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Constructive Heterocyclic Ring Systems in a Single Frame Work

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Abstract: The re-emergence of antimicrobial infections which are resistant to conventional drug therapy has demonstrated the need for alternative chemotherapy. For these regard developed, screened antibacterial and antifungal activity of [1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-benzooxazole analogs (**5a** – **5c)** successfully. The compound (**5c**) especially showed good activity again for B. *Subtilis (antibacterial)* against *Norfloxacin,* and E.*ville* against *Griseofulvin.*

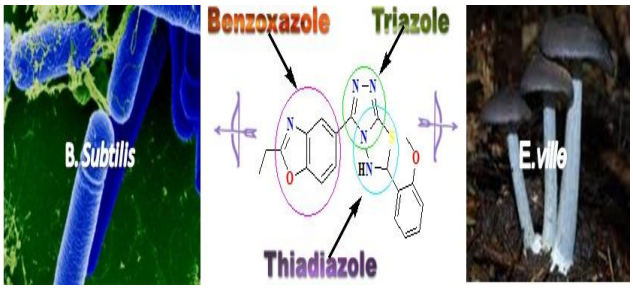
Key words:Benzoxazole, Triazole, Thiadiazole analogs

Introduction

The heterocyclic's play critical roles as core structures in the design of drugs show different bioactivity. The specific orientation of bioactive motifs in 3D space is pivotal in ligand-receptor and enzyme-inhibitor complexes, which are the underlying mechanism of action for many pharmaceuticals.

For example of our first pharmacophoric ring Benzoxazole have been reported to show a broad spectrum of biological activities. Notable among these are antihistaminic, antiulcer, antifungal, cyclo-oxygenase inhibiting, antitumor, anticonvulsant, hypoglycemic, anti-inflammatoryand antitubercular activity

Inspired by the biological profile of benzoxazoles, 1, 2, 4-triazoles, thiadiazoles and their increasing importance in pharmaceutical and biological fields. It is thought worthwhile to undertake the synthesis of the title compounds with the view to obtain certain new chemical entities with three active pharmacophores in a single molecular frame work for the intensified biological activities.



Methods:

Synthesis of substituted 5-([1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)-1,3-benzoxazoles (5a-5c)

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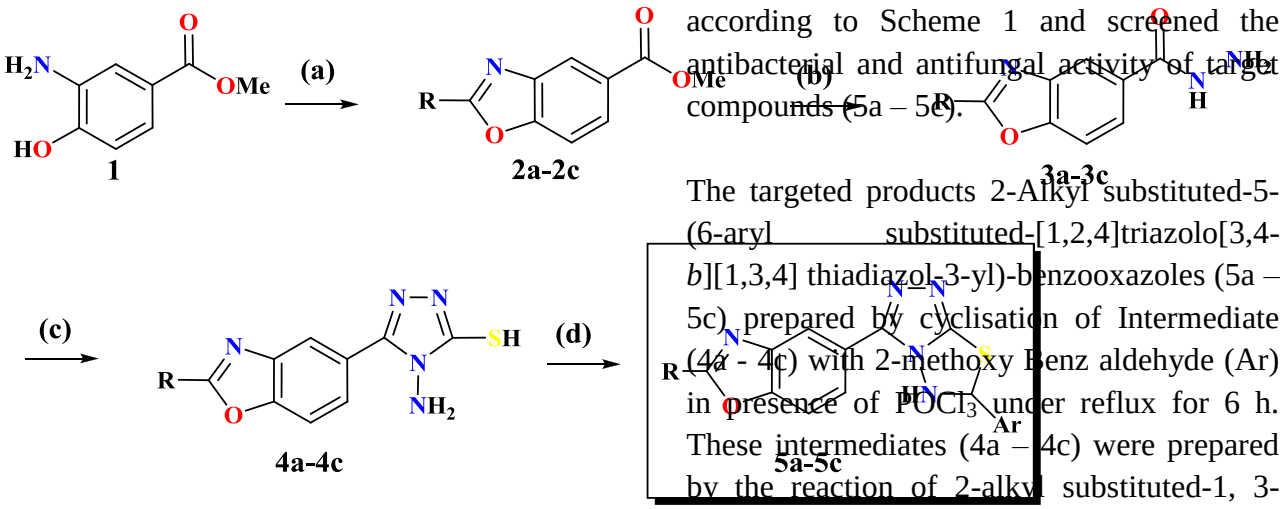

2a,3a,4a: R = H;
2b,3b,4b: R = CH_3;
2c,3c,4b: R = C_2H_5;

5a: R = H, **Ar** = 2-MeO-C_6H_5;
5b: R = CH_3, **Ar** = 2-MeO-C_6H_5;
5c: R = C_2H_5, **Ar** = 2-MeO-C_6H_5;

Reagent and conditions

(a) R-COOH, EtOH, rfx, 10-12h;
(b) NH2NH2.H2O, EtOH, rfx, 6h;
(c) CS2, KOH, NH2NH2.H20, EtOH, rfx, 2h;
(d) Ar-CHO, POCl3, rfx, 6h

The present research performed the synthesis of various novel 2-alkyl substituted-5-(6-aryl substituted-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazol-3-yl)-benzooxazoles (5a – 5c), from 3-amino-4-hydroxybenzoate (1) according to Scheme 1 and screened the antibacterial and antifungal activity of target compounds (5a – 5c).

The targeted products 2-Alkyl substituted-5-(6-aryl substituted-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazol-3-yl)-benzooxazoles (5a – 5c) prepared by cyclisation of Intermediate (4a - 4c) with 2-methoxy Benz aldehyde (Ar) in presence of $POCl_3$ under reflux for 6 h. These intermediates (4a – 4c) were prepared by the reaction of 2-alkyl substituted-1, 3-benzoxazole-5-carbohydrazides (3a – 3c) with CS_2 in KOH and in presence of ethanol as a solvent under reflux for 2h. Based on sequence the Intermediates (3a – 3c) were preparedfrom 2-alkyl substituted-1, 3-benzoxazole-5-carboxylates (2a – 2c) on reaction with hydrazine hydrate in ethanol solvent under reflux for 6 h. On reaction between 3-amino-4-hydroxybenzoate (1) andsuitable carboxylic acid in ethanol solvent under reflux for 10-12 h afforded the 2-alkyl substituted-1,3-benzoxazole-5-carboxylates (2a – 2c).

Results

Antibacterial and antifungal activity of final targets (5a – 5c).

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Compound	Antibacterial activity*						Antifungal activity*					
	E.*Coli*		B. *Subtilis*		S. *typhi*		A. *Niger*		C. *Albican*		E. *Vittalii*	
	50µg	**100 µg**	**50 µg**	**100 µg**	**50 µg**	**100 µg**	**50 µg**	**100 µg**	**50 µg**	**100 µg**	**50 µg**	**100 µg**
5a	14	16	14	-	10	08	09	12	--	16	11	16
5b	10	-	10	16	-	16	12	16	-	13	09	22
5c	12	18	**18**	**24**	12	15	10	20	16	24	**18**	**26**
Norfloxacin	18	21	16	20	14	22	-	-	-	-	-	-
Griseofulvin	-	-	-	-	-	-	15	22	18	26	17	24
DMF	-	-	-	-	-	-	-	-	-	-	-	-

*Zone of inhibition (mm)

The compound 5c especially showed good activity again for B. *Subtilis* (antibacterial) against *Norfloxacin*, and E.*ville* (antifungal)against *Griseofulvin*.

Discussion

In the last few decades, the chemistry of benzoxazoles, 1,2,4-triazoles, thiadiazoles, and their fused heterocyclic derivatives has received considerable attention owing to their synthetic and effective biological importance.

For example of our first pharmacophoric ring Benzoxazole have been reported to show a broad spectrum of biological activities. Notable among these are antihistaminic, antiulcer[1], antifungal[2], cyclo-oxygenase inhibiting[3], antitumor[4], anticonvulsant[5], hypoglycemic[6], antiinflammatory[7] and antitubercular activity[8]

In case of second pharmacophoric 1,2,4-triazole containing ring system have been incorporated into a wide variety of therapeutically interesting drug candidates including anti-inflammatory, CNS stimulants sedatives, antianxiety, antimicrobial agents[9] and antimitotic activity such as fluconazole, intraconazole, voriconazole[10].

The last pharmacophoric ring, thiadiazole nuclei have antimicrobial[11], anti-inflammatory[12], Anticancer[13], Anticonvulsant[14], Antidepressant[15], antioxidant, radio protective[16], antileishmanial activitiesand carbonic anhydrase inhibitors[17].

Inspired by the biological profile of benzoxazoles, 1,2,4-triazoles, thiadiazoles and their increasing importance in

pharmaceutical and biological fields. It is thought worthwhile to undertake the synthesis of the title compounds with the view to obtain certain new chemical entities with three active pharmacophores in a single molecular frame work for the intensified biological activities.

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