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Synthesis and Biological Evaluation of Some Novel Substituted Triazoles

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ABSTRACT:

A series of 3-(methylthio)-5-phenyl-4H-1, 2, 4-triazol-4-substituted amine were synthesized. The synthesized compounds were characterized through various instrumental techniques viz., FTIR, FT-NMR, and MS. All the compounds were tested against two different strains of fungi. Compound 7a, 7b, 7c, 7d emerged as most potent molecule against Aspergillus niger. Compound 7e have shown MFC at 12.5 µg/ml against Candida albicans and all the other compounds have shown MFC value 50 µg/ml against Candida albicans.

KEY WORDS: Synthesis, Cilostazole, Triazoles, Aspergillus niger, Candida albicans.

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INTRODUCTION:

Recently there is a predominant incidence of life threatening fungal infections in patients having reduced immunity, patients undergoing chemotherapy for cancer, patient recovered from organ transplant and AIDS patients. Most of these fungal infections are caused by opportunistic pathogenic fungi like Candida spp., Aspergillus spp., Pneumocystics carni and Cryptococcus neoformans. The available antifungal agents having drawbacks such as toxicity, narrow spectrum of activity, fungistatic profile rather fungicidal, drug drug interactions, as a result therapy becomes complex. Steadily increasing patient population demands the newer agent with good potential, broad spectrum of activity, good pharmacokinetic profile and minimum potential for development of resistance. Within the available drugs to treat fungal infections, the azole class appears to be more promising. Triazoles constitute an important class of biologically active heterocyclic compounds that have received a great attention since their discovery. Triazole nucleus possess various biological activities such as Antifungal, Antibacterial, Antiinflammatory, Anticancer, Antidepressant, Antimycobacterial and Anticonvulsant.

Antifungal activity determination: 1, 2, 3, 4

The antifungal activities of the compounds were evaluated against two different strains of fungi using broth dilution method. Fluconazole was used as standard drugs for antifungal activity.

All the synthesized compounds were screened for antifungal activity using broth dilution method and Suboroud's nutrient media, against Candida albicans (ATCC 10231) and Aspergillus niger (ATCC 16404).

Each synthesized compounds were diluted to obtain 2000 µg/ml concentration, this would be act as a stock solution.

Primary screening: In primary screening the compounds were tested at 500 µg/ml, 250 µg/ml, 100 µg/ml and 50 µg/ml concentrations. The active compounds found in this primary screening were further tested in a second set of dilution against all fungal strains.

Secondary screening: The drugs found active in primary screening were similarly diluted to obtain 25 µg/ml, 12.5 µg/ml, 6.25 µg/ml, and 3.1 µg/ml concentrations.

Reading results:

The minimum Fungicidal Concentration (MFC) is the lowest drug concentration that showed absence of growth or complete growth inhibition (99% inhibition).

Antifungal activity of compounds:

Compound code	Minimum fungicidal concentration(µg/ml)	
	C. albicans ATCC 10231	*A.niger* ATCC 16404
7a	50	<3.125
7b	50	<3.125
7c	50	<3.125
7d	50	<3.125
7e	50	50
7f	50	12.5
Fluconazole	0.5	1

RESULTS:

All the synthesized compounds were screened for antifungal activity using broth dilution

method and Suboroud's nutrient media, against Candida albicans and Aspergillus niger.

Significant antifungal activity was observed with MFC valves in the range of <3-50 µg/ml against A. niger and 50 µg/ml against C. albicans species.

The standard drug Fluconazole showed MFC value 0.5 µg/ml against Candida albicans and 1

µg/ml against Aspergillus niger.

Compound 7a, 7b, 7c, 7d showed good activity against A. niger species having MFC value less than 3 µg/ml.

Compound 7e have shown MFC at 12.5 µg/ml. and all the other compounds have shown MFC

value 50 µg/ml against Candida albicans.

All the compounds have shown MFC value 50 µg/ml against Candida albicans species. Compound 7a, 7b, 7c, 7d emerged as most potent molecule against A. niger. Species.

EXPERIMENTAL:

Melting points were determined in open glass capillaries and are uncorrected.IR spectra of all compounds were recorded on Shimadzu FTIR 8400s spectrophotometer, using KBr as an internal reference. Mass spectra were recorded on SHIMADZU LCMS 2010 EV Mass spectrometer.1H NMR spectra were obtained in CDCl3 on BRUKER Advance-II 400 MHz instrument and chemical shift were measured as parts per million (δ ppm) downfield from tetramethylsilane (TMS) as internal standard.

Synthesis of Methyl benzoate[5, 6, 7]

A mixture of benzoic acid (10 mmol) was refluxed in 20 ml methanol in presence of few drops of concentrated sulfuric acid (98%) for 3-5 hrs. The reaction mixture was cooled poured into ice-water and crude ester was separated. Solid obtained was filtered and dried.

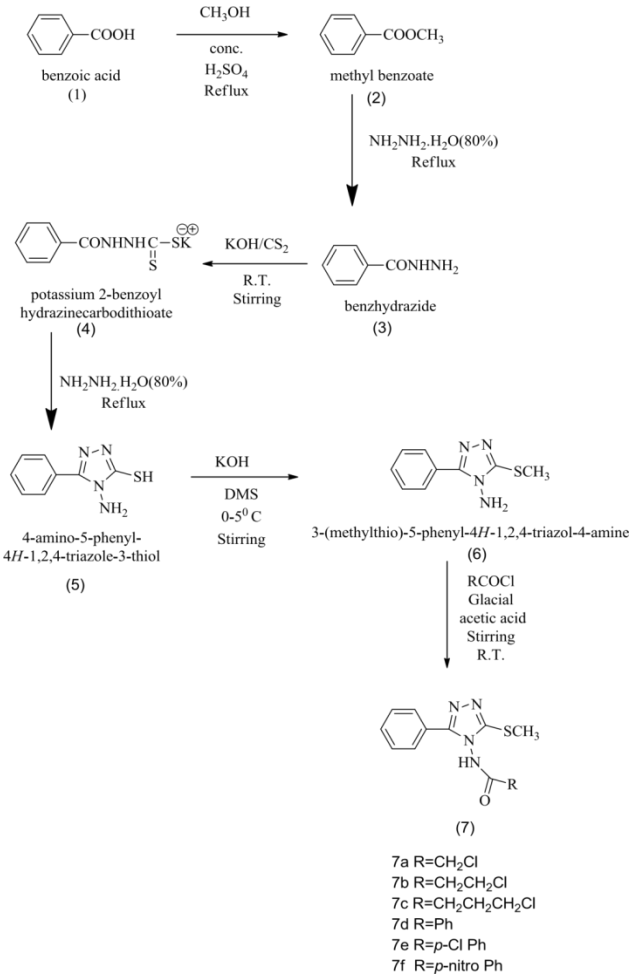
Synthesis of Benzhydrazide[5, 6]

A crude mixture of crude methyl benzoate (10 mmol) and hydrazine hydrate (99%, 25 mmol) was refluxed in 20 ml methanol for 3-5 hrs. The reaction mixture was cooled or poured into ice-water and crude acid hydrazide was separated. Solid obtained was filtered and dried.

Synthesis of 4-amino-3-mercapto-5-phenyl-(4H) 1, 2, 4-triazole[6, 7]

Potassium hydroxide (1.68 g, 30 mmol) was dissolved in 20 ml methanol and stirred for 10 min. Benzhydrazide (2.72 g, 20 mmol) was added at once to the above reaction mixture. After

15 min, carbon disulfide (2.28 g, 30 mmol) was added dropwise and the reaction mixture was stirred at 20-25°C. After 3 hrs, diethyl ether (100 ml) was added to the



reaction mixture to precipitate the solid; the solid separated was filtered and washed repeatedly with diethylether. The precipitates were mixed with hydrazine hydrate (1.68 g, 32 mmol) and 2 ml of water and the solution was refluxed for 1 hr until the color of the solution became clear green. After cooling at room temperature, the solution was poured in ice-water and neutralized with dilute hydrochloric acid. The solid obtained was filtered, washed with water and dried. Recrystallised from ethanol.

Synthesis of 3-(methylthio)-5-phenyl-4H-1, 2, 4-triazol-4-amine.

In a 50 ml round bottom flask pottasium hydroxide (2 mol) was dissolved in minimum quantity of water with constant stirring in an ice bath, then triazole (1 mol) was added and DMF was added as a solvent. Then DMS (2 mol) was added drop by drop with constant stirring. Reaction mixture was stirred for 1 hr. After that reaction mixture was poured in ice-water to get precipitates. Precipitates were washed with water and dried.

Synthesis of 3-(methylthio)-5-phenyl-4H-1, 2, 4-triazol-4-substituted amine.

3-(methylthio)-5-phenyl-4H-1,2,4-triazol-4-amine (1 mmol) was dissolved in 10 ml glacial acetic acid and then substituted acyl chloride (1 mmol) was added at once and the reaction mixture was stirred for 1hr. Reaction mixture was poured in ice cold water to obtain precipitates. Precipitates was filtered, washed with cold water and dried. Recrystallized from methanol.

The physical and analytical data of the synthesized final products are given as follows:

2-chloro-N-(3-(methylthio)-5-phenyl-4H-1,2,4-triazole-4-yl)acetamide(7a): yield: 98% ; melting point: 135-137°C; IR(KBR, cm-1: 1693.38(-CO- str),3188.11(-NH-str),688.54(-Cl str); Mass:

283.3(M+1), 285.3(M+2).

3-chloro-N-(3-methylthio)-5-phenyl-4H-1,2,4-triazole-4yl)propanamide(7b): yield: 94% ; melting point: 134-137°C; IR(KBR, cm-1: 1693.36 (-CO- str), 3299(-NH- str), 688.54(-Cl str); Mass: 297.4(M+1); 1H NMR (δ ppm, CDCl3): 8.8-8.9 (s,-1H,-NH-), 7.4-7.8(m,-5H,ArH), 2.0-3.0 (t,-2H,C-H), 2.0-3.0 (t,-2H,C-H), 3.0-4.0(S,-3H,SCH3).

4-chloro-N-(3-methylthio)-5-phenyl-4H-1,2,4-triazole-4-yl)butamide(7c): yield: 95% ; melting point: 120-121°C; IR(KBR, cm-1: 1708.81(-CO- str), 3143.75(-NH- str), 688.54(-Cl str); Mass:

311.4(M+1).

N-(3-methylthio-5-phenyl-4H-1, 2, 4-triazole-4yl)benzamide(7d): yield: 95% ; melting point:

180-182°C; IR(KBR, cm-1: 1693.38(-CO- str), 3190.04(-NH-str); Mass: 311.4(M+1).

4-chloro-N-(3-(methylthio)-5-phenyl-4H-1, 2, 4-triazol-4-yl)benzamide(7e): yield: 96% ; melting point: 239-241°C; IR(KBR, cm-1: 1693.38(-CO- str), 3155.33 (-NH- str), 595.67(-Cl str); Mass:

345(M+1), 347(M+2).

N-(3-(Methylthio)-5-phenyl-4H-1, 2, 4-triazol-4-yl)-4-nitrobenzamide (7f): yield: 94%; melting point: 235-237°C; IR (KBR, cm-1: 1687.60(-CO- str), 3195.83 (-NH-str), 1519.80(N-O asym. Str.), 1353.94(N-O sym. Str.);

Mass: 356(M+1); 1H NMR (δ ppm, CDCl3): 7.5-7.8(m,-5H, Ar-H),

8.1-8.4(m,-4H, Ar-H), 9.2-9.3(s,-1H,-NH), 3.7-4.0(s,-3H, SCH3).

REFERENCES

1. Talavia S. Design, synthesis and screening of some 4-amino-3phenyl-2-[(substituted) phenylimino]-2, 3-dihydrothiazole-5-carboxamides as potential antiinflmmatory and antifungal agents [dissertation]. Gujarat University. 2008.

2. Yeo SF and Livermore DM.Effect of innoculum size on the in vitro susceptibility to beta- lactam antibiotics of M. catarrhalis isolates of different different beta-lactamase types, The Journal of Medical Microbiology, 1994; 40(4): 252-255.

3. George, ZG and James AK. In vitro activity of a new semisynthetic echinocandin, against systemic isolates of Candida species, Cryptococcus neoformans and Aspergillus species, Antimicrobial agents and chemotherapy, 1997; 41(4): 863-865.

4. John HR, Michael AP and Thomas JW. Antifungal susceptibility testing: Practical Aspects and Current Challenges, Clinical Microbiology Reviews, 2001; 14(4): 643-658.

5. Hoggarth E. Compounds related to thiosemicarbazide VIII. Oxidation of thiosemicarbazones, Journal of Chemical Society, 1952; 4811.

6. Bala S, Gupta RP, Sachdeva ML, Singh A and Pujari HK. Heterocyclic systems containing bridgehead nitrogen atom Part XXXIII. Synthesis of of s-triazolo [3, 4-b] quinoxaline & triazino[3,4-b][1,3,4] thiadiazines, Indian Journal of Chemistry, 1978; 16: 481-483.

7. Saikachi H and Kanaoka M. Synthesis of related compounds of thiosemicarbazide VIII. Reaction of hydrazine hydrate with 1, 3, 4-thiadiazoles, Yakugaku Zassi, 1962; 683.

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