Biological Potentials of Biological Active Triazole Derivatives: A Short Review

Mohammad Asif*

Department of Pharmacy, Guru Ram Das Institute of Management and Technology, Dehradun, Uttarakhand, India

Abstract

Triazole is a versatile lead molecule for designing potential bioactive agents. The triazole derivatives have been found to exhibit diverse biological activities such as anti-fungal, antibacterial, antitubercular, anti-inflammatory, analgesic, anticancer, antiviral and other biological properties. Consequently, they have attracted increasing attention in the field of drug discovery. Similarly, oxazoles and their fused heterocyclic derivatives have received considerable attention owing to their effective medicinal importance.

Keywords: Heterocycles; Triazole; Oxazole; Biological activities

Introduction

Heterocycles make up an exceedingly important class of compounds. In fact, more than half of all known organic compounds are heterocycles. Many natural drugs are heterocyclic in nature. Many synthetic drugs are also heterocycles. Heterocyclic compounds occupy a central position among those molecules that make life possible. Heterocycles have been explored for developing pharmaceutically important molecules. In recent decades there has been constant interest in the chemistry of azoles because more than hundred azole derivatives are used today as drugs. Azoles are heterocyclic compounds characterized by a five-membered ring which contains an atom of nitrogen and at least one other non-carbon atom, nitrogen, sulfur or oxygen. These compounds are aromatic and have two double bonds.

Triazoles and related compounds

Five inembered aromatic rings with three nitrogen atoms are called triazoles. The two possible combinations of the five atoms account for vicinal(v) and symmetrical(s) triazoles In chemical abstracts, v-triazoles is also listed as 1H-1,2,3-triazole or pyrrodiazole and 2H-1,2,3-triazole or pyrrodiazole. The pyrrodiazole was occasionally used to designate triazole. The term osotriazole refers to derivatives of 2H-1,2,3-triazole particularly those prepared from osazones (Schemes 1 and 2).

Heterocyclic compounds bearing a symmetrical triazoles moiety have been reported to have a broad spectrum of pharmacological activities (Schemes 3-9).

Triazoles have been reported to possess wide variety of biological activity. Some of these activities are mentioned here.

Anti-inflammatory activity: Anti-inflammatory activity of some new 2,5-di-substituted 1,3,4-oxadiazole derivative (1) [1]. The presence of n-butyl amino group at 2nd position of 1,3,4-oxadiazole nucleus la showed maximum activity, where as the presence of cyclohexyi amino group lb showed minimum activity (Scheme 10).

1a R=CH2CH2CH2CH2

Keywords: Heterocycles; Triazole; Oxazole; Biological activities

Introduction

Heterocycles make up an exceedingly important class of compounds. In fact, more than half of all known organic compounds are heterocycles. Many natural drugs are heterocyclic in nature. Many synthetic drugs are also heterocycles. Heterocyclic compounds occupy a central position among those molecules that make life possible. Heterocycles have been explored for developing pharmaceutically important molecules. In recent decades there has been constant interest in the chemistry of azoles because more than hundred azole derivatives are used today as drugs. Azoles are heterocyclic compounds characterized by a five-membered ring which contains an atom of nitrogen and at least one other non-carbon atom, nitrogen, sulfur or oxygen. These compounds are aromatic and have two double bonds.

Triazoles and related compounds

Five inembered aromatic rings with three nitrogen atoms are called triazoles. The two possible combinations of the five atoms account for vicinal(v) and symmetrical(s) triazoles In chemical abstracts, v-triazoles is also listed as 1H-1,2,3-triazole or pyrrodiazole and 2H-1,2,3-triazole or pyrrodiazole. The pyrrodiazole was occasionally used to designate triazole. The term osotriazole refers to derivatives of 2H-1,2,3-triazole particularly those prepared from osazones (Schemes 1 and 2).

Heterocyclic compounds bearing a symmetrical triazoles moiety have been reported to have a broad spectrum of pharmacological activities (Schemes 3-9).

Triazoles have been reported to possess wide variety of biological activity. Some of these activities are mentioned here.

Anti-inflammatory activity: Anti-inflammatory activity of some new 2,5-di-substituted 1,3,4-oxadiazole derivative (1) [1]. The presence of n-butyl amino group at 2nd position of 1,3,4-oxadiazole nucleus la showed maximum activity, where as the presence of cyclohexyi amino group lb showed minimum activity (Scheme 10).

1a R=CH2CH2CH2CH2

Scheme 3: Fluconazole (Anti-fungal agent).

Scheme 4: Ribavirin (Antiviral agent).

Scheme 5: Rizatriptan (Anti-inflammatory Agent).

*Corresponding author: Mohammad Asif, Department of Pharmacy, Guru Ram Das Institute of Management and Technology, Dehradun-248 009, Uttarakhand, India, Tel: 01352734327; E-mail: aasif321@gmail.com

Received: September 30, 2016; Accepted: October 30, 2016; Published: November 16, 2016

Citation: Asif M (2016) Biological Potentials of Biological Active Triazole Derivatives: A Short Review. Organic Chem Curr Res 5: 173. doi: 10.4172/2161-0401.1000173

Copyright: © 2016 Asif M. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
These compounds are dual inhibitors of cyclooxygenase and 5-Lox. Among these 2c is more active (80%) than 2a and 2b.

The inflammatory, analgesic and antihypertensive properties of 3,6-diaryl-1,2,4 triazoles[3,4-a] phthalazines (3a and 3b) [3] (Scheme 12).

3a=R = C₆H₅ R₁=H, p-OCH₃, 3,4-dimethoxy, p-CH₃, o –NO₂,
3b=R = p- CH₃ C₆H₄ R₁= H, p-OCH₃, 3,4 - dimethoxy, p-CH₃, o-NO₂

Compounds of 3a series exhibited promising antiinflammatory activity (40, 51 and 52%) compared to phenylbutazone at a dose of 100 mg/kg body wt. These compounds also showed mild to moderate analgenre activity (4-40%) in comparison to aspirin (60%) at 100 mg/ kg body wt. Some of these compounds at a dose of mg/kg, i.v also produced rapid fall in blood pressure followed by quick recovery whereas hydrakizine at 2 mg/kg i.v. produced gradual and transient fail in the blood pressure (42 mm Hg) with long duration and slow recovery.

Anti-inflammatory activity of 3-(substituted phenyl)4'(substituted phenyl 5-(alkyl/alkenyl-mercapto)-1 H-1,2,4 triazoles (4a-h) [4] (Scheme 13).

4a R=Cl R₁=H R₂=CH₂
4b R=Cl R₁=H R₂=C₂H₅
4c R=Cl R₁=H R₂=CH₂CH=CH₂
4d R=OH R₁=H CH=CH₂CH=CH₂
4e R=OH R₁=p-Br R₂=C₆H₅
4f R=OH R₁=p-Br R₂=CH₂CH=CH₂

In vitro inhibition of cyclooxygenase and 5-lipoxygenase activities of 1,3,4-oxadiazole derivatives (2) [2] (Scheme 11).

1b R = C₆H₁₃
1c R=p-Cl-C₆H₄
1d R=p-F-C₆H₄
1e R=p-CH₂-C₆H₄

Anti-inflammatory activity of some new 2,5-di-substituted 1,3,4-oxadiazole derivative.

2b R=2,6-di-Cl, 3-CH₃
2b R=3-CF₃
2b R=2,3-(CH₂)₂

In vitro inhibition of cyclooxygenase and 5-lipoxygenase activities of 1,3,4-oxadiazole derivatives (2) [2] (Scheme 11).
Antibacterial activity: The antibacterial activity of pyrazole and 1,3,4-oxadiazole derivatives of 2-phenyl-1,8-napthyridine (Scheme 15).

Anti-inflammatory activity: The antibacterial activity of pyrazole and 1,3,4-oxadiazole derivatives of 2-phenyl-1,8-napthyridine (Scheme 15).

Compounds 6b, 6c, 6d, 6b, 7d and 7e were most effective while 6b, 6i, 7a, 7g and 7b were found to have low activity. The remaining compounds were moderate activity. Antibacterial activity of 1, 3, 4-oxadiazoles (8) [7] (Scheme 16).

All the compounds were screened for their antibacterial activity against E. coli and B. Cirroflagellous are decreases in the order like 8a>Sb>8c>8d. Antibacterial activity of coumarin incorporated 1,3,4-oxadiazoles (9a-d) [8] (Scheme 17).

All the compounds were screened for their antibacterial activity against E. coli and Staphylococcus using ciprofloxacin as std. drug. The compound 9d showed 80% inhibition against S. aureus while, 9a showed 80% inhibition against E. coli. The 3-aryloxy methyl/phenyl ethyl-4-phenyl-5-(5'-mercapto-4'-phenyl-1,2,4-thiazol-3'-yl-methyl mercapto)-1,2,4triazoles (10a-c) for evaluating antibacterial activity [9] (Scheme 18).

All these compounds exhibited promising antibacterial activity against E. coli and S. aureus. Antibacterial activity of 4-(psubstituted phenyl)-3-mercaptopo-5-(2'-morphothiono)quinaxolinol-1,2,4triazoles (11a-c) at a concentration of 2, 3 and 5 mg/ml, against S. aureus, S. typhi, E. coli and B. subtilis [10] (Scheme 19).

Compound 11b was found to inhibit all the test organisms whereas 11a was totally inactive against all the organisms. A series of substituted 2-(5'-mercapto-4'-phenyl-1,2; 4'-triazole-3'-yl)indoles (12a-k) [11] (Scheme 20).

Scheme 14: Methyl/ethyl-4-amino-5-mercapto-1,2,4-triazole.

Scheme 15: The antibacterial activity of pyrazole and 1,3,4-oxadiazole derivatives of 2-phenyl-1,8-napthyridine (a, b) [8].
Anticonvulsant activity: The anticonvulsant activities of the triazoles were tested against mice. All these compounds were found to possess significant against E. coli, S. aureus, E. coli, S. typhi, and P. aeruginosa except 13b, which was inactive against Pseudomonas.

Anticonvulsant activity of some new 1,3,4-oxadiazole derivatives (14) [13]. Anticonvulsant activity of 2,4-dihydro-3H-1,2,4 triazol-3-ones (15) (Schemes 22 and 23).

15a Ar=C₆H₅ R₁=H R₂=H
15b Ar=C₆H₅ R₁=CH₃ R₂=H
15c Ar=C₆H₅ R₁=H R₂=CH₃
15d Ar=C₆H₅ R₁=H R₂=C₆H₅

The anticonvulsant activities of the triazoles were tested against maximal electroshock and pentylenetetrazole-induced seizures in mice. The compounds having monohalogenated aryl substituents were found to be most active.

Antifungal activity: Most of the recently clinically used anti-fungal drugs contain triazole nucleus, none of the drug used today are from other azoles like oxadiazole, pyrazine, and triazine. The main drawback of triazoles is CYP₃₄Isoform inhibition selectivity. This results in many drug interactions when given concomitantly with certain medications also metabolized by this CYP Isoform. For example, fluconazole inhibits the metabolism of warfarin leading to increase in bleeding time. Fluconazole also decrease the metabolism of the CYP₃₄Isoform substrate phenytoin, an anti-epileptic drug with a narrow therapeutic index. On the basis of above facts, different types of azoles are still in progress to get a better drug, some are given as follows. Antifungal activity of 3-aryl ethyl-4-phenyl-5-mercapto-1,2,4 triazoles (13a-c) [12] (Scheme 21).

All these compounds were found to possess significant against E. coli, S. aureus and antifungal activity against C. utilis and S. cerevisiae. Antibacterial activity of 3-aryl ethyl-4-phenyl-5-mercapto-1, 2, 4, triazoles (13a-c) [12] (Scheme 21).

All these compounds were active against S. aureus, E. coli, S. typhi, and P. aeruginosa except 13b, which was inactive against Pseudomonas.

Antifungal activity: Most of the recently clinically used anti-fungal drugs contain triazole nucleus, none of the drug used today are from other azoles like oxadiazole, pyrazine, and triazine. The main drawback of triazoles is CYP₃₄Isoform inhibition selectivity. This results in many drug interactions when given concomitantly with certain medications also metabolized by this CYP Isoform. For example, fluconazole inhibits the metabolism of warfarin leading to increase in bleeding time. Fluconazole also decrease the metabolism of the CYP₃₄Isoform substrate phenytoin, an anti-epileptic drug with a narrow therapeutic index. On the basis of above facts, different types of azoles are still in progress to get a better drug, some are given as follows. Antifungal activity of 2-aryl-5-(3,5-diphenylpyrazole-4-yl oxymethyl)-1,3,4-oxadiazoles (16a-c) [14] (Scheme 24).
Compound 16b show promising antifungal activity against fungi as compared to 16a and 16c. Fungicidal activity of 3,6,9-triaryl-2-thioxothiazolo[4,5-d]-[1,3,4]oxadiazolo[2,3-b]pyrimidines (17) [15] (Scheme 25).

\[
\begin{align*}
17a & : R=H \ R'=H \\
17b & : R=4-Cl \ R'=H \\
17c & : R=2-CH_3 \ R'=H \\
17d & : R=H \ R'=2-Cl \\
17e & : R=4-Cl \ R'=2-Cl \\
17f & : R=2-CH_3 \ R'=2-Cl \\
17g & : R=H \ R'=4-OCH_3 \\
17b & : R=4-Cl \ R'=4-OCH_3 \\
17i & : R=2-CH_3 \ R'=4-OCH_3
\end{align*}
\]

Compounds 17b, 17e and 17h have very strong activity against Aspergillus niger and Pseudocilium citrinum at 1000, 100 and 10 ppm concentration. All these three compounds have either 2-Cl, 4-Cl or 4-OCH_3 groups (electron donar group) in their structure.

Thus, it can be concluded that Cl-group imparts much towards fungicidal activity of this series of compounds. Antifungal activity of oxadiazoles (18) [16], Good anticonvulsant activity is shown by 18b and 18c. Moderate activity produced by compound 18a (Scheme 26).

Fungicidal activity of some 5-methylene-2-[5'-aryl-1',3'4'-oxadiazol-2'-yl]amino-4-thiazolones (19) against A. niger [17] (Scheme 27).

Among tested compounds 19a is more active against A. niger then 19b and 19c. Activity is decreases on dilution to 100 and 10 ppm. The fungicidal activity of 2'-substituted spiro[indoline-3,5'-[5H][1,3,4]-oxadiazolo[3,2-C]-thiazol]-2-ones against H. oryzae (20) [18] (Scheme 28).

\[
\begin{align*}
20a & : R=H \\
20b & : R=2-CH_3 \\
20c & : R=4-CH_3 \\
20d & : R=3-CH_3 \\
20e & : R=4-Cl, 3-CH_3
\end{align*}
\]

Among these compounds 20e was the most active. It inhibited 90% growth of fungus. This compound has a -CH_3 group along with a chloro function on the phenyl ring which probably enhances fungitoxicity. Antifungal activity of 4-substituted-3,7-dimethyl-pyrazolo[3,4-e][1,2,4]triazole (21) [19] (Scheme 29).

The antifungal activity of the compounds was carried out by the poison food technique. Tie compounds used were tested in potato dextrose broth in concentration of 10mg/ml, 5mg/ml, 2.5 mg/ml and 1 mg/ml. Compounds 21a and 21d are more active against fungus strain, because of presence of acidic group in these compounds. The fungitoxicity of 1,2,4-triazolo and thiadiazolo[3,2-b]-1,3,4-oxadiazoles (22, 23) [20] (Scheme 30).

\[
\begin{align*}
23a & : R=2-F \ R'=2-Cl \\
23b & : R=4-F \ R'=2-Cl \\
23c & : R=3-F \ R'=2-Cl \\
23d & : R=2-F \ R'=4-Cl \\
23e & : R=3-F \ R'=4-Cl \\
23f & : R=2-F \ R'=4-CH_3 \\
23g & : R=4-F \ R'=4-CH_3 \\
23h & : R=3-F \ R'=4-CH_3
\end{align*}
\]

Compound 22c, 23a, 23e and 23g showed full activity against fungus at 10ppm. The fungicidal data indicate that the presence of toxophoric group -Cl, -OCH_3 on phenyl ring enhances the activity. Antifungal activity of some 1,3,4-oxadiazole derivatives (24, 25) [21] (Scheme 31).
The cytotoxic/antiproliferative effects of m-Br-C(S)OCH,p-OCH,R cant antifungal activity of 5-arylidene-2-aryl-3-(1,2,4-triazoloacetamidyl)l,3-thiazol-4-ones (26) (Scheme 32). Among the compounds tested, compound (26h), carrying a morpholino methyl substituent possess highest degree of antifungal activity.

The antifungal activity of 5-substituted -I, 3, 4- oxadiazoIine-2-thiones (28) (Table 2) (23) (Scheme 33). The compounds (28a) and (28c) showed significant antifungal activity against A. niger and C. albicans at 1000 g/ml concentration.

Table 1: The antifungal activity of 5-arylidene-2-aryl-3-(1,2,4-triazoloacetamidyl) l,3-thiazol-4-ones (27). Compounds (27a), (27b) and (27d) showed good antifungal activity.

| Compound | R                  |
|----------|--------------------|
| 27a      | o-Br-C₆H₅          |
| 27b      | p-Br-C₆H₅          |
| 27c      | o-Cl-C₆H₅          |
| 27d      | m-Br-C₆H₅          |

Scheme 32: Antifungal activity of 5-substituted -I, 3, 4- oxadiazoIine-2-thiones.

Scheme 33: Antifungal activity of 5-arylidene-2-aryl-3-(1,2,4-triazoloacetamidyl) l,3-thiazol-4-ones (27).

Scheme 34: Antifungal activity of 7/9-substituted-4-(3-alkyl/aryl-5,6-dihydro-s-triazoio[3,4-b]thia-diazol-6yl)-tetrazolo [1.5-a] quinolines (28).

The fungicidal activity of 3-aryloxy/arylmethyl [-4-aryl-5-mercapto-1,2,4triazoles (29a-1) (Table 3) (25) (Scheme 35).

Against A. niger and H. oiyzae by agar plate technique at 1000, 10 ppm concentration. The highest activity was shown by compounds having 3,4 dichlorophenyl moieties.

Some cyclic analogs of SM 8668, compound (30), these thiolene triazole derivatives had 4-chloro or 2,4-dichlorophenyl substituents (X=4Cl or 2Cl₂) instead of 2,4-difluorophenyl moiety of SM 8668 (Scheme 36).

| Compound | R                  | R₁    | R₂    |
|----------|--------------------|-------|-------|
| 30a      | n = 1; X=2,4-Cl₁   | H     | H     |
| 30b      | n = 1; X=4-Cl      | H     | H     |
| 30c      | n = 2; X=2,4 Cl₂   | H     | H     |

These compounds were tested in-vitro and in-vivo antifungal activity, out of which (30a), (30b), and (30c) showed promising antifungal activity.

Antitubercular activity: Antituberculosis activity relationship study in a series of 5-(4-amino phenyl)-4-substituted-2,4-dihydro-3H-1,2,4-triazole-3-thiones, some of the compounds give moderate activity (26).

Anticancerous activity: The cytotoxic/antiproliferative effects of (1,2,4)-triazolo(4,3-c) quinazolines in tumor cell lines hela and B16. Some of the compounds produced moderate activity (27) (Figures 1-4).

Ravuconazole: It is found to be more potent than flucofiazole and itraconazole against clinical isolates of Cryptococcis deofonnans.
Figure 1: Antifungal drugs possessing azole nucleus.
Triazoles have been reported to possess wide variety of biological activity [28,29].

Table 3: The compounds 28a and 28c showed significant antifungal activity against A. niger and C. albicans at 1000 g/ml concentration. The fungicidal activity of 3-arylox/arylmethyl-4-aryl-5-mercapto-1,2,4-triazoles.

| Compound | R_1         | R_2         |
|----------|-------------|-------------|
| 28a      | p-Cl, 3-CH_3-CH_2-OH | 2-Cl       |
| 28b      | p-Cl, 3-CH_3-C_6H_5-OH | 3,4-Cl     |
| 28c      | 2,4-(CH_3)_2, C_6H_5-OH | 2-Cl       |
| 28d      | 2,4-(CH_3)_2, C_6H_5-OH | 3,4-Cl     |
| 28e      | C_6H_5CH_2 | 3,4-Cl     |

Figure 2: Antifungal agents under clinical trial.

Figure 3: Orally acting triazole, which is completing phase-I clinical trials.

Figure 4: Wide spectrum orally acting antifungal agent.

References
1. Boschelli HD, Connor TD, Bornemeier AD (1902) J Med Cheni 36: 993.
2. Razvi M, Ramalingam T, Satur PB (1989) Ind J Chem 28: 695.
3. Tandon M, Bhandari JP, Bhat MA (1981) Ind J Chem 20B: 1017.
4. Laddi UV, Talawar MB, Desai SR, Somannavar YS, Bhatta TN (1981) Ind J Chem 20B: 1017.
5. Mogliaiah K, Srinivasa DC, Babu RR (2001) Synthesis and antibacterial activity of pyrazole and 1,3,4-oxadiazole derivatives of 2-phenyl-1,8-naphthyridine. Ind J Chem 40B: 43-48.
6. Talawar MB, Desai SR, Somannavar YS (1998) Synthesis and antimicrobial activity of 1, 2, 4-triazoles, 1, 3, 4-oxadiazoles and 1, 3, 4-thiadiazoles. Ind J Het Chem 5: 215-218.
7. Bhat MA, Khan SA, Siddiqui N (2005) Synthesis and antibacterial activity of coumarin incorporated 1, 3, 4-oxadiazoles. Ind J Het Chem 14: 271-272.
8. Khan RH, Srivastava S, Rastogi RC (1987) Ind J Pharm Sci 55: 917.
9. Fernandes OS, Sonar M (1986) J Ind Chem Soc 63: 427.
10. Hireniath S, Sonar V, Sekhar R (1989) Ind J Chem 25B: 626.
11. Charanjit LA, Linear P, Ratna A (1986) J Ph Arm Sci 48: 192.
12. Khan MSY, Drabu S (2001) Anticonvulsant and antibacterial activity of some new 1,3,4-oxadiazole derivatives. Indian J Heterocycl Chem 11: 119.
13. Dubey AK, Sangwan N (1994) Ind J Chem 33B: 1043.
14. Nizamuddin M, Mishra M, Kumar M, Srivastava M (2001) Synthesis and fungicidal activity of 3,6,9-2-thioxothiazol[4,5-d][1,3,4] oxadiazolo [2,3-b]pyrimidine and 3,10-diaryl-2-thioxothiazolo[4,5-d]pyrimidines. Ind J Chem 40B: 49-53.
15. Upadhyya PS, Vansdalia SP, Baxi AJ (1990) Studies on Sulphone Derivatives: Preparation and Antimicrobial Activity of Thiosulphuric acid, Triazoles, Oxadiazoles and Thiadiazoles. Ind J Chem 29B: 793.
16. Khare RK, Srivastava MK, Sing H (1995) Ind J Chem 34B: 828.
17. Kumud S, Ninipama T, Nizamuddin (1993) Ind J Chem 32B: 1080.
18. Ashish KT, Lily M, Verma HN (2002) Synthesis and antifungal activity of 4-substituted-3, 7-dimethylpyrazolo [3,4-e] [1,2,4] triazine. Ind J Chem 41B: 664-667.
19. Harendra S, Manoj K, Srivastava S, Kishore BS (2001) Synthesis and fungicidal activity of fluorinated-1,2,4-triazole-and thiadiazolo[3 2-b]:1,3,4 oxadiazoles. Ind J Chem 40B: 159-162.
20. Hoser MC, Talawar MB, Laddi UV (1994) Synthesis and antimicrobial activities of some new 1,3,4-oxadiazoles. Ind J Het Chem 3: 237-242.
21. Holla S, Poojary NK, Kalluraya BK (1996) Ind J Het Chem 5: 273.
22. Srivastava SK, Srivastava S, Srivastava SD (2002) Synthesis of 5-arylidene-2-aryl-3(1, 2, 4-triazolocetamidyl)-1, 3-thiadiazole-4-ones as antibacterial, antifungal, analgesic and diuretic agents. Ind J Chem 41B: 1937-1945.
23. Gupta R, Gupta AK, Paul S, Somal P (2000) Microwave-assisted synthesis and biological activities of some 7/9-substituted-4-(3-alkylaryl)-6-hydroy-a- triazolo[3,4-b]-1,3,4-thiadiazolo[3,4-b]-1,3,4-thi皇后line. Ind J Chem 39B: 847-852.
24. Bahl SC, Srivastava SC, Pathak RB (1989) Ind J Pharm Sci 28: 254.
25. Drugs fut (1999) 24: 349.
26. Drugs fut (1999) 24: 217.
27. Drugs fut (2001) 26: 71.
28. Ana EI, Rezusta A (2002) E-Test Method for Testing Susceptibilities of Aspergillus spp. to the New Triazoles Voriconazole and Posaconazole and to Established Antifungal Agents: Comparison with NCCLS Broth Microdilution Method. J Clin Microbiol 40: 2101-2107.
29. Pfaller MA, Diekema DJ, Boyken L, Messer SA (2003) Evaluation of the Etest Method. J Clin Microbiol 40: 2101-2107.