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Antihistamine Activity of 1,2,4-Triazolo[1,5-a]quinazolines

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This work was aimed to study and evaluate the antihistamine activity (bronchodilation) for prepared series of 1,2,4-triazolo[1,5-a]quinazolines. Screening of the bronchodilation activity of 1,2,4-riazoloquinazolines (**1-27**) was investigated *in vitro* using isolated thoracic tracheal rings of male guinea pigs pre-contracted with histamine. Screening procedure of bronchodilation test was performed in light to the standard reported method by examining the effects of the target molecules on isolated thoracic tracheal rings of male guinea pigs. The observed bronchodilation screening results are recorded and the potency (IC_{50}) was determined in mM in comparison with theophylline as a reference drug. The tested triazoloquinazolines have exhibited promising antihistaminic activity against histamine-induced bronchospasm. Our findings have shown that compounds **2**, **3**, **11**, **20** and **21** were found to possess the highest activity and could be useful as templates for further development through modification or derivatization to design more potent antihistamine.

Keywords: Triazoloquinazolines, Bronchodilation, Histamine, Theophylline, Bronchospasm, Tracheal rings.

INTRODUCTION

Histamine, chemically called (2-[4-emidazolyl]ethylamine), is an organic nitrogenous compound involved in local immune responses as well as regulating physiological function in the gut and acting as a neurotransmitter. It is produced and released by different human cells especially basophils, mast cells, lymphocytes and enterochromaffin cells[1]. It was found that H1-antihistamines are the inverse antagonists at the histamine H1-receptor, rather than antagonist[2,3]. The development of antihistamine drugs began more than 5 decades ago with the discovery that piperoxan was able to protect animals from the bronchial spasm induced by histamine. This finding was followed by elaborating of a number of *N*-phenylethylene-diamines with antihistaminic effects superior to piperoxan. The H1-antihistamines are now commonly subdivided into two broad groups, the first generation are related structurally and include a number of aminoalkyl ethers, ethylenediamines, propylamines, piperazines and phenothiazines. The second generation bear some structural resemblance to the first generation class as terfenadine and cetirizine but have been modified to be more specific in action, non-sedating and limited in their distribution profiles[4]. Despite the efficacy of the different H1 antihistamines in the treatment of allergic patients is similar, even when two broad groups antihistamines are compared, they are very different in profiles of their pharmacology and toxic potential. A literature survey reveals excellent antihistaminic activity in quinazolines and condensed quinazolines[5,6]. In addition, a number of synthesized 1,2,4-triazolo-4*H*-[4,3-a]quinazolin-5-ones have been found to display as good antihistamine agents[7,8]. In view of these points, the present work is an extension of our ongoing efforts in the field of triazolo-quinzolines chemistry[9-16], towards the development and designing of new compounds. Therefore, we aimed to investigate a new set of synthesized 1,2,4-triazolo-[1,5-a]quinazolines as antihistamine agents.

EXPERIMENTAL

Antihistaminic activity: Screening procedure of bronchodilation activity was performed in light to the standard reported methods by testing the effects of the target compounds on isolated thoracic tracheal rings of male guinea pigs (350-400 g)[17-19]. After light ether anesthesia, the guinea pigs were sacrificed by cervical dislocation. The tracheae were rapidly excised, placed in oxygenated (95 % O_2, 5 % CO_2) Krebs-Henseleit (KH) solution (composition in mM: NaCl 118, KCl 5.9, $NaHCO_3$ 25.5, $MgSO_4$ 1.2, $CaCl_2$ 2.5, NaH_2PO_4 1.2 and glucose 5.6) at room temperature and trimmed free of adherent

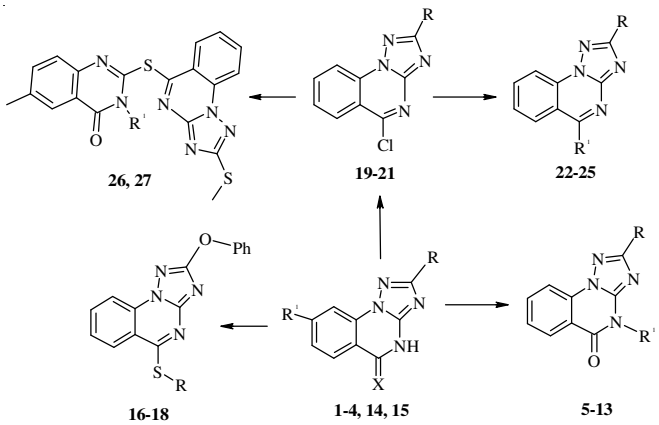
fat and connective tissue. Each trachea was cut into rings each containing three to four adjacent cartilage plates and placed in a vertical chamber "10 mL jacketed automatic multi-chamber organ bath system (Model no. ML870B6/C, Panlab, Spain)" filled with KH. Each tracheal ring was mounted between two stainless steel hooks passed through its lumen. The lower hook was fixed between two plates, while the upper one was attached to a force displacement transducer (Model no. MLT0201, Panlab, Spain) connected to an amplifier (Power Lab, AD Instruments Pty. Ltd.), which is connected to a computer. The chart for windows (v 3.4) software was used to record and elaborate data. Preparations were stabilized less than 1 g resting tension and allowed to equilibrate for 45 min during which time tissues were washed frequently. After equilibration the effects of cumulative concentrations of the compounds on histamine-precontracted rings were recorded. Pre-contraction was done with 1×10^{-5} M histamine. Finally, the observed data of bronchodilation activity are reported and the potency (IC_{50}) was determined (Table-1, Fig. 1).

TABLE-1
CONCENTRATION OF COMPOUNDS **1-27** NECESSARY TO REDUCE HISTAMINE-INDUCE CONTRACTURE BY 50 % (IC_{50}) IN PIGS THORACIC TRACHEAL RINGS

Compound no.	R		R^1	IC_{50} (mM)
1	O-Ph	X=O	H	0.5425
2	S-CH_3	X=O	H	0.4591
3	O-Ph	X=O	CH_3	0.3113
4	SO_2-CH_3	X=O	H	0.756
5	O-Ph		*p*-NO_2-Benzyl	0.6321
6	O-Ph		Ethyl	0.7176
7	O-Ph		Allyl	0.5338
8	O-Ph		Benzyl	0.5431
9	SO_2-CH_3		*p*-NO_2-Benzyl	0.7125
10	SO_2-CH_3		Ethyl	0.6960
11	SO_2-CH_3		Allyl	0.1976
12	S-CH_3		Allyl	0.6528
13	S-CH_3		Ethyl	0.7589
14	O-Ph	X=S	H	0.7530
15	S-CH_3	X=S	H	0.5319
16	Ethyl		-	0.5505
17	Allyl		-	0.6227
18	Phenyl		-	0.6354
19	O-Ph		-	0.8826
20	S-CH_3		-	0.4547
21	SO_2-CH_3		-	0.4716
22	O-Ph		Ethoxy	0.6618
23	O-Ph		Phenylhydrazide	0.6157
24	S-CH_3		Ethoxy	0.5332
25	S-CH_3		Phenylhydrazide	0.6641
26	-		4-Bromophenyl	0.8648
27	-		Benzyl	0.6321
Theophylline	-		-	0.01996

RESULTS AND DISCUSSION

In our previous papers[10,15,20,21], we have described the synthetic methodology for preparation of the triazoloquinazoline derivatives **(1-27)** (**Scheme-I**, Table-1). Histamine causes bronchospasm and the guinea pigs are the most susceptible animals for histamine, hence this investigation has done on isolated thoracic tracheal rings of male guinea pigs. The bronchodilation test against histamine-induced bronchospasm was adopted to determine the antihistaminic potential of the tested compounds. Screening of the bronchodilation activity of the synthesized 1,2,4-triazoloquinazoline compounds **1-27** was investigated *in vitro* using isolated thoracic tracheal rings of male guinea pigs pre-contracted with histamine according to standard technique[17-19]. The data reveal that all the tested compounds were found to exhibit remarkable significant bronchodilation effects and their IC_{50} values were determined in the range of 0.1976-0.8826 mM (Table-1). In parent structures, biological studies based on the observed results indicated that the type of substituent attached at 2, 4 and 5 positions is a controlling factor governing the total observed pharmacological properties. Compounds **1**, **2** and **4** have shown good activity (IC_{50} = 0.5425, 0.4591 and 0.756 mM, respectively) in regard to the reference drug (IC_{50} = 0.01996 mM). However, the presence of a methyl substituent in compound **3** was enhanced significantly the observed bronchodilation profile with respect to theophylline (IC_{50} = 0.3113 mM). Throughout in present study, we have noticed that structure modifications in the parent compounds **1-4** have led to remarkable bronchodilation depending on chemical feature of the substituents. For example, regioselective *N*-alkylation of lactam (**1**,**2**,**4**) into **5-13** has demonstrated noticeable bronchodilation activity and displayed a significant IC_{50} values (Table-1) in comparison with their parents and theophylline as well. Furthermore, compound **11** represents one of the most active and populated compounds obtained during this study (IC_{50} = 0.1976 mM). Moreover, variation of alkyl groups in 4^{th} position showed a variety in bronchodilation terms in regards to their parent compuond (Table-1). Conversion of lactam in compounds **1**, **2** and **4** into an imidoyl chloride function (**19-21**) gave enhanced significant effect in bronchodilation profile in case of **20** and **21** (IC_{50} = 0. 4547 and 0.4716 mM) and slight decreasing in the activity was occured with compound **19** (IC_{50} = 0.8826 mM). This indicated to the chemical feature of sulfanyl and sulfonyl groups (electrons donating) together with chloro atom (electron withdrawing) for increasing the lipophilicity. Whereas, further chemical transformation of chlorine in **19** and **20** into ethoxyl derivatives (**22**, **24** with IC_{50} = 0.6618 and 0.5332 mM) and amidrazone



Scheme-I: Main routes for synthesis of the target triazoloquinazolines (**1-27**)

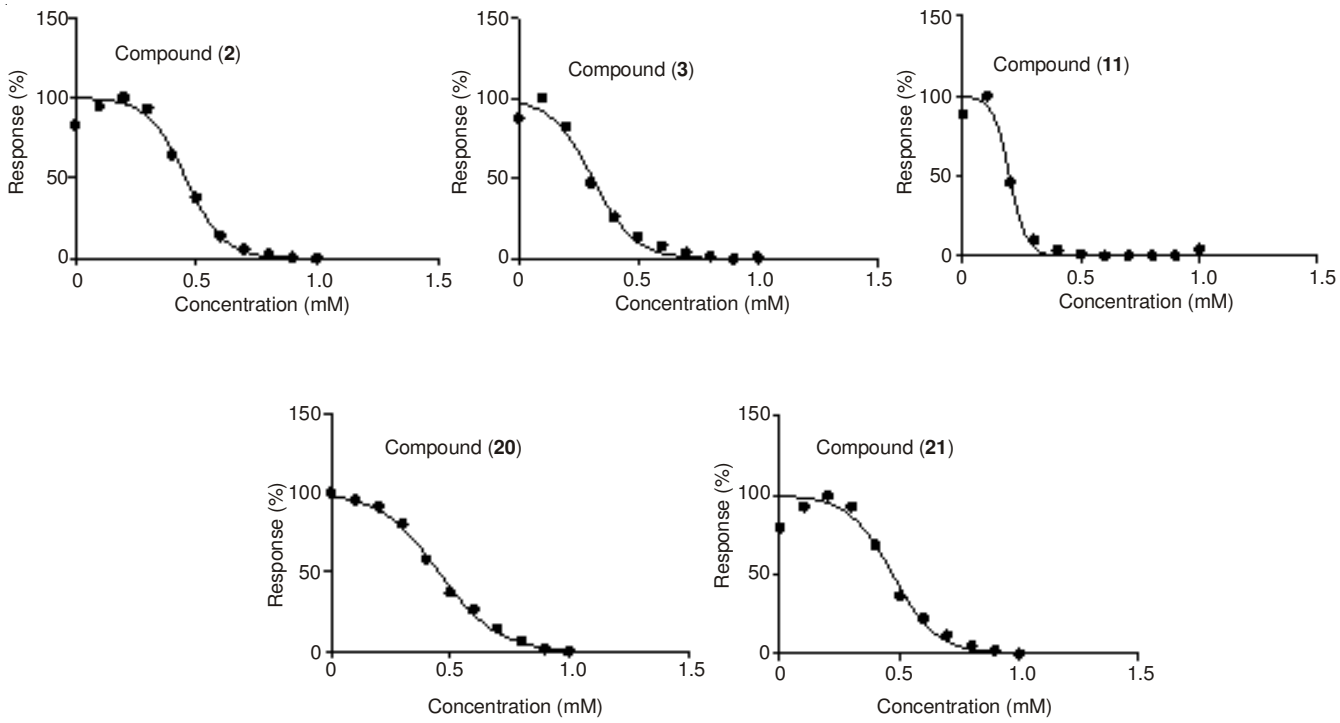


Fig. 1. Bronchodilation effects of the most active compounds (**2**, **3**, **11**, **20**, **21**)

derivatives (**23**, **25** with IC_{50} = 0.6157 and 0.6641 mM) was not offered advantageous in the activity terms. The *S*-arylation of **20** into **26** and **27** has led to slightly decrease in the bronchdilation activity (IC_{50} = 0.8648 and 0.6321 mM). Thionation products **14** and **15** were emerged less active than the parent compound (IC_{50} = 0.7530 and 0.5319 mM), however the thioether compounds **16-18** of **14** have shown slightly increase in the bronchodilation activity (IC_{50} = 0.5505, 0.6227 and 0.6354 mM, respectively). This could be attributed to the enhancing of the lipophilicity comparable to that of parent **14**.

In conclusion, the titled triazoloquinazolines have exhibited promising antihistaminic activity against histamine-induced bronchospasm on isolated thoracic tracheal rings of male guinea pigs. Among the series, compounds **2**, **3**, **11**, **20** and **21** were emerged the most active compounds (Table-1, Fig. 1) and could be useful as templates for further development through modification or derivatization to design more potent antihistamine.

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