Bioorganic & Medicinal Chemistry Letters 19 (2009) 3564–3567

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis of novel 3-(1-(1-substituted piperidin-4-yl)-1*H*-1,2,3-triazol-4-yl)-1,2,4-oxadiazol-5(4*H*)-one as antifungal agents

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ARTICLE INFO

Article history:
Received 27 February 2009
Revised 13 April 2009
Accepted 29 April 2009
Available online 3 May 2009

Keywords:
1,2,3-Triazole
Piperidine
1,2,4-Oxadiazole
MIC values
SAR

ABSTRACT

A novel series of 1,2,3 triazole compounds possessing 1,2,4 oxadiazole ring were efficiently synthesized. Synthesized compounds were evaluated for their in vitro antifungal activities using standard cup plate method. SAR for the series has been developed by comparing their MIC values with miconazole and fluconazole. Compound **11a** from the series was more potent than miconazole against *Candida albicans* (MIC-20) and *Aspergillus flavus* (MIC-10) whereas equipotent with miconazole against *Fusarium oxysporum* (MIC-25) and *Aspergillus niger* (MIC-12.5). Also compound **11h** was more potent than miconazole against *Candida albicans* (MIC-20) and *Aspergillus niger* (MIC-10) and equipotent with miconazole against *Fusarium oxysporum*. Compound **11h** was equipotent with fluconazole against *Aspergillus niger* (MIC-10).

1,2,3-Triazole and its derivatives have occupied a pivotal position in medicinal chemistry in the past few decades due to their chemotherapeutic value.[1] Many 1,2,3-triazoles are found to be potent antineoplastic,[2] antimicrobial,[3–5] analgesic,[6] anti-inflammatory, local anesthetic,[7] anticonvulsant,[8] antimalarial,[9] and anti-HIVagents,.[10] Some 1,2,3-triazole derivatives were used as DNA cleaving agents,[11] and potassium channel activators.[12] Very recently disubstituted 1,2,3-triazole analogues have been reported as cannabinoid CB1 receptor antagonists,[13] and antitubercular agents.[14]

1,2,4-Oxadiazole and its derivatives are important pharmacophore with diversified pharmacological activities like antibacterial, analgesic and anti-inflammatory.[15] Piperidine and its analogues are reported in literature for varied pharmacological activities like antihistaminics and antibacterial,[16] AChE inhibitors,[17] antitubercular agents.[18] Piperidine nucleus is important core of many drug molecules. From the literature survey it is observed that no efforts have been made for developments of a molecular scaffold containing these three important cores. In continuation of our work on synthesis of some pharmacologically important heterocycles,[19] here we wish to report synthesis and antifungal activity of novel series of 3-(1-(1-substituted piperidin-4-yl)-1*H*-1,2,3-triazol-4-yl)-1,2,4-oxadiazol-5(4*H*)-one. From the activity data SAR for the series is developed.

The amidoxime compound **8**, that is, *tert*-butyl 4-(4-(*N*′hydroxycarbamimidoyl)-1*H*-1,2,3-triazol-1-piperidine-1-carboxylate was synthesized from the commercially available starting material *N*-Boc piperidone (**1**) as outlined in Scheme 1. *N*-Boc piperidone was reduced using sodium borohydride to give *N*-Boc piperidinol (**2**). It was subjected to O-mesylation using methane sulfonyl chloride to give the corresponding *O*-mesyl derivative (**3**) with 95% yield. The *tert*-butyl 4-azidopiperidine-1-carboxylate (**4**) was prepared by nucleophilic substitution reaction using sodium azide in DMF at 80 °C with 84% yield. It was subjected to 1,3-dipolar cycloaddition reaction using ethyl propiolate and copper iodide as a catalyst in acetonitrile to get the compound (**5**) with 86% yield. The catalyst copper iodide was used in 0.20 equiv to give the better yield. It is interesting that use of increased quantity of copper iodide is not affecting the reaction time and on the contrary, it gives the lower yield (75%). The cyano compound (**7**) was obtained in **82**% yield, by treating ester compound (**5**) with liquid ammonia to yield amide derivative (**6**) and subsequently dehydration using trifluoroacetic anhydride (TFAA). The cyano compound thus prepared was treated with hydroxylamine hydrochloride and sodium bicarbonate to give corresponding amidoxime compound (**8**) with 87% yield.

Amidoxime compound (**8**) was subjected to cyclization as per reported procedure in literature, using carbonyl diimidazole (CDI) in presence of pyridine base in dioaxne solvent at 100 °C to give *tert*-butyl-(4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-1*H*-1,2,3-triazol-1-yl)piperidine-1-carboxylate (**9**) as shown in Scheme 2. Although, the reaction was completed in 50 min, unfortunately, the yield obtained of expected compound was very low (52%). In this reaction, formation of unknown impurities was found. To control the formation of unknown impurities, amidoxime compound (**8**) was treated with CDI and tetrahydrofuran under reflux for

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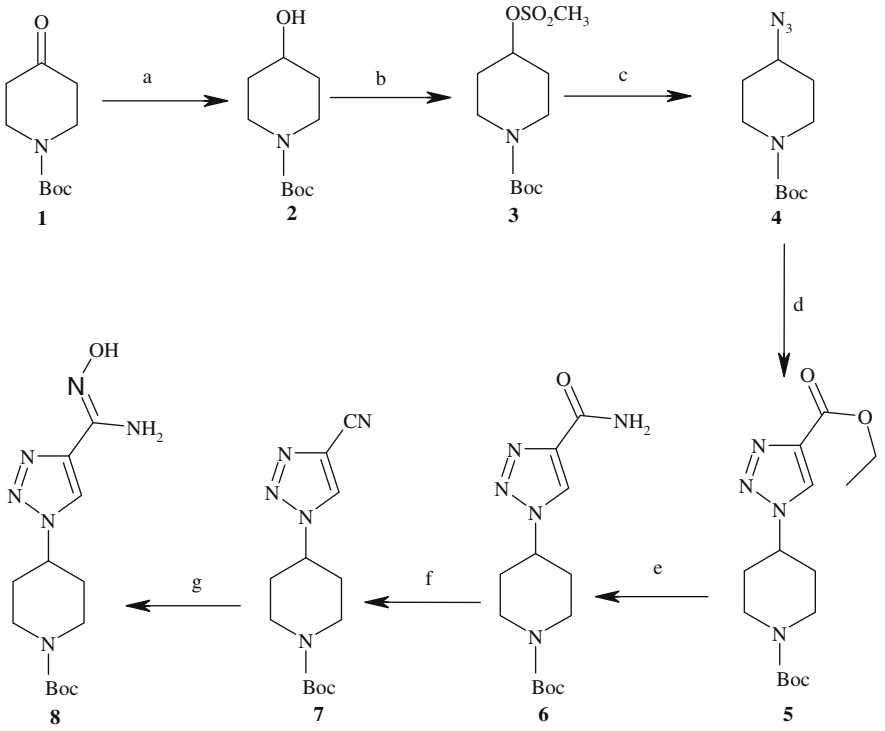
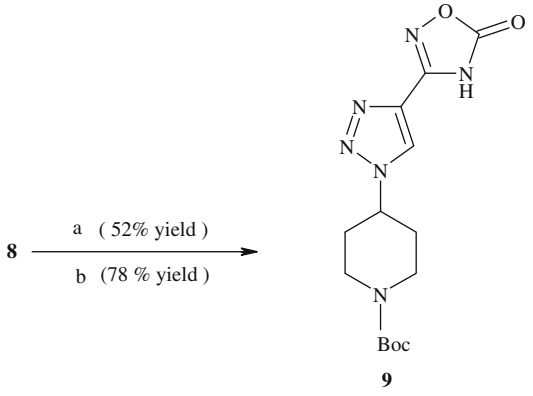
doi:10.1016/j.bmcl.2009.04.134



Scheme 1. Reagents and conditions: (a) $NaBH_4$, ethanol, rt, 2 h; (b) Methanesulfonyl chloride, triethylamine, dichloromethane; (c) NaN_3, DMF, 80 °C, 8 h; (d) Ethyl Propiolate, CuI, acetonitrile, rt, 12 h; (e) ammonia, ethanol, rt,12 h; (f) TFAA, dichloromethane, rt, 2 h; (g) Hydroxylamine hydrochloride, sodium bicarbonate, methanol, reflux, 14 h.



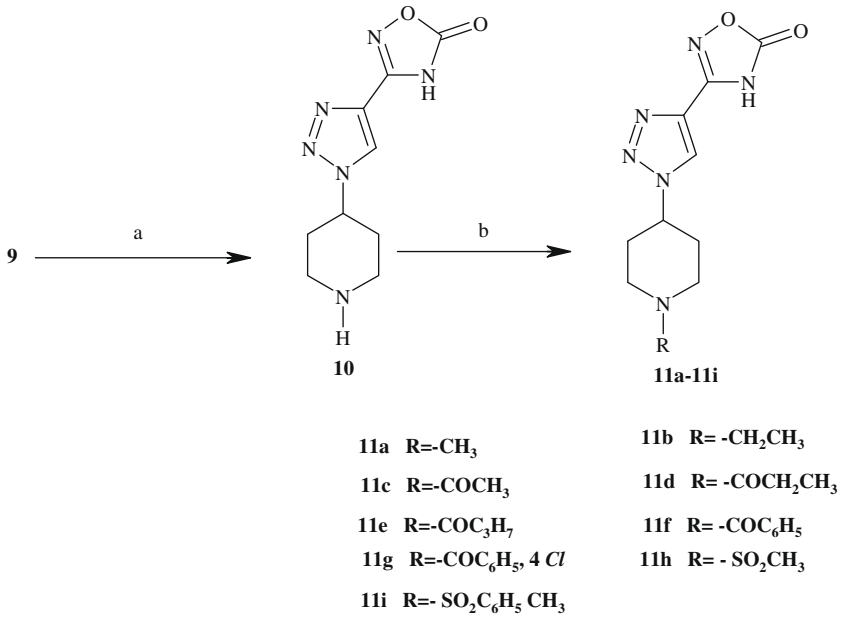
Scheme 2. Reagents and conditions: (a) CDI, 1,4-dioxane, 100 °C, 50 min; (b) CDI, tetrahydrofuran, reflux, 10 h.

10 h to get target compound with 78% yield. The compound **9** was treated with trifluoro acetic acid (TFA) in dichloromethane for Boc-deprotection to yield corresponding amine compound (**10**). The compounds **11a-11i** were synthesized by treating compound **10** with alkyl halide/acyl halide/mesyl halide to give the corresponding target compounds with 84–89% yield as shown in Scheme 3.

All the synthesized compounds were screened for in vitro antifungal activity. The antifungal activity was evaluated against different fungal strains such as *Candida albicans* (NCIM3471), *Fusarium oxysporum* (NCIM1332), *Aspergillus flavus* (NCIM539), *Aspergillus niger* (NCIM1196) and *Cryptococcus neoformans* (NCIM576). Minimum inhibitory concentration (MIC) values were determined using standard agar plate method.[20] Miconazole and Fluconazole were used as a standard for the comparison of antifungal activity. Dimethyl sulfoxide was used as solvent control. MIC values of the tested compounds are presented in Table 1.

Many of the newly synthesized compounds were found to show good antifungal activity. From the antifungal activity data (Table 1), it was observed that compound **11a** and **11h** are the most active among all tested compounds against all the tested organisms except *Cryptococcus neoformans*. Compound **11h** is more potent than miconazole and comparable to fluconazole as shown by the lower MIC. Compounds **5**–**8** are the important intermediates in the synthesis of final compounds. These compounds were also tested for antifungal activity. Among these compounds compound **8** bearing amidoxime groups was more active showing moderate activity. Introduction of 1,2,4 oxadiazole ring in the skeleton (**9**) enhances the antifungal activity compared to compound **8** as evidenced by the decreased MIC**.** Deprotection of the Boc of nitrogen in piperidine further enhances the antifungal activity against all the tested organisms except *C. neoformans*. Substitution of methyl group (**11a**) on nitrogen increases the antifungal activity compared with unsubstituted nitrogen (**10**). Compound **11a** was more potent than miconazole against *Candida albicans* (MIC-20) and *Aspergillus flavus* (MIC-10) whereas equipotent with miconazole against *Fusarium oxysporum* (MIC-25) and *Aspergillus niger* (MIC-12.5). The further increase in the alkyl chain decreases antifungal activity resulting in enhanced MIC. Introduction of acetyl group on nitrogen reduces the antifungal activity compared with unsubstituted piperidine against all tested organisms. There was further decrease in antifungal activity if acetyl group replaced by propionyl **(11d)** and butyryl (**11e**). Introduction of benzoyl group on nitrogen shows marginal enhancement of activity compared with acetyl or propionyl substituent. Introduction of mesyl group on nitrogen gave most active compound of the series, that is, **11h.** Compound **11h** was more potent than miconazole against *Candida albicans* (MIC-20) and *Aspergillus niger* (MIC-10) and equipotent with miconazole against *Fusarium oxysporum.* Compound **11h** was equipotent with fluconazole against and *Aspergillus niger* (MIC-10).

In conclusion, synthesis and antifungal activity of a novel series of piperidino-1,2,3 triazoles with 1,2,4 oxadiazole ring at 4 posi-



Scheme 3. Reagents and conditions: (a) TFA, dichloromethane, rt, 14 h; (b) Triethylamine, R–X or RCOX, tetrahydrofuran, 0–5 °C to rt, 2 h.

Table 1
Antifungal activity of the synthesized compounds

Compound	MIC Values[a] (μg/mL)				
	C. albicans	*F. oxysporum*	*A. flavus*	*A. niger*	*C. neoformans*
5	40	44	22	19	35
6	50	55	27	25	45
7	—*	90	55	50	—*
8	35	35	20	20	40
9	30	25	15	20	—*
10	27.5	25	15	15	—*
11a	20	25	10	12.5	60
11b	37	39	19	19	39
11c	60	61	31	31	65
11d	85	90	42	42	85
11e	90	95	—*	—*	85
11f	85	88	42	42	85
11g	40	55	20	25	40
11h	20	25	15	10	27.5
11i	30	33	25	20	40
Miconazole	25	25	12.5	12.5	25
Fluconazole	5	5	5	10	5

* No activity was observed up to 200 μg/mL.
[a] Values are the average of three readings.

tions has been demonstrated. Based on the activity data, SAR for the series has been developed. From SAR it can be said that compound **11a** and **11h** and are most active compounds from the series. Thus suggesting that the present series containing 1,2,3 triazole with piperidine ring and 1,2,4 oxadiazole nucleus with methyl or methyl sulphone group on piperidine nitrogen can serve as important pharmacophore for the design of new antifungal agent with potent activity and minimal toxicity.

Acknowledgements

The authors are thankful to Council for Scientific and Industrial Research (CSIR), New Delhi for financial assistance. The authors are also thankful to the Head, Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431004 (MS), India for providing the laboratory facility.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.04.134.

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