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Synthesis and anti-*candida* activity evaluation of new [1,2,4] triazolo[3,4-b][1,3,4] thiadiazines

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Abstract

Candida species have emerged as the most common cause of systemic fungal infections worldwide over the last two decades. 1,2,4 - triazole moieties have been incorporated into a wide variety of therapeutically interesting drug candidates and antimycotic ones such as fluconazole, itraconazole, voriconazole. The mercapto and thione substituted 1,2,4- triazol ring system have been reported to possess a variety of biological activities such as antibacterial , antifungal, anti-tubercular, anticancer, diuretic and hypoglycemic. The recent literature survey revealed that a special attention was given to those incorporating N-C-S linkage as in the skeleton of the 1,2,4 -triazolo[3,4-b][1,3, 4]thiadiazine derivatives, which proved to have promising biological activities such as antiviral, anti-HIV, CNS stimulant and antifungal. Studies have also confirmed that triazolothiadiazine derivatives possess anti-*Candidal* activity. Designing new drugs is based on development of hybrid molecules by combining different pharmacophore fragments in a single structure, which may lead to compounds with interesting biological activities. Herein we describe the synthesis of new triazolothiadiazine derivatives, which were tested, *in vitro* against eleven *Candida* species. Treatment of 1,2,4-triazole-5-thione derivative **3** with hydrazonoyl chlorides **(4a-h)** in refluxing ethanol, in the presence of triethylamine, afforded compounds identified as (7Z) -7-[2-substituted phenyl hydrazinylidene] - 6-methyl -3- (pyridine - 4 -yl) -7H-[1,2,4] triazolo[3,4-b][1,3, 4] thiadiazines **(5a-h).** All compounds were tested *in vitro* against eleven *Candida* species and compared with itraconazole. Among these compounds **5a, 5c, 5e** and **5g** exhibit the highest inhibitory activity against the *Candida* species at 6.25 µg/ml. This outcome confirms that phenyl, p-methoxy, p-chloro and p-sulfonamido phenyl groups on triazolothiadiazine ring may have a considerable effect on antifungal activity against *Candida* species. The compounds with p-bromophenyl **(5d)** and p-flourophenyl **(5f)** substituents exhibit inhibitory activity against *Candida* species at 12.5 µg/ml. The compounds with ortho methyl and p-methyl phenyl substituents were devoid of activity upto 100 µg/ml.

Biography

Mashooq Ahmad Bhat has completed his Ph.D. from Hamdard University, New Delhi, India in 2008. Currently working as Assistant professor in College of Pharmacy, King Saud University, Riyadh, KSA. He has published more than 25 papers in journals of international repute. He is serving as reviewer of many reputed journals of medicinal chemistry. His area of research is structure based drug design as anticonvulsants and anti-tubercular agents. He has published many Single crystal X-ray reports of the synthesized compounds.