Heterocyclic Letters
Vol. 8| No.3|613-617|May-July|2018
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS AND ANTIFUNGAL ACTIVITY OF NOVEL 1,2,4-TRIAZOLE DERIVATIVES

K.Yashaswini, B.C. Revanasiddappa*, M.Vijay Kumar, Hemanth Kumar

**Department of Pharmaceutical Chemistry, NGSM Institute of Pharmaceutical Sciences of Nitte (Deemed to be University), Paneer, Deralakatte, Mangalore-575 018,Karnataka, India*
Email: revan@nitte.edu.in

ABSTRACT
Reaction of 4-amino-3-mercapto-1,2,4-triazole **(1)** with appropriately N-substituted-α–chloroacetanilides **(2)** in aq. potassium hydroxide yielded corresponding 2-(4-amino-5-(4-hydroxyphenyl)-4H-1,2,4--triazol-3-ylthio)-N-phenylacetamides**(3a-j)**. All the new compounds were evaluated for *In-vitro* antifungal activity. The newly synthesized compounds were assigned on the basis of ^{1}H-NMR, IR and Mass spectral data.

KEY WORDS: Methyl paraben, Potassium dithiocarbazinate salt, 1,2,4-triazole, antifungal activity

INTRODUCTION
Five membered heterocyclic compounds which includes three nitrogen as a hetero atom is acquiring more interest in the present field of research and synthesis of new compounds. Triazoles are said to be the isosters of Imidazole in which carbon atom of the Imidazole is isosterically replaced by nitrogen. Triazoles are five membered heterocyclic compounds with molecular formula $C_2H_3N_3$ which contains three nitrogen and two carbon atoms.
The most common nitrogen containing heterocyclic compounds are azoles that includes isoxazoles, thiazoles, pyrazoles and triazoles that are used in the present field of research and development. Among these azoles triazoles are one of the important moiety which fulfill the requirements of new drug discovery and developments. Triazole derivatives are the promising heterocycles in the field of medicine. Based on the position of the nitrogen atom triazole exist in two isomeric form that is 1,2,3-triazole and 1,2,4-triazole.Although in last few decades 1,2,4-triazoles are considered to be a pharmacologically more important isomer due to their synthetic utility and broad spectrum of biological activity.
1,2,4-triazoles exhibit wide range of biological activities such as antibacterial[I], antifungal[II], anti-inflammatory[III], anticancer[IV], antiviral[V], antitubercular[VI], anticonvulsant[VII] etc. There are so many drugs are available in the market which contain 1,2,4-triazole ring in their structure such as antifungal azoles (fluconazole, itraconazole, posaconazole, ravuconazole, terconazole, voriconazole, isavuconazole, albaconazole) aromatase inhibitors (anastrozole

,letrozole, vorozole), diazepine analogs (alprazolam, estazolam, triazolam), antiviral agent (ribavarin), antimigraine agent (rizatriptan), anxiolytic agent (alprazolam).
Based on the above pharmacological profile, it was planned to synthesize, a novel series of 1,2,4-triazole derivatives and also evaluation of the new compounds for antifungal activity.

EXPERIMENTAL

Materials and Methods

All the reagents and the solvents that are used in the reactions such as methyl paraben, carbon disulphide, hydrazine hydrate were purchased from Loba Chemie Pvt.Ltd Mumbai and were used without further purifications. The melting points are uncorrected. The IR spectra are recorded by using Alpha Bruker IR Spectrometer using a thin film on KBr pellet technique and frequencies are expressed in cm^{-1}. The ^{1}H-NMR spectra were recorded on Bruker Avance II 300 NMR Spectrometer. All spectra were obtained in DMSO. Mass Spectrum was recorded on Perkin Elmar Clarus 680 GC-MS spectrometer.

Synthesis of 4-amino-3-mercapto-1,2,4-triazole (1)

Potassium dithiocarbazinate salt (0.01 mol) was dissolved in water (5ml) and hydrazine hydrate (6ml) is added to this solution and refluxed for 6 hrs. The reaction mixture was cooled and poured into crushed ice (100ml) and acidified with HCl (10%). The precipitated compound was filtered, washed with water and dried**.**

Synthesis of 2-(4-amino-5-(4-hydroxy phenyl)-4H-1,2,4--triazol-3-ylthio)-N-phenylacetamide derivatives (3a-j)

4-amino-3-mercapto-1,2,4-triazole **(1)** (0.01mol) and α-chloroacetanilides **(2)** (0.01mol) was dissolved in alcohol (20ml), potassium hydroxide was added (0.01mol) and refluxed for 8-9 hrs. The reaction mixture was cooled and poured into crushed ice (100ml). The precipitated compound was filtered, washed with water, dried and recrystallized from alcohol. The physical data of the compounds **(3a-j)** is given in the table-01.

N-(4-amino-3-nitrophenyl)-2-(4-amino-5-(4-hydroxyphenyl)-4H-1,2,4-triazole-3-ylthio) acetamide

3a: IR (KBr) (V_{max} cm^{-1}): 3437(NH_2), 2968 (C-H), 1638(C=O), 1596(C=N), 1519(C=C). ^{1}H-NMR(300 MHz, $CDCl_3$) 4.12 (s, SCH_2, 2H), 5.94 (s,NH_2, 2H), 6.12 (s,NH_2, 2H), 6.71-7.91(m, Ar-H, 7H), 9.15 (s, NH, IH), 11.23(s, OH, 1H); MS m/z: 401[M^+].

2-(4-amino-5-(4-hydroxyphenyl)-4H-1,2,4-triazole-3-ylthio)-N-(2,5-dimethylphenyl) acetamide

3b:IR (KBr) (V_{max} cm^{-1}): 3252(NH), 1651(C=O), 2916(C-H),1611 (C=N), 1457(C=C) ^{1}H-NMR (300 MHz $CDCl_3$); 1.62 (s, 2XCH_3, 6H), 4.49 (s, SCH_2, 2H), 5.77 (s,NH_2, 2H), 6.84-7.84 (m, Ar-H, 7H), 9.88 (s, NH, IH), 11.76 (s, OH, 1H); MS m/z: 369 [M^+].

Antifungal activity

All the final synthesized compounds **(3a-j)** were evaluated for antifungal activity against *A.niger* and *A. fumigatus* by using cup-plate method[VIII] in the Sabouraud agar media (dextrose 4%, peptone 1%, and agar 1.5%). The zone of inhibition (mm) of each compound was determined and compared with standard drug, Bavistin. In this method, cups were filled with test solution in petridish which was inoculated with the organisms. After the incubation, the plates were observed for of zone of inhibition against organism and compared with the standard drug. The antifungal activity of the compounds (**3a-j)** is given in table-02.
The medium was prepared and sterilized in an autoclave at 15 psi for 15 min. Then, it was poured into sterilized petri plates, aseptically. The fungal strains were inoculated on the surface of petri plates separately after 2 hr of pouring the agar media, when the media sets on

petri plates the cups (diameter 6 mm) were made in the sabouraud agar medium using sterilized cup borer under aseptic conditions. The synthesized compounds were tested at 100 µgm/ml. The compounds were prepared by dissolving in DMSO and the solution was added into cups. The petri plates were incubated at 28 ± 2^{O}C for 48 hr growth and zone of inhibition (in mm) was recorded.

Table-01: Physical data of compounds (3a-j)

Comp	Ar	Molecular formula	Molecular weight	M.P (ºC)	Yield (%)
3a	4-NH_2-3-NO_2	$C_{16}H_{15}N_7O_4S$	401	224-26	74
3b	2,5-$(CH_3)_2$	$C_{18}H_{19}N_5O_2S$	369	232-34	81
3c	3-NH_2-4-NO_2	$C_{16}H_{15}N_7O_4S$	401	259-61	72
3d	2,4,5-$(Cl)_3$	$C_{16}H_{12}Cl_3N_5O_2S$	444	248-50	68
3e	2-Cl	$C_{16}H_{14}ClN_5O_2S$	375	253-55	79
3f	2-OCH_3	$C_{17}H_{17}N_5O_3S$	393	238-40	75
3g	2-Cl-4-F	$C_{16}H_{13}ClFN_5O_2S$	393	217-19	72
3h	4-F	$C_{16}H_{14}FN_5O_2S$	359	212-14	78
3i	4-Br	$C_{16}H_{14}BrN_5O_2S$	420	207-09	67
3j	C_6H_5	$C_{22}H_{20}N_6O_2S$	432	201-03	77

Table-02: Data of antifungal activity of compounds (3a-j)

Percentage of inhibition		
Comp	**A. niger**	**A. fumigatus**
3a	62.35±0.095	61.22±0.069
3b	**72.21±0.097**	53.28±0.147
3c	**77.81±0.08**	52.31±0.151
3d	**76.64±0.019**	**99.59±0.21**
3e	59.81±0.047	49.78±0.109
3f	**71.24±0.053**	**74.63±0.044**
3g	69.57±0.118	46.58±0.029
3h	61.16±0.02	**72.33±0.056**
3i	64.42±0.041	43.43±0.068
3j	68.34±0.022	60.2±0.101
Std (Bavistin)	99.87±0.02	99.87±0.02

RESULTS AND DISCUSSION

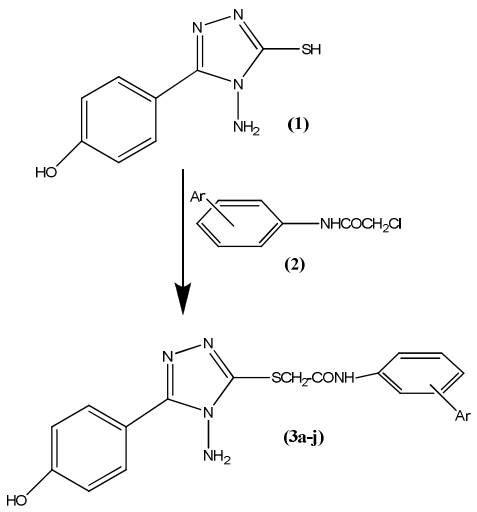
The synthesis of intermediates and target compounds **(3a-j)** was performed as illustrated in **Scheme-01.** The reaction key intermediate 4-amino-3-mercapto-1,2,4-triazole **(1)** is prepared as per the reported procedure[1X]. Various substituted α - chloroacetanilides **(2a-j)** were synthesized from the reaction of chloroacetic chloride and corresponding aromatic amines in glacial acetic acid- sodium acetate medium as reported[X]. The proposed structures of synthesized compounds **(3a-j)** were confirmed by ^{1}H-NMR, mass spectra, and IR analysis. The objective of the present study was to synthesize and to investigate the

antifungal activity of a new series of 1,2,4-triazole derivatives with the hope of discovering new structure leads serving as potential antifungal agents.

In ^{1}H-NMR spectra, compounds **(3a-j)** showed a singlet for two protons at δ 4.12 –4.49 ppm, which was assigned to NH_2 proton. The SCH_2 protons resonated as singlet at δ 5.77–5.94 integrating for two protons. Aromatic protons resonated as multiplets at δ 6.71-7.91. The presence of NH group of amide (CONH) is appeared as singlet at δ 9-10 ppm integrating for one proton. Further, the presence of signal due to OH proton is appeared as singlet at δ 11-12 ppm of the phenyl ring confirms formation of the product. Finally, compounds **(3a-j)** showed significantly stable (M+) mass peak with a relative abundance ranging up to 85%,

The synthesized 1,2,4-triazole derivatives were evaluated for their *In-vitro* antifungal activity against two fungal strains. The synthesized compounds exhibited a wide range of antifungal activity against the tested fungi. The results are summarized in table-02. The absence of substitution in compound **3j** resulted in moderate activity against both the fungi.

Scheme-01



CONCLUSION

Our aim is to develop an efficient procedure for the synthesis of novel 1,2,4-triazole derivatives and to study their antifungal activity. The synthesis of 1,2,4-triazole derivatives by prescribed method resulted in the product with good yields. *In-vitro* antifungal activity of the compounds was evaluated by cup plate method. Compound **3d** showed promising activity among all the tested compounds. Most of the tested compounds exhibited moderate activity against both the fungal strains.

ACKNOWLEDGEMENTS

The authors of thankful to authorities of NGSM Institute of Pharmaceutical Sciences, Nitte-Deemed to be University, Mangalore for providing all the necessary facilities. The authors also thankful to Vellore Institute of technology, Vellore, for providing NMR and Mass spectral data.

REFERENCES

I. Patil, B.S; Krishnamurthy, B; Naik, H.B; Latte, P.R and Ghate M. *Eur. J. Med. Chem.* **2010,** 45, 3329.

II. Xu J et al.. *Eur. J. Med. Chem.* **2011,** 46, 3142.
III. Tozkpran, B; Kupeli, E; Yesilada, E and Ertan M. *Bio.Org. Med. Chem.* **2007,** 15, 1808.
IV. Holla, B.S; Veerandra, B; Shivananda, M.K and Poojary, B. *Eur. J. Med. Chem.* **2003,** 38, 759.
V. Abdel-Aal, M.T; El-Sayed, W.A; El-Kosy, S.M and Elashy, E.S.H. *Achiv. Der. Pharm. Chem.* **2008,** 34, 307.
VI. Kucukguzel, I; Kucukguzel, S.G; Rollas and Kiraz, S.M. *Bio.Org. Med. Chem Lett*. **2001,** 11, 1703.
VII. Almagirad, A; Tabatabai, S.A and Faizi M. *Bio.Org. Med. Chem. Lett.* **2004,** 14, 6057.
VIII. Indian Pharmacopoeia, Third Edition, Govt. of India, New Delhi, **1985,** 3, 90
IX. Subrahmanyam, E.V.S; Revanasiddappa,B.C; Ishwar Bhat, K; Prems, J and Surya, P.S. *J. Chem. Pharm. Res.* **2010**, 2, 323.
X. Somani, R.R; Shirodkar, P.Y; Toraskar, M.P and Kadam, V.J. *Ind. J. Pharm. Edu. Res.* **2008,** 42, 53.

.

Received on May 7, 2018.