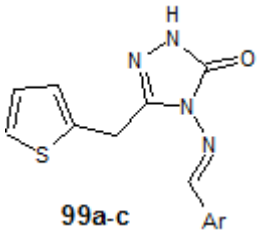
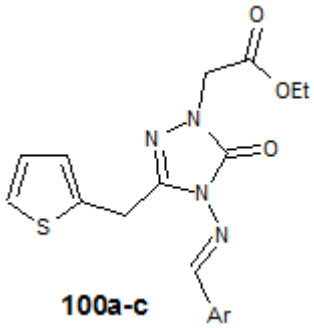


99a-c



100a-c

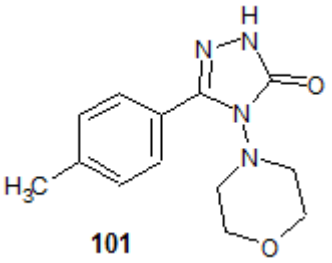
99a (Ar= pyridyl), **99b** (Ar= *p*F-C_6H_4), **99c** (Ar= *p*NO_2-C_6H_4)

100a (Ar= pyridyl), **100b** (Ar= *p*F-C_6H_4), **100c** (Ar= *p*F-C_6H_4)

Compounds **94a** and **94h** were only effective against *Pseudomonas aeruginosa* ATCC 10145. The best activity was observed against *Candida albicans* ATCC 60193 and *Candida tropicalis* ATCC 13803 by compound **98** [14].

Bektas *et al.*, synthesized 4-amino-5- (4-chlorophenyl)-2- [(5-mercapto-1, 3, 4-oxadiazol-2-yl) methyl] -2,4-dihydro-3*H*-1, 2, 4-triazol-3-one derivatives. All newly synthesized compounds were screened for their antimicrobial activities and none of the synthesized compounds showed antimicrobial activity against *Candida tropicalis* and *Candida albicans*. Among the compounds 4,5-disubstitue-2,4-dihydro-3*H*-1,2,4-triazol-3-ones (**101, 103, 105**) and **106a,b**; the compounds **101** and **105** exhibited moderate activities towards *Escherichia coli* and *Klebsiella pneumoniae* which are containing a morpholine (for **101**) or indol-3-ylethyl moiety (for **105**) in the position 4 of 1,2,4-triazol-3-one ring. Similarly, compound **107** having an imine bond and compound **108**

possesing hydrazide function in their structures showed moderate activities against *Enterobacter aerogenes, Staphylococcus aureus, Enterococcus faecalis and Bacillus careus.* Good antimicrobial activities were found for compounds **109** and **110** against the test microorganisms, which are including a 5-mercapto-1,3,4-oxadiazole ring bearing to 1,2,4-triazole nucleus via a methylene linkage. The conversion of the amino group in position 4 of 1,2,4-triazole ring into 4-methoxy-phenylenamino group caused no change in the antimicrobial activity for compound **110**.



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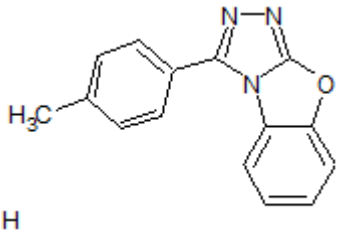
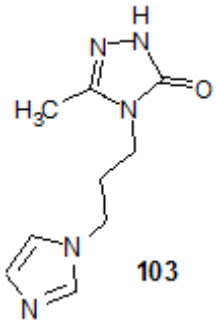
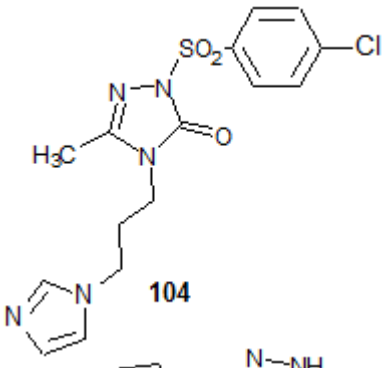


102



103



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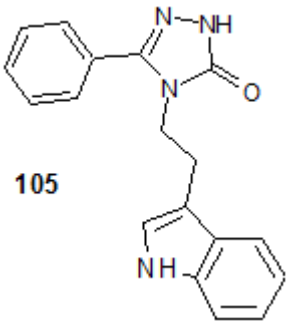
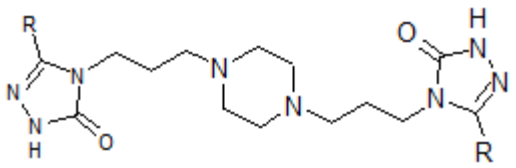
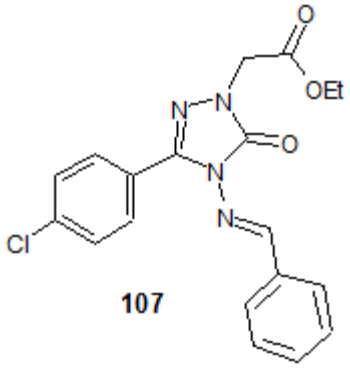


105

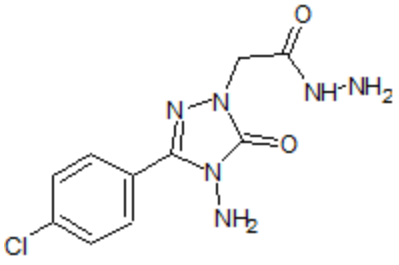


106a-b



107

106a; R= CH_3, **106b;** R= *p*CH_3-C_6H_5



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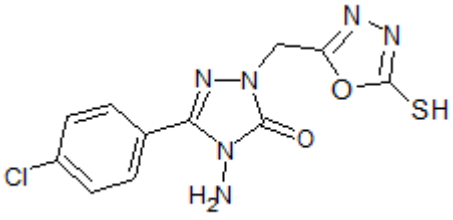
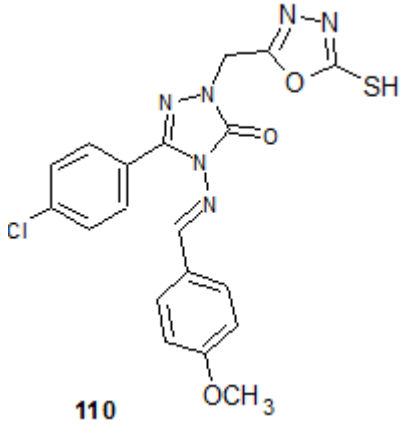


109



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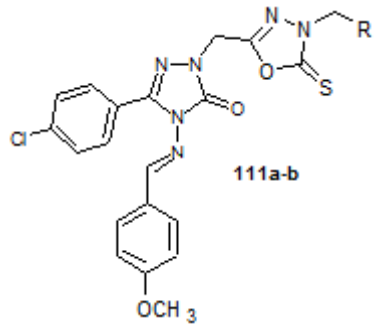
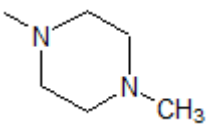
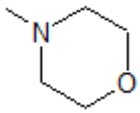




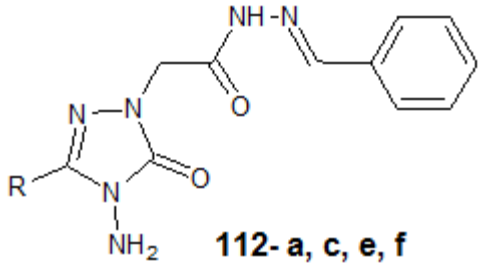


111a; R= **111b;** R=

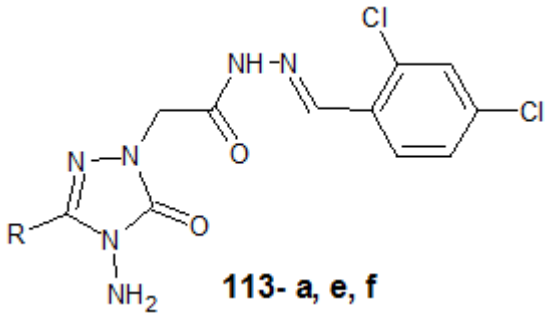
Among the Mannich bases of compound **110**, **111b** displayed good antimicrobial activities against the test microorganisms that contain an additional morpholine moiety beside 1,2,4-triazole and 1,3,4-oxadiazole rings, while other Mannich base, **111a,** that has a methyl piperazine nucleus instead of morpholine, exhibited good or moderate activities towards the test microorganisms except *Escherichia coli* and *Klebsiella pneumoniae* [15].

Neslihan *et al.,* reported the synthesis of some new 1- (5-phenylamino[1, 3, 4] thiadiazol-2-yl) methyl -5-oxo-[1,2,4] triazole and 1- (4-phenyl-5-thioxo -[1, 2 ,4] triazol-3-yl) methyl-5-oxo- [1, 2, 4] triazole derivatives and evaluated synthesized compounds for antimicrobial activity.

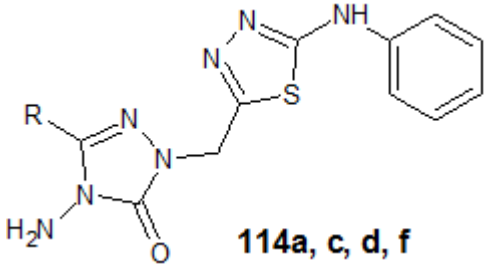
Compounds **112a, 113a** and **114a**, which contain a methyl group on position 3 of 5-oxo-[1,2,4] triazole or [1,3,4] thiadiazol-2-yl-5-oxo-[1,2,4] triazole ring were found to be effective on *E. coli, Pseudomonas aeruginosa, K. pneumonia* and *Bacillus subtilis*. No antimicrobial activity was observed on the yeast like fungi. The compounds including a phenyl group on position 3 of 5-oxo-[1,2,4] triazole ring **(112f)** or [1,3,4] thiadiazol-2-yl-5-oxo-[1,2,4] triazole ring **(114f)** showed activity against *Klebsiella pneumoniae* and lower activity against *P. aeruginosa*. Compounds **114d** which has a benzyl group on position 3 and consists of [1,3,4] thiadiazol-2-yl-5-oxo-[1,2,4] triazole ring exhibited activity towards *K. pneumoniae*, *Escherichia coli*, *Staphylococcus aureus* and *B. subtilis*, while the compound having a benzyl group at position 3 of 5-thioxo-[1,2,4] triazol-2-yl-5-oxo-[1,2,4] triazole ring **(115d)** was found to be effective only against *S. aureus*. Compound **112e**, which has a *p*-chlorobenzyl group on position 3 showed moderate activity against *S. aureus* and lower activity against *B. subtilis*, while the other compound **(113e)** including *p*-chlorobenzyl group on position 3 exhibited no activity. Among the compounds containing a phenyl group at position 3, compounds **112f** and **114f** showed activity on *K. pneumoniae*, while **115f** incorporating both 5-oxo- and 5-thioxo- [1,2,4] triazole rings exhibited no activity on test microorganisms. Compound **115c** having an *n*-propyl group on position 3 of 5-thioxo-[1,2,4]triazol-3-yl-5-oxo-[1,2,4] triazole structure showed only lower activity against *Candida albicans* and *Candida tropicalis*. Inhibitory effect on mycelial growth has been especially observed by compounds **112e, 114d** and **115f** [16].



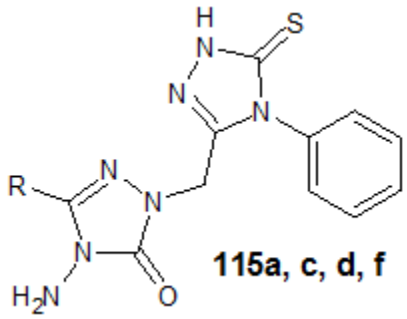
112- a, c, e, f



113- a, e, f



114a, c, d, f



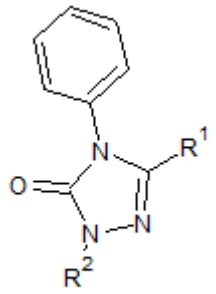
115a, c, d, f

a: methyl, **b:** ethyl**, c:** propyl**, d:** $CH_2C_6H_5$, **e:** $CH_2C_6H_4$ (p-Cl), **f:** C_6H_5

Stefañska *et al.*, reported a series of 2, 4-dihydro-[1, 2, 4]-triazol-3-one derivatives and evaluated them for antibacterial and antifungal activity by disc diffusion method. The MIC of the synthesized compounds was determined. Total 40 compounds were synthesized but 12 compounds exhibited antimicrobial activity, which were divided into two groups depending on their structure:

Group I: compounds no **126, 127, 128, 129, 130, 131, 133**

Group II: compounds no **147, 148, 150, 151, 152**



116-155

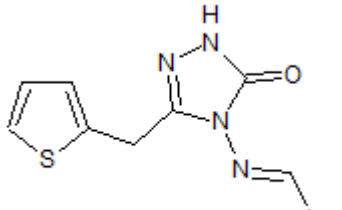
116: R_1=R_2= H; **117:** R_1=Ph, R_2= H; **118:** R_1=CH_3, R_2=H; **119:** R_1=Ph, R_2=$CH_2COOC_2H_5$; **120:** R_1=CH3, R_2= $CH_2COOC_2H_5$; **121:** R_1=H, R_2=COOEt; **122:** R_1=H, R_2= $CH_2CH=CH_2$; **123:** R_1= CH_3, R_2= $CH_2CH=CH_2$; **124:** R_1=Ph, R_2=$COCH_3$; **125:** R_1=CH_3, R_2=$COCH_3$; **126:** R_1=H, R_2= CH_2-piperidine; **127:** R_1= H, R_2= CH_2-morpholine; **128:** R_1=Ph, R_2=CH_2-morpholine; **129:** R_1=H, R_2= CH_2-pirrolidine; **130:** R_1=Ph, R_2=CH_2-pirrolidine; **131:** R_1= H, R_2= CH_2N-Et_2; **132:** R_1= H, R_2= CH_2-N-phenyl-N-benzyl; **133:** R_1= Ph, R_2= CH_2-N-phenyl-N-benzyl; **134:** R_1= H, R_2= CH_2CH_2CN; **135:** R_1= H, R_2=CH_2CH_2CN; **136:** R_1= H, R_2= CH_2CH_2COOH; **137:** R_1= H, R_2= $CH_2CH(OH)CH_2$-piperidine; **138:** R_1= H, R_2= $CH_2CH(OH)CH_2$-piperidine; **139:** R_1=H, R_2= $CH_2CH(OH)CH_2$-morpholine; **140:** R_1= H, R_2= $CH_2CH(OH)CH_2$-pirrolidine; **141:** R_1=Ph, R_2= $CH_2CH(OH)CH_2$-pirrolidine; **142:** R_1=H, R_2= $CH_2CH(OH)CH_2$-diethylamine; **143:** R_1= Ph, R_2= $CH_2CH(OH)CH_2$-diethylamine; **144:** R_1=H, R_2= $CH_2CH(OH)CH_2$-N-phenyl-N-benzyl; **145:** R_1= Ph, R_2= $CH_2CH(OH)CH_2$-N-phenyl-N-benzyl; **146:** R_1= H, R_2= CH_2CONH_2; **147:** R_1= H, R_2= $CH_2CONHCH_2$-piperidine; **148:** R_1=Ph, R_2= $CH_2CONHCH_2$-piperidine; **149:** R_1= H, R_2= $CH_2CONHCH_2$- morpholine; **150:** R_1= H, R_2= $CH_2CONHCH_2$- pirrolidine; **151:** R_1=Ph, R_2= $CH_2CONHCH_2$- pirrolidine; **152:** R_1= H, R_2= $CH_2CONHCH_2$- diethylamine; **153:** R_1= Ph, R_2= $CH_2CONHCH_2$- diethylamine; **154:** R_1= H, R_2= $CH_2CONHCH_2$- triazole; **155:** R_1=H, R_2= $CH_2CONHCH_2$- triazole

In the first group, the typical constituent in position 2 was a methylene group (-CH2-) connected with both 2, 4-dihydro-[1, 2, 4] -triazol-3-one ring and nitrogen atom (N). Nitrogen can be present either as the constituent of the ring structure, e.g. pyrolidyne (comp. no **129**, **130**), morfoline (comp. No **127**, **128**), piperidine (comp. no **126**) or as a disubstituted amine (comp. No **131**, **133**). Depending on the amines type an increase or a decrease of antibacterial activity can be observed. Best results were obtained for compounds no **1129** (N in a pyrolydine ring) and **131** (N as a component of N, N-diethylamine) as they were characterized by stronger and broader spectra of activity. Both compound no **129** and **131** were active against all Gram-negative bacterial strains and most of the tested Gram-positive bacteria except *E. hirae* ATCC 10541. Moreover, compound no. **131** showed antifungal activity against *C. parapsilosis* ATCC 22019. In case of compounds **127** and **128** any changes in activity depending on the type of substituents in 4 and 5 positions were not observed.

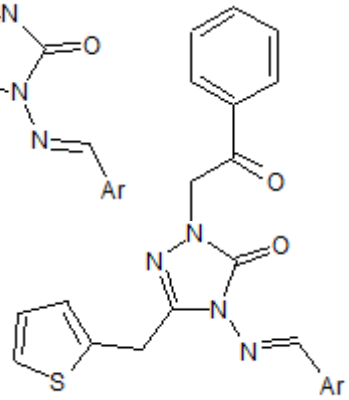
In group II, the structure of substituents found in position 2 of the ring was far more complicated. It was composed of an amide group connected with

2 methylene groups by nitrogen and carbon atoms. One methylene group was combined with 2, 4-dihydro-[1, 2, 4]-triazol-3-one and the other with an amine. The activity of substances classified as group II doesn't differ significantly. Any differences can derive from the presence of substituents in 4 and 5 positions of the ring. The phenyl group found in compound **148** may be the reason of its stronger anti-staphylococcal activity in comparison with compound **147** [17].

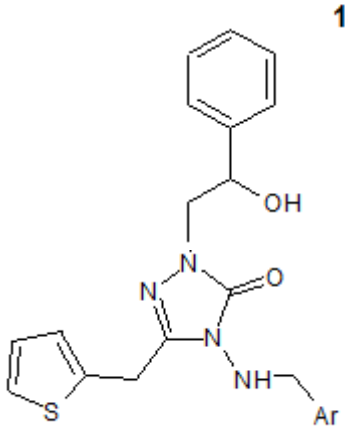
Yasemin *et al.,* synthesized some new [1, 2, 4] - triazol-5-one derivatives and screened them for antimicrobial and antitumor activity. Compounds **156a, 156c, 156g, 157f, 158b, 158f**, and **158g** showed good antifungal activity against *Candida albicans* ATCC 60193 and *Candida tropicalis* ATCC 13803, while none of the compounds showed antimicrobial activity against bacteria. Compounds selected by the National Cancer Institute (NCI, USA) were investigated for anti-tumor activity and were found to be inactive [18].



156a-g



157a-g

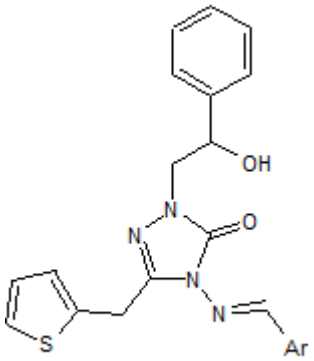


158a-g

156-158; a (Ar= thiophene), **b (Ar=** furan), **c (Ar=**pyridyl), **d (Ar=** phenyl), **e(Ar=** *m*-Br-Ph), **f(Ar=** 2-Cl,6-F-C_6H_3), **g(Ar=** 2,4-di-Cl-C_6H_3)

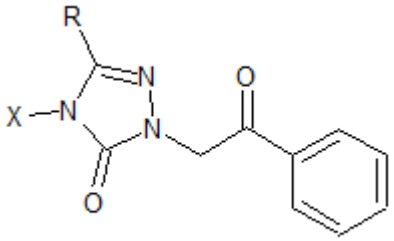
Triazolone derivatives as Anti-tumour agents

Demirbaº *et al.,* synthesized various 1, 2, 4-triazol-3-one derivatives and screened for antitumor activity against 3 human tumor cell lines: *viz*., breast cancer (MCF7), non small cell lung cancer (NCI-H460) and CNS (SF-268).

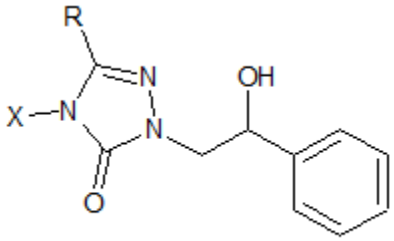


159b, d, e

159; b(Ar= furan), **d**(Ar= phenyl),**e**(Ar= *m*-Br-Ph)



160a-e

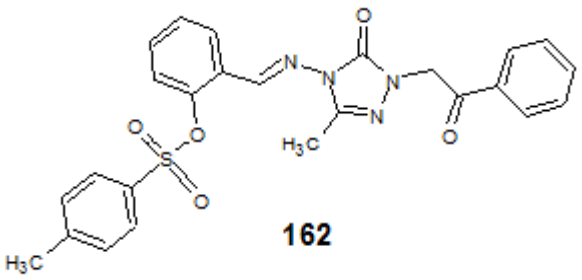


161a-c

R=benzyl, p-chlorobenzyl, n-propyl
X=NH_2, CHC_6H_32, 4CL, N=CHC_6H_3,o-OH

Among the compounds with a tosyl group in their structures **(162)-(165),** the reduced derivatives **164** and **165** were found to possess antitumor activity, whereas **162** and **163** that contain a tosyl group

and schiff base exhibited no antitumor activity.



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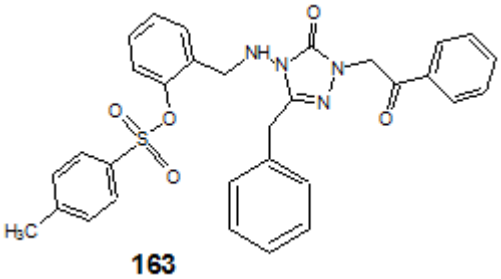

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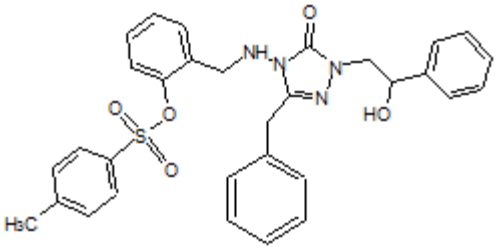

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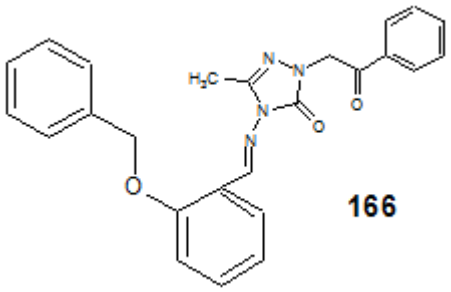

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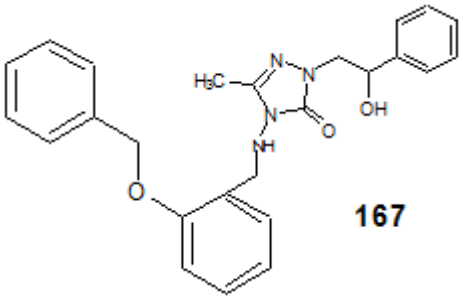
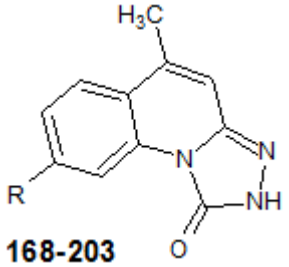


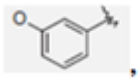
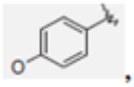
167

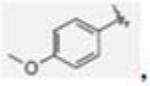
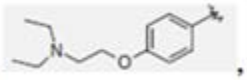
Among the benzoylated compounds **166** and **167**, only **167**, reduced and benzylated at phenolic hydroxyl, displayed an antitumor activity. The results do not permitted any evaluation of structure activity relationship within the series of **160a-e** and **161a-c**, since **160e** displayed antitumor activity while its reduced derivative **161c** not. On the contrary, **160d** was found to be inactive, while its reduced derivative **161b** possess an antitumor activity [7].

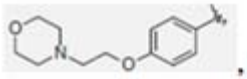
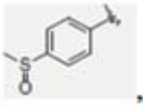
Oza *et al.*, designed and synthesized various 4-methyl-7-substituted aryl triazolones and screened them for checkpoint kinase-1 (Chk1) inhibitor activity. Chk-1 is a Ser/Thr protein kinase that mediates the cellular response to DNA damage.

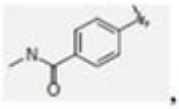
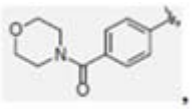


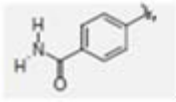
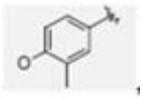
168-203

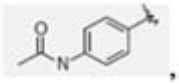
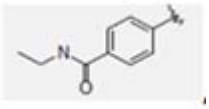
168a=  , **168b=**  ,

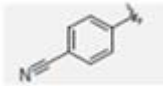
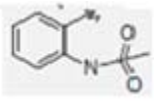
169=  , **170=**  ,

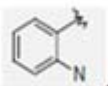
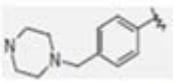
171=  , **172=**  ,

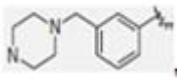
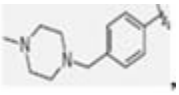
173=  , **174=**  ,

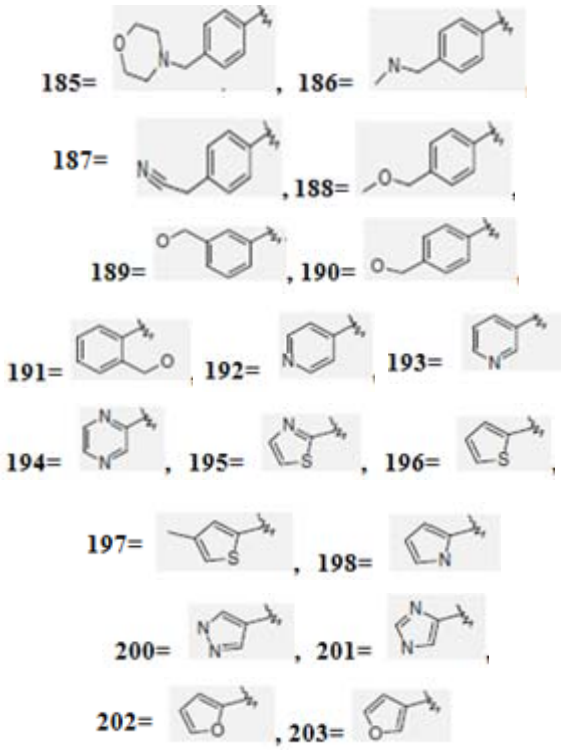
175=  , **176=**  ,

177=  , **178=**  ,

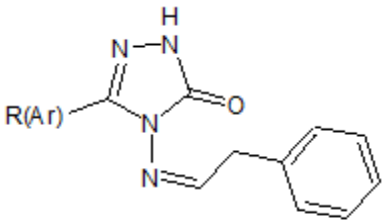
179=  , **180=**  ,

181=  , **182=**  ,

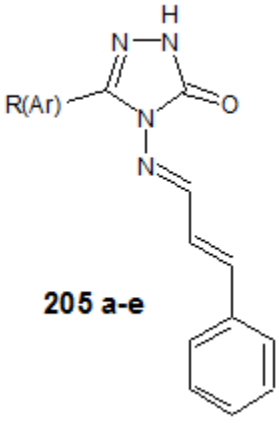
183=  , **184=**  ,



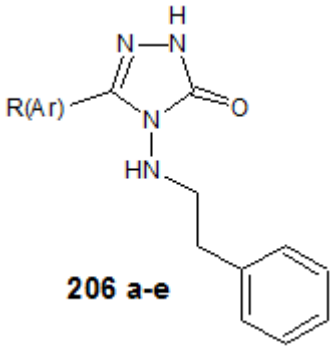
SAR study revealed that aryl substituted polar groups in compound **168a** appeared to make key interactions with sugar binding pocket resulting in an increase in potency about 10 folds compared to parent triazolone. 4-hydroxy phenyl substitution yielded a very potent compound, **168b**. Methylation of the phenolic group of **168b** resulted in an approximate 50 fold drop in potency (compound **169**). Ether linked analogs bearing a terminal amino group yielded even more potent compounds **170** and **171**. 4-cyano (**179**) and 4-methyl sulfoxide (**172**) aryl substituents also gave a modest increase of about 8 fold. Additional exploration of the SAR centered on the methylene spaced analogs containing cyclic as well as acyclic amines (**182-185**). The acyclic amine 20 showed ~39 nM potency, but cyclic variants showed an approximate 10 fold boost in potency. Inserting a methylene spacer in case of **188**, proved to be detrimental and resulted in a decrease in potency from 80 nM (**169**) to 3.4 µM (**186**). The corresponding *m*- and *o*-substituted hydroxymethylphenyl analogs (**189** & **190**) suggest that both the *p*- and *m*- hydroxymethylphenyl substituents were favoured over *o*-hydroxymethylphenyl isomer. Among 7-heterocyclyl substituted triazolones, six-membered heterocyclic analogs were generally less potent than five- membered heterocycles with the exception of the 4-pyridyl compound (**192**). Within five- membered heterocyclic triazolones, thiazole substituent in **195** was associated with loss of potency. In contrast, 2 and 3 furanyl substituted analogs, **202** and **203** had activity in nanomolar range.a striking difference was observed in the activities of 2- and 3- substituted pyrroles, **198** and **199** respectively**,** where the former was significantly more potent than the later. 2- pyrazole substitution yielded a 41 nM compound **200**. Compounds **198** and **200** were the most potent inhibitors at the enzyme level [19]. Demirbas *et al.,* also reported 3-alky l (aryl)-4-alkylidenamino-4, 5-dihydro-1H-1, 2, 4-triazol-5-ones and 3-alkyl-4-alkylamino-4, 5-dihydro-1H-1, 2, 4-triazol-5-ones and screened for antitumor activity.



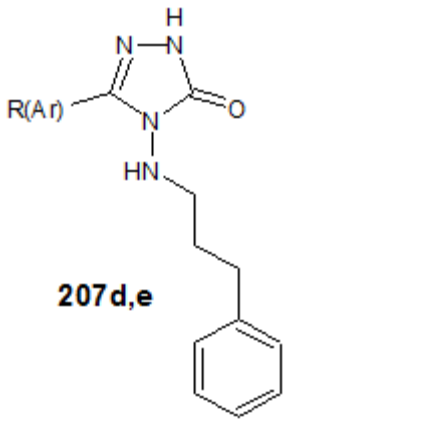
204 a-e

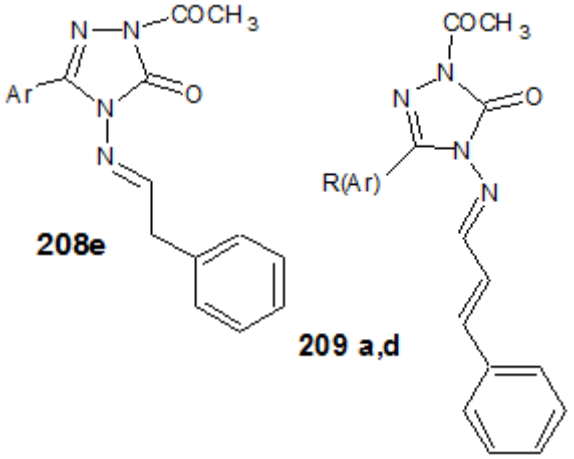


205 a-e



206 a-e

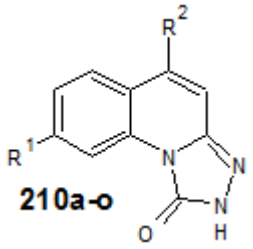


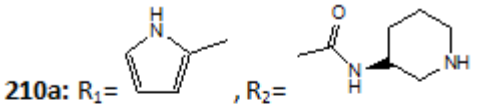


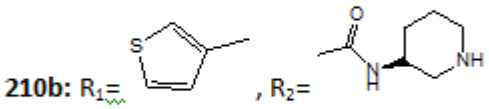
a: CH_3, **b:** $CH_2C_6H_5$, **c:** $CH_2C_6H_4$(*p*-Cl), **d:** C_6H_5, **e:** $C_6H_4CH_3$(*p*-)

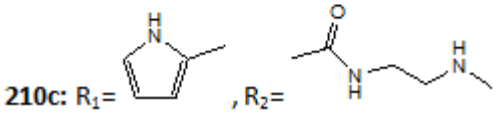
The screening experiments were carried out on all the compounds except **204d, 205e, 207d** and **207e** against 3 human tumor cell lines: *viz*., breast cancer (MCF7), non-small cell lung cancer (NCI-H460) and CNS (SF-268). The highest activity was observed for phenylethylidenamino and phenylethylamino groups at position 4 of the triazolone ring. The compounds **205b** and **205c** containing 3-phenylallylidenamino group at position 4 of triazolone ring have less cytostatic effect against two cell lines [20].

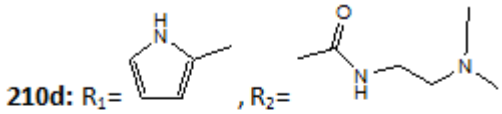
Oza *et al.*, also designed and evaluated various 4-amino /4-hydroxymethyl -7-substituted aryl triazolones for checkpoint kinase-1 (Chk1) inhibitor activity. SAR trend evident from the data was that the presence of the 2-aminoethyl moiety was the key for activity against Chk1 enzyme. Extension of the 2-aminoethyl group as in the case of **210h** or replacement of the terminal amine by a more neutral moiety such as the 2-hydroxyethyl group as depicted in **210e** and **210g** resulted in about a 10-20 fold drop in enzyme potency.

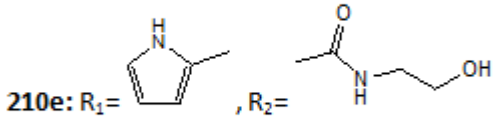


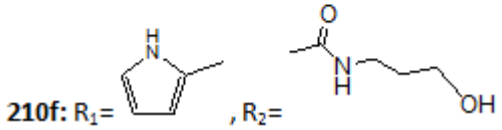


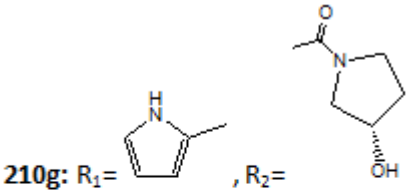


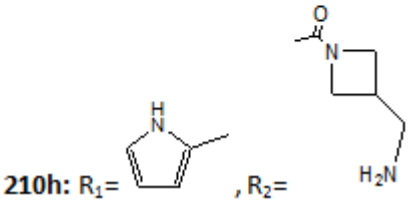


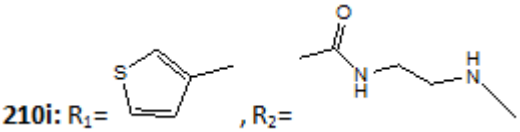


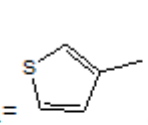
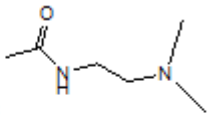


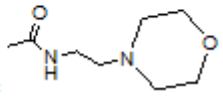


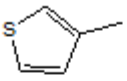
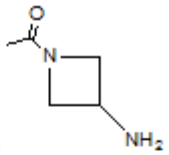


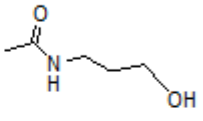


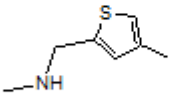
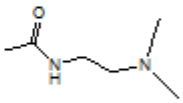


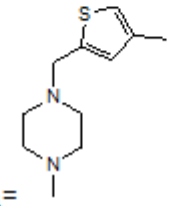
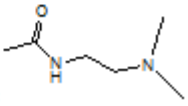
210j: R_1=  , R_2= 

210k: R_1=  , R_2= 

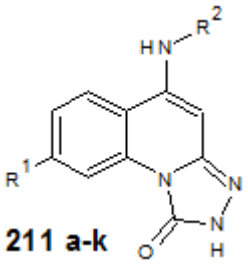
210l: R_1=  , R_2= 

210m: R_1=  , R_2= 

210n: R_1=  , R_2= 

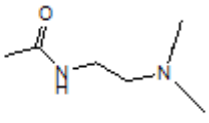
210o: R_1=  , R_2= 

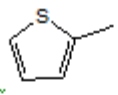
Compounds **210d, 210i** and **210j** exhibited a reasonable balance of potency and solubility. Among various heterocyclic substituted 4-aminotriazolones synthesized, **211c** and **211h** exhibited high cellular potency. Amongst the five membered heterocycles, 2- as well as 3-thieno and 2-pyrrolo groups (compounds **211c**, **211d** and **211h** respectively) were found to be the most potent analogs in terms of both enzyme and cellular potency.

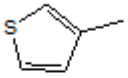


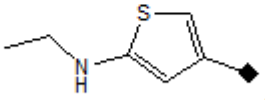
211 a-k

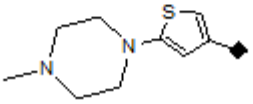
211a: R_1= Br, R_2= H

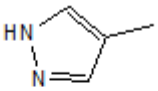
211b: R_1=  , R_2= 

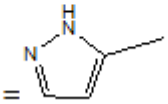
211c: R_1=  , R_2= H

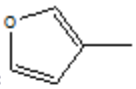
211d: R_1=  , R_2= H

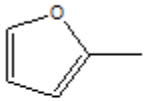
211e: R_1=  , R_2= H

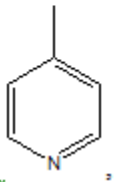
211f: R_1=  , R_2= H

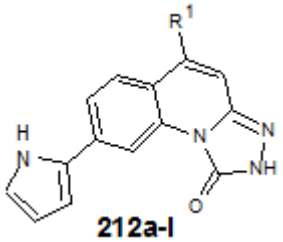
211g: R_1=  , R_2= H

211h: R_1=  , R_2= H

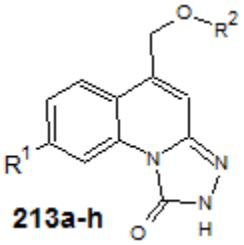
211i: R_1=  , R_2= H

211j: R_1=  , R_2= H

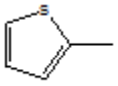
211k: R_1=  , R_2= H

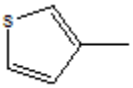


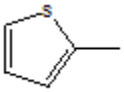
212a-l

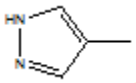


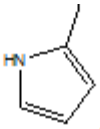
213a-h

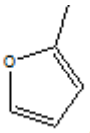
213a: R_1=  R_2= H;

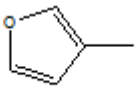
213b: R_1=  , R_2= H;

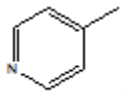
213c: R_1=  , R_2= CH_3;

213d: R_1=  , R_2= H;

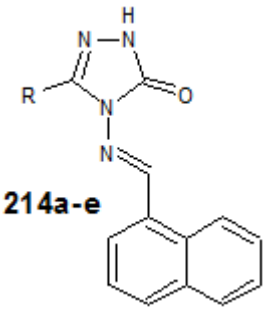
213e: R_1=  , R_2= H;

213f: R_1=  , R_2= H;

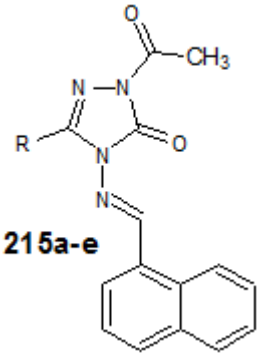
213g: R_1=  , R_2= H;

213h: R_1=  , R_2= H

Additionally, 4-pyridyl substituted analog **211k** was somewhat active in the Chk1 cellular assay while the corresponding 4- methyl triazolone was not, suggesting a key contribution of the 4- amino moiety in this scaffold to the observed cellular potency. SAR studies led to identification of potent compounds such as **211c**, **211h** and **213e** [21]. Neslihan *et al.*, reported the synthesis and antitumor activity of some new 4- (1-Naphthyl-idenamino) and 4- (1-Naphthylmethylamino) - 1, 2, 4- triazol-5-one derivatives. Twenty one compounds (**214b, 214e, 215a-e, 216c, 217a-e, 218a, 219b, 218d, 219e, 220a-c, 220e**) were evaluated for screening on 3 human tumor cell lines, i.e. breast cancer (MCF7), non small cell lung cancer (NCI-H460) and CNS (SF-268). The highest inhibition of the 3 tumor cell lines was observed for four compounds, two of which contain a p-tolyl group at the position 3 of the -1,2,4-triazol-5-one ring (**214e** and **217e**) while the other two contain a p-chlorobenzyl group at the same position (**216c** and **220c**) [22].

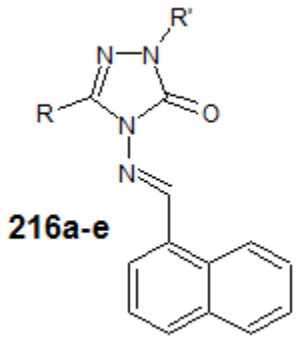


214a-e



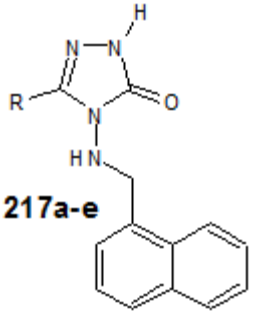
215a-e

214, 215; a = CH_3, **b** = $CH_2C_6H_5$, **c** = $CH_2C_6H_4$(*p*-Cl), **d** = C_6H_5, **e** = C_6H_4(*p*-CH_3)

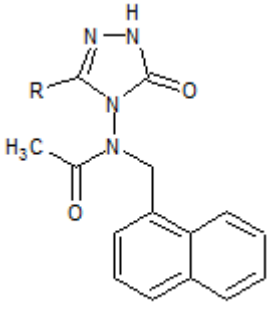


216a-e

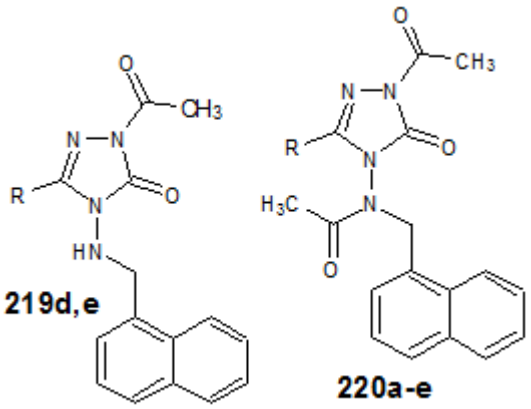
216a: R= $CH_2C_6H_5$, R'= $CH_2C_6H_5$
216b: R= $CH_2C_6H_4$(*p*-Cl), R'= $CH_2C_6H_5$
216c: R= $CH_2C_6H_4$(*p*-CH_3), R'= $CH_2C_6H_5$
216d: R= $CH_2C_6H_4$(*p*-Cl), R'= CH_3
216e: R= C_6H_4(*p*-CH_3), R'= CH_3



217a-e

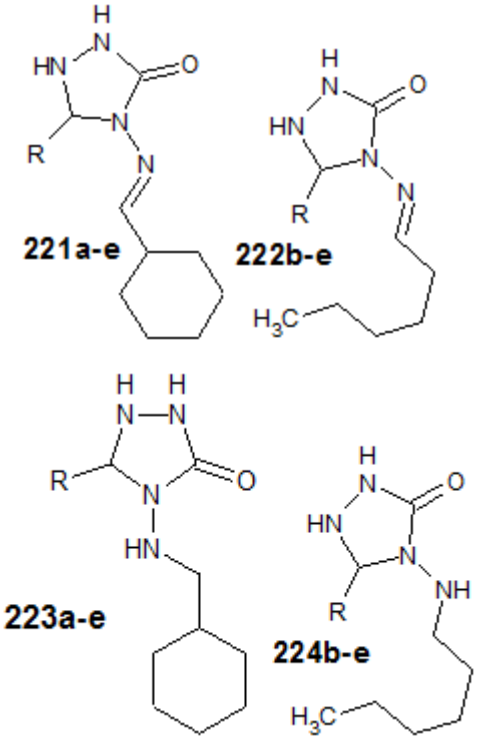


218a-c



217-220: **a** = CH_3, **b** = $CH_2C_6H_5$, **c** = $CH_2C_6H_4$(*p*-Cl), **d** = C_6H_5, **e** = C_6H_4(*p*-CH_3)

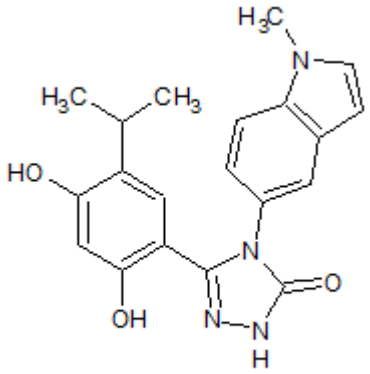
Neslihan *et al.,* also synthesized a series of novel 3-alkyl-4-cyclohexylmethylenamino-5-oxo-4,5-dihydro-[1,2,4]triazoles (**221**) and 3-alkyl-4-hexylidenamino-5-oxo-4,5-dihydro-[1,2,4]triazoles (**222**). The results demonstrated that the acetyl group at position 1 of the 5-oxo-[1, 2, 4] triazole ring is not essential for antitumor activity.



221-224: **a** = CH_3, **b** = $CH_2C_6H_5$, **c** = $CH_2C_6H_4$(*p*-Cl), **d** = C_6H_5, **e** = C_6H_4(*p*-CH_3)

Compound **221c** exhibited activity towards leukemia, non-small cell lung cancer (except HOP-62), colon cancer (except HCT-116 and ACHN), breast cancer (except MDA-MB-435 and HS 578T), brain tumor (SF-268), melanoma (except MALME-3M, M14), ovarian cancer (except OVCAR 5) and renal cancer to inhibit 50% of the growth of tumor cells with GI50 values less than 100_M. Compound **221c** showed marginal activity against HOP-62, HCT-116, ACHN, MDA-MB-435, HS 578T, SF-268, MALME- 3M, M14 and OVCAR 5. Compound **224c** displayed moderate activities for HT29, SW-620, SNB-75, OVCAR-4 and OVCAR-5. Compound **222d** was more selective towards the test cell lines; moderate activities were observed against the leukemia cell line (except CCRF-CEM), HOP-62, HT29, MCF7, HS 578T, T-47DSK-MEL-5 and A498 [23].

Ying *et al.,* showed that Ganetespib (**225**) a unique resorcinolic inhibitor of Hsp90 exhibited potent in vitro cytotoxicity in solid and hematologic tumor cell lines including those that express mutated kinases that confer resistance to small-molecule tyrosine kinase inhibitors.

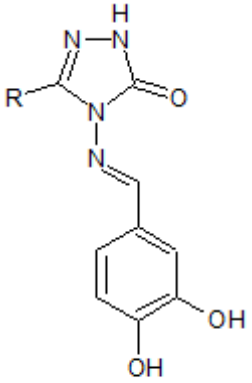


Ganetespib treatment rapidly induced the degradation of known Hsp90 client proteins, displayed superior potency to the ansamycin inhibitor 17-allylamino-17-demethoxygeldanamycin (17-AAG), and exhibited sustained activity even with short exposure times. *In vivo*, ganetespib showed potent antitumor efficacy in solid and hematologic xenograft models of oncogene addiction, as evidenced by significant growth inhibition and/or regressions. Notably, evaluation of the microregional activity of ganetespib in tumor

xenografts showed that ganetespib was efficiently distributed throughout tumor tissue, including hypoxic regions >150 mm from the microvasculature, to inhibit proliferation and induce apoptosis. Ganetespib showed no evidence of cardiac or liver toxicity [24].

Triazolone derivatives as antioxidant agents

Haydar *et al.*, reported the synthesis and antioxidant activity of some 4- benzylidenamino-4, 5-dihydro-1H-1, 2, 4-triazol-5-one derivatives. Antioxidant activity was determined by DPPH (2, 2-diphenyl-1-picrylhydrazyl) free radical scavenging measurement with butylated hydroxytoulene (BHT) as reference.

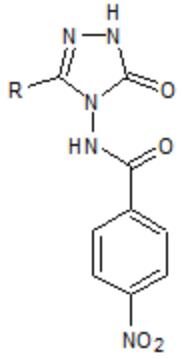


226a-h

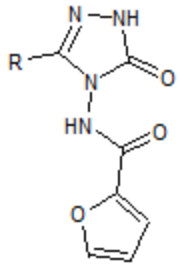
a = CH_3, **b** = C_2H_5, **c** = $CH_2C_6H_5$, **d**= $CH_2C_6H_4$ (*p*- CH_3), **e** = $CH_2C_6H_4$ (*p*-Cl), **f**= $CH_2C_6H_4$ (*p*-OCH_3), **g**= C_6H_5, **h**= cyclopropyl

All test compounds, except **226d**, showed considerable DPPH radical scavenging activity. IC_{50} values of **226a**, **226c** and **226e** were found to be same and were highest [25].

Haydar *et al.*, also synthesized 4, 5-dihydro-1H-1, 2, 4-triazol-5-one derivatives (**227 a-f**) and reported their antioxidant activity. The compounds along with 3-alkyl-4-(2-furoylamino)-4, 5-dihydro-1*H*-1,2,4-triazol-5-ones (**228a-c,e,f**) screened for their *in-vitro* antioxidant activities by reducing power method, DPPH method and ferrous ion chelating activity method. No compound showed the ability of electron donor to scavenge free radicals in reducing power method. In DPPH test, compounds showed mild activities as a radical scavenger. In ferrous ion chelating activity **227a** and **227e** showed good anti-chelating activity at concentration of 37.5 mg/DL. Compounds **227c**, **227d** and **227f** did not show any chelating activity. The compounds **228a**, **228b**, **228c**, **228e** and **228f** exhibited 66.9, 5.4, 72.4, 12.9 and 23.5 % chelation of ferrous ion at the concentration of 12.5 mg/L, respectively. The antioxidant activities of compounds varied with the tree test models. Results have revealed that all of the tested compounds showed mild antiradical activity and the compounds, except **227c**, **227d** and **227f**, revealed good chelating activities [26].



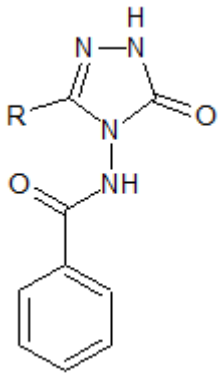
227a-f



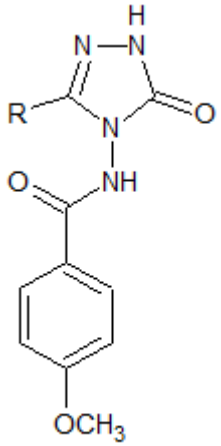
228a-f

227-228; a = CH_3, **b** = C_2H_5, **c** = $CH_2C_6H_5$, **d**= $CH_2C_6H_4$ (*p*- CH_3), **e** = $CH_2C_6H_4$ (*p*-Cl), **f**= C_6H_5

Muzaffer A *et al.*, reported the antioxidant activity of 3-alkyl-4-phenylacetylamino-4, 5-dihydro-1*H*-1, 2, 4-triazol-5-ones (**229-230a-e**) [27] and 3-alkyl (aryl)-4-(4-diethylaminobenzylidene-amino)-4, 5-dihydro-1*H*-1, 2, 4-triazol-5-ones



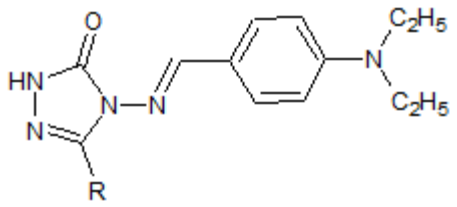
229a-e



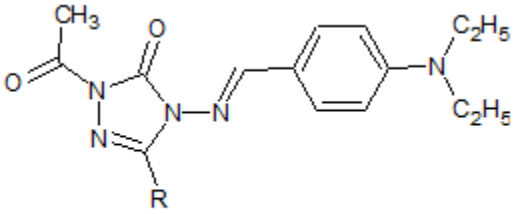
230a-e

229-230; a= CH_3, **b** = C_2H_5, **c** = $CH_2C_6H_5$, **d**= $CH_2C_6H_4$ (*p*- CH_3), **e** = $CH_2C_6H_4$ (*p*-Cl)

(**231a-g)** along with five new 1-acetyl-3-alkyl (aryl)-4-(4-diethylamino-benzylideneamino)-4, 5-dihydro-1*H*-1, 2, 4-triazol-5-ones (**232a-e)** [28].



231a-g



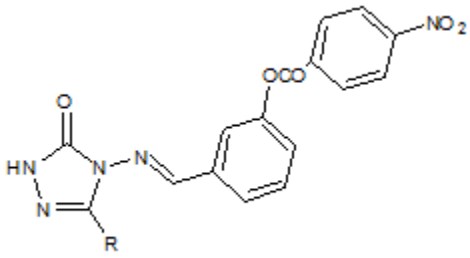
232a-g

231-232; a = CH_3, **b** = C_2H_5, **c** = $CH_2C_6H_5$, **d**= $CH_2C_6H_4$ (*p*- CH_3), **e** = $CH_2C_6H_4$ (*p*-Cl), **f**= C_6H_5, **g**= cyclopropyl

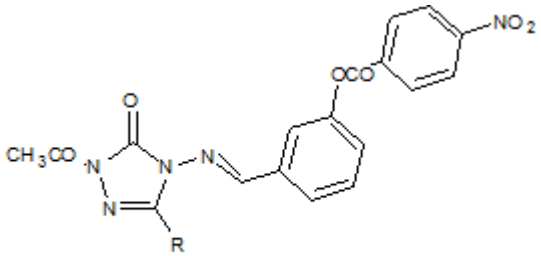
The compounds were screened for their antioxidant activities by reducing power method and free radical scavenging measurements. All the compounds tested with these methods exhibited marked DPPH free radical scavenging activity in a concentration-dependent manner.

Only compounds **231g**, **232a** and **232b** may reduce metal ions complexes to their lower oxidation state or to take part in electron transfer reaction which showed their ability to scavenge free radicals [28].

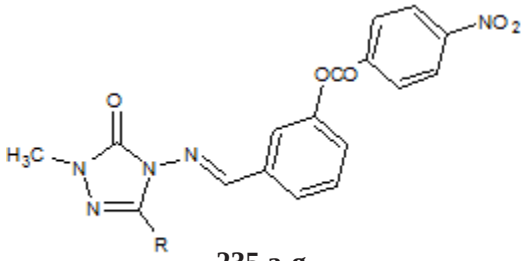
Yuksek H *et al.,* also evaluated 4, 5-dihydro-1H-1, 2, 4-triazol-5-one derivatives for antioxidant activity using above mentioned three methods; reducing power method, DPPH free radical scavenging measurement method and ferrous ion chelating method. The SAR studies of compounds revealed that, when compared with compounds **233**, *N*-acetyl substitution of 4, 5-dihydro-1*H*-1, 2, 4-triazol-5-one ring in compounds **234** decreased the reducing activity but increased the scavenging activity significantly. On the other hand, compounds **235** that have *N*-methyl substituted showed a significant increase in their reducing power when compared with *N*-acetyl substituted compounds **234**, and also significant increase in the scavenging activity of them when compared with unsubstituted compounds **233**. Hence, these modifications included acetylation and methylation of the compounds **233** may be affected their electron transfer ability and hydrogen donating ability. All of the compounds demonstrate a marked capacity for iron binding [29].



233 a-g



234 a-g



235 a-g

Additional Activities of triazolones

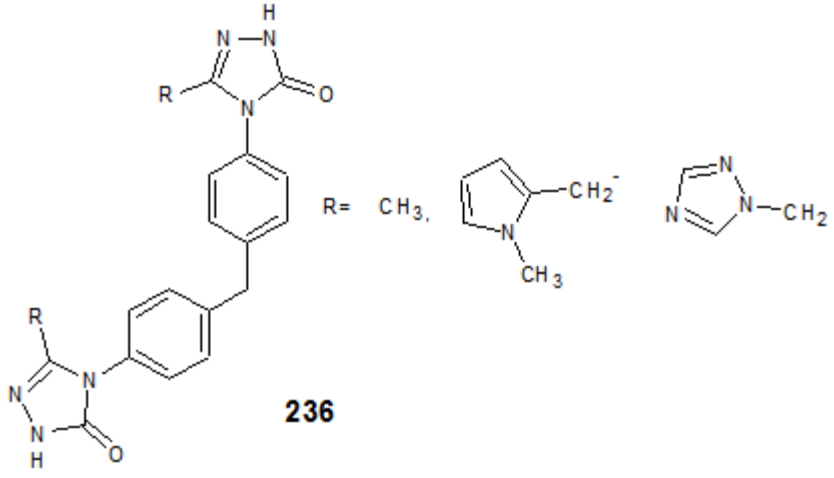
Triazolone containing compounds have also exhibited other activities which have been reported by several workers. Pitucha *et al.,* reported the antinociceptive activity of 4, 4'-bis (3-substituted-4, 5-dihydro-1H-1, 2, 4-triazol-5-one-4-yl) diphenylmethane derivatives (**236**) [30]. Kamble *et al.,* reported the synthesis and antihaemostatic activity of 1, 2, 4- triazoles incorporating 1, 2, 4-triazine ring. Only compounds containing the C=S group with *p*-bromophenyl substituent **237j** and *p*-chlorophenyl substituent **237i** showed

considerable activity [31]. Xu Y *et al.,* further synthesized a new series of hPPARá agonists conataining a 2,4-dihydro-3H-1,2,4-triazol-3-ones and evaluated for *in vitro* potency and selectivity by direct receptor binding as well as by cell based assays to determine their functional activity. The compound **245** possessed a disubstituted triazolone tethered by a 2-C atom alkyl linker to phenoxy-isobutyrate (fibrate) moiety.

This compound possessed activity on both hPPARα and hPPARγ receptors. Investigation of the substituent effects on triazolone N^2 and N^4 positions led to conclusion that compounds with 3-C atom linker (n=3) showed 450 folds increase in activity. SAR studies revealed that activity was retained or increased by utilizing nonpolar substituents at 3- or 4- positions of benzyl ring in compounds **247**, **248**, **251** and **252**. Compound **251** showed highest hPPARα functional potency and >700 fold more selectivity over the other subtypes [32].

Triazolone derivatives have also reported to be openers of the cloned mammalian large conductance, Ca^{2+}- activated potassium (maxi-K) channel as reported by Romine *et al.,* who synthesized a series of 4, 5-diphenyl triazol-3-ones. Among series **255a-h**, 4-hydroxy analogue **(255g)** and 2-chloro-5-hydroxy analogue (**255h**) were found inactive, whereas compounds **255a**, **255b**, **255d** and **255e** showed channel opening properties. The position of CF_3 group on the electron deficient aromatic ring appears less critical for activity but removal of electron withdrawing group like F or CF_3 (**255f**) eliminated activity. SAR studies suggested existence of a lipophilic pocket adjacent to the binding region of the channel. The presence of a hydrogen donor on the heterocyclic ring and its spatial relationship to the ortho phenol were found paramount for maxi-K channel activity [33].

Further, Hewawasam *et al.,* also evaluated series of 1, 3-diaryl 1,2,4-(4H)-triazol-5-ones (**256a-g**) for the same activity. SAR studies suggested that the p-chlorophenol element is essential for maxi-K opening activity. It was also reported that an electron withdrawing substituent is also essential for activity and introduction of CF_3 markedly enhanced activity as shown by **256a-d**. Furthermore, both the para regioisomer **256d** and



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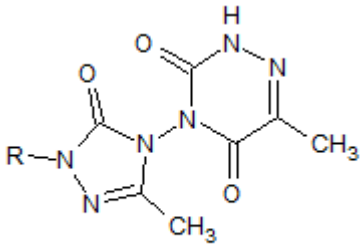
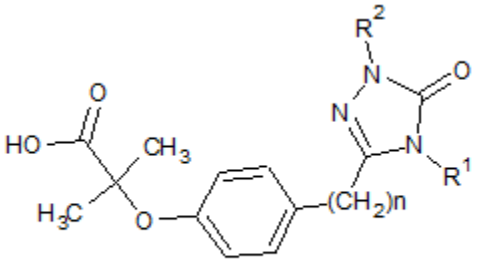
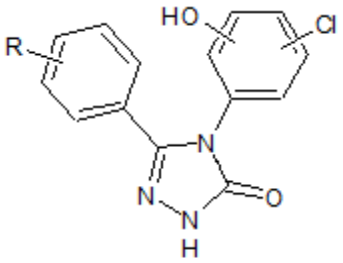


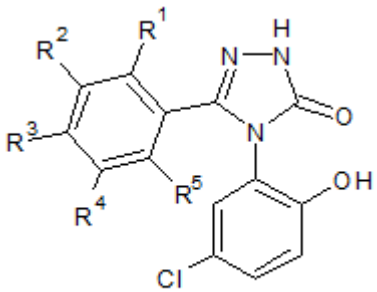
237 a-j



238, 245-254



255a-h

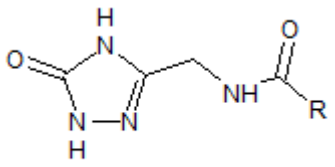


256 a-g

meta regioisomer **256c** were found to be superior to the ortho CF_3 substituted analogue **256b**. Similarly, **256e** and **256g** also exhibited good efficacy [34].Additionally, Sheppeck *et al.*, discovered selective and potent TACE (TNFα Converting Enzyme) inhibitors which replaces the common hydroxamate zinc binding group with triazolone nucleus. These triazolone derivatives inhibited zinc metalloprotease and were designed using a pharmacophore model. Compound **257** proved ineffective whereas its sulfonamide derivative (**258**) possessed some activity at 439 nM. Triazolone derivative containing pyrrolidinyl linker (**3R,4S- 260**) was found to be 3-fold more potent at 162 nM against TACE. Lastly, introduction of a benzyl linker provided compound **259** with an IC_{50} of 34 nM [35].

Conclusion

Triazolone derivatives have primarily been reported to be useful as antimicrobial, antitumor, anticonvulsant, antioxidant activities. Additionally other activities of triazolones like antinociceptive, analgesic and antihemostatic activities were also studied, but still they are required to be explore well for pharmacophoric feature analysis. Based on reported pharmacological activities of various triazolone derivatives, triazolone nucleus seems to be a promising lead for the development of future active compounds and has potential to explore for better pharmacological activities with less toxic effects.



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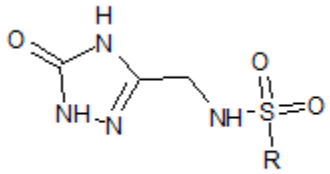

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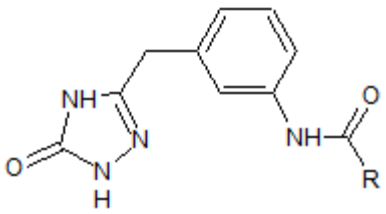

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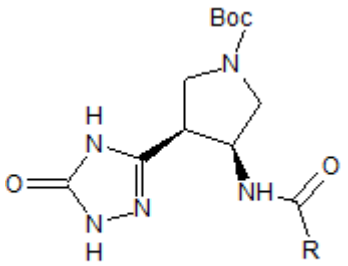

260

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