Computer-aided Design, Synthesis, and Biological Evaluation of 5-Substituted Aminomethylenepyrimidine-2,4,6-Triones as H_1 Antihistaminic Agents (Part2)†

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Abstract: As a part of a research project pertaining to the synthesis of novel candidates as nonsedating, nonclassic H_1 histaminergic (H_1) blockers with low toxicity profiles, some new 5-substituted aminomethylenepyrimidine-2,4,6-triones were designed based on the H_1 histaminic receptor pharmacophore model. The interactions between the designed compounds and the H_1 receptor were studied using molecular docking on the homology model of H_1 receptor. The designed compounds were synthesized and biologically evaluated for H_1-blocking activity; using isolated segments of guinea pig ileum. Compounds **15**,**18**,**19** and **21** exhibited comparable activities to acrivastine (**22**) as reference nonsedating drug. The C log P of designed compounds revealed lower values in reference to acrivastine (**22**) which might indicate decreased tendency for crossing the blood brain barrier.

Keywords: Synthesis, aminomethylenepyrimidine-2,4,6-triones, antihistaminic, pharmacophore modeling, docking.

1. INTRODUCTION

Histamine is namely one of the most frequently studied local hormones, which plays an important role in several physiological processes, specifically, in the central nervous, gastrointestinal, respiratory and immune systems [1-4]. The effects of histamine are mediated by a family of G protein coupled receptors, H_1, H_2, H_3 and H_4 receptors [5]. The H_1 receptor is mainly responsible for the inflammatory effect of histamine, e.g. smooth muscle contraction, increasing blood vessel permeability, releasing other local hormones [6]. It has been considered an attractive target for drug discovery for several years and H_1 receptor antagonists have proved to be effective therapeutic agents for respiratory distress, thus contributing to an important class of drugs today.

The most recent antihistaminic compounds were almost exclusively based on modifying the structure of some old H_1 antagonists. Cloning of the human histamine H_1 receptor (hHR_1) however, will be capable of opening new ways to examine the binding of histamine and its antagonists, and to find the important receptor-ligand interactions. It is also possible to compare the binding affinity of the newly synthesized analogs to predict their expected pharmacological action [7, 8].

As a result of our interest to establish potential nonsedating, nonclassic histaminergic (H_1) blockers with low toxicity profiles, our previously published work described the synthesis of some substituted aminomethylenepyrimidine-2, 4, 6-triones with different aliphatic substituents at the side chain of the pyrimidinyl moiety [9]. According to this investigation these derivatives exhibited pronounced antihistaminic activities.

The present work designed and generated a pharmacophore model using five of the previously synthesized compounds which were then validated using other six of the previously synthesized compounds.

According to this pharmacophore model new aminomethylenepyrimidines (Fig. **1**) linked to different aromatic amines were designed and evaluated for H_1-blocking activity using isolated segments from guinea pig ileum. The newly designed agents together with the previously prepared compounds were all docked inside the binding site of the H_1-receptor homology model and the new ones showed better docking scores comparable to the old members and the reference drug acrivastine (**22**).

In order to verify the nonsedating capacity of the newly synthesized candidates, the partition coefficient Clog p was calculated using a routine computer-assessed program described by Leo [10].

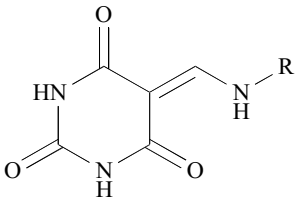

Fig. (1). Molecular structure of newly synthesized substituted aminomethylenepyrimidine-2, 4, 6-triones.

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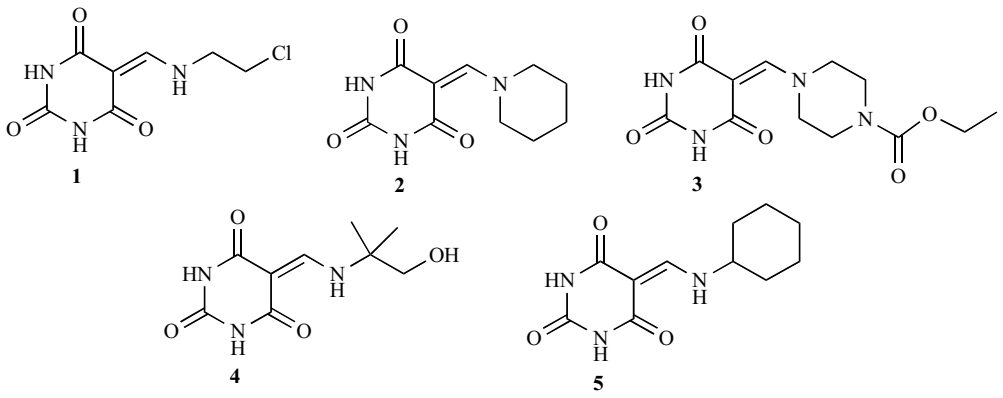


Fig. (2). H_1-antagonists used for building the pharmacophore model.

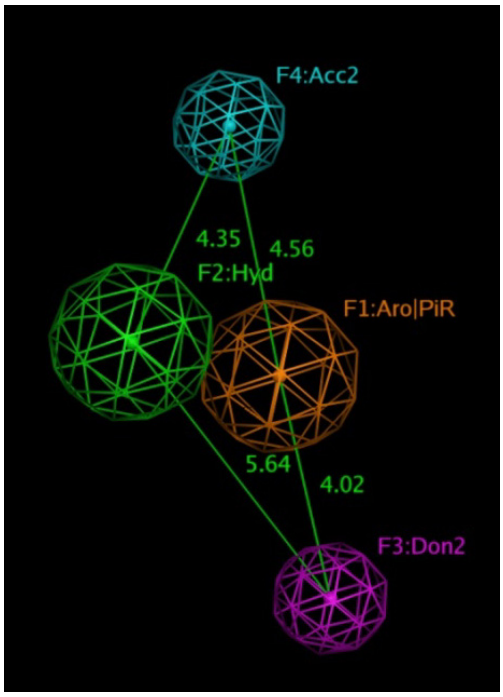


Fig. (3). Pharmacophore model which derived from H_1-antagonists and used in the selection of the proposed compounds (numbers indicate distances in Å).

2. MATERIALS AND METHODS

2.1. Molecular Modeling

2.1.1. Generation of the Pharmacophore Model

All compounds were built using the Builder module of the Molecular Operating Environment (MOE) version 2008.10 [11] program and subjected to energy minimization using MMFF94X force field.

The training set compounds **1-5** (Fig. **2**) were used for pharmacophore model generation (Fig. **3**) using the Unified scheme present in the Pharmacophore Elucidation module. The generated pharmacophore model (query) was saved as .ph4 file.

The pharmacophore model was then validated by mapping compounds **6-11** (Fig. **4**) on the pharmacophore model using the Pharmacophore Search module and the conformer having the lowest root mean square distance (RMSD) was selected. This procedure was also used for mapping the new designed compounds **15-21** (Fig. **5**) on the pharmacophore model.

2.1.2. Molecular Docking Study

A docking study was performed using Molegro Virtual Docker (MVD) [12] version 2010.4.0.2. All docking calculations were carried out using the grid-based MolDock score (GRID) function available in MVD with a grid resolution of 0.30 Å. The binding site on the receptor was defined as a sphere with a radius of 15 Å extending from the center of the largest cavity which was identified using the Detect Cavities function present in MVD. The MolDock SE search algorithm with a maximum of ten runs was used through the calculations, with all other parameters kept as defaults. One pose per run was retained and all poses were examined manually and the best pose was used. Ligand interactions were generated using the Ligand Interactions module in MOE.

2.2. Chemistry

Melting points were determined in open glass capillaries on a Gallenkamp melting point apparatus and were uncorrected. The infrared (IR) spectra were recorded on Perkin-Elmer 1430 infrared spectrophotometer using the KBr plate technique. 1H-NMR spectra were determined on Jeol spectrometer (500 MHz) at the Microanalytical unit, Faculty of Science, Alexandria University and on a Varian spectrometer (300 MHz), Faculty of Science, Cairo University using tetramethylsilane (TMS) as the internal standard and DMSO-d_6 as the solvent (Chemical shifts in δ, ppm). Splitting patterns were designated as follows: bs: broad singlet; s: singlet; d: doublet; m: multiplet; t: triplet. Microanalyses were performed at the Microanalytical Unit, Faculty of Science, Cairo University, Egypt. The found values were within ±0.4% of the theoretical values. Follow up of the reactions and checking the homogeneity of the compounds were made by TLC on silica gel-protected glass plates and the spots were detected by exposure to UV-lamp at λ 254.

2.2.1. Synthesis of 5- Ethoxymethylenepyrimidine-2,4,6-trione (14)

A mixture of pyrimidine-2,4,6-trione (**12**) (1.28 g, 0.01 mol) and triethyl orthoformate (**13**) (7.4 g, 0.05 mol) was heated under reflux for 30 min. After cooling, ether was

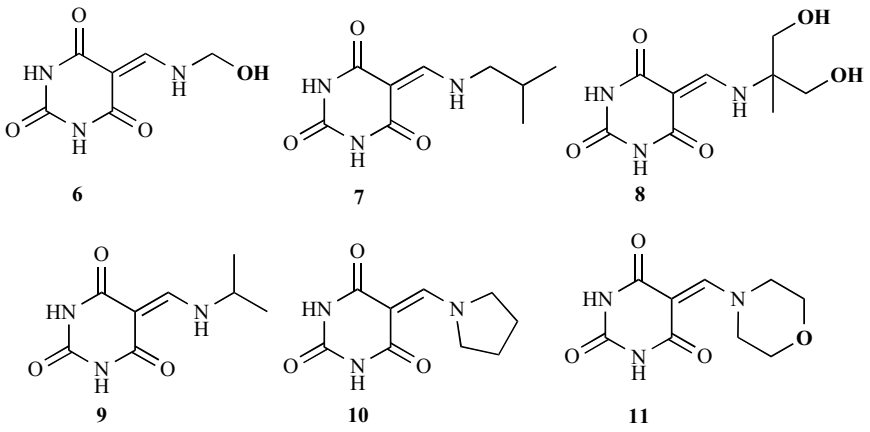


Fig. (4). H_1-antagonists used for validating the pharmacophore model.

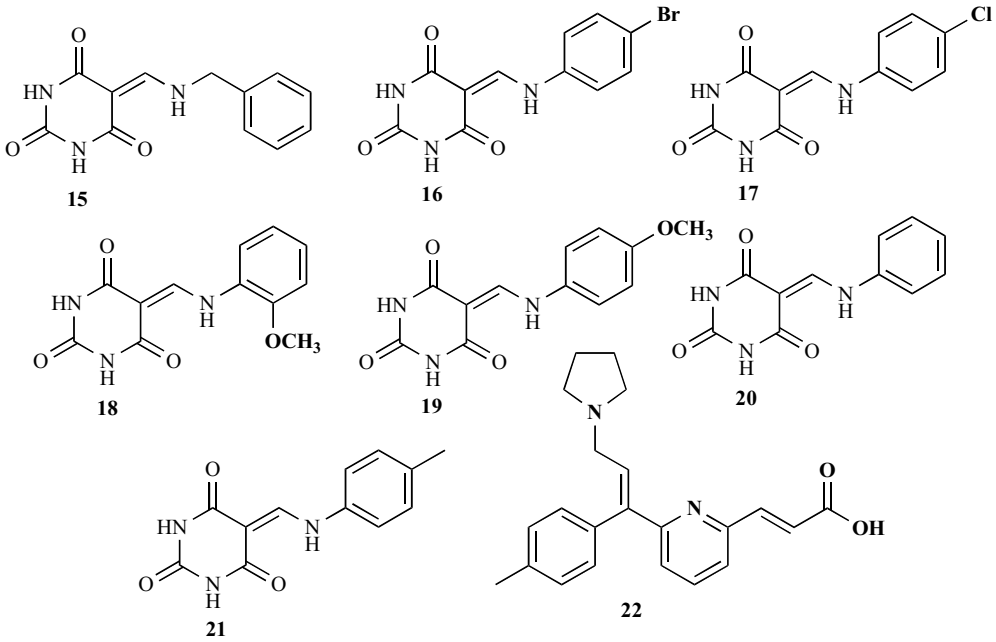


Fig. (5). Chemical structure of the newly designed H_1-antagonists and Acrivastine (**22**).

added to the reaction mixture, the separated product was filtered, dried and utilized, directly in the next step, without further purification [9].

2.2.2. General Procedure for the Synthesis of 5- (Substituted Aminomethylene)pyrimidine-2,4,6-triones(15-21)

A mixture of the appropriate amine (0.003 mol) and the ethoxymethylene derivative **14** (0.184 g, 0.001mol) contained in a round bottomed flask, was gently heated until fusion. The fused reaction mixture was maintained at 150 °C for 1 h. The mixture was then allowed to cool to RT, triturated with water, filtered, dried and recrystallized from ethanol/water.

2.2.2.1. 5-[(Benzylamino)methylene]pyrimidine-2,4,6-trione(15)

Yield: 81%, mp: > 300°C .IR (cm^{-1}): 3421(NH); 3078 (=C-H); 1695 (C=O); 1510 (C=C); 1H-NMR (δ ppm): 4.69 (d, *J*= 6.3Hz, 2H, CH_2); 7.28 (d, *J*= 6.3 Hz, 2H, Ar-H); 7.31 (t, *J*= 6.3 Hz ,2H, Ar-H); 7.36 (t, *J*=6.3Hz, 1H, Ar-H); 8.24 (d, *J*=6.3 Hz, 1H, -C=CH); 10.34 (bs, 3H, NH, D_2O exchangeable). Anal. Calcd for $C_{12}H_{11}N_3O_3$ (245.23): C, 58.77; H, 4.52; N, 17.13. Found: C, 58.41; H, 4.71; N, 17.31.

2.2.2.2. 5-[(4-Bromophenylamino)methylene]pyrimidine-2,4,6-trione(16)

Yield: 73%, mp: > 300°C .IR (cm^{-1}): 3427 (NH); 3095 (=C-H); 1702 (C=O); 1599(C=N); 1506 (C=C); 1H-NMR (δ ppm): 7.27 (d, *J*= 6.1 Hz, 2H, Ar-H); 7.48 (d, *J*= 6.2 Hz, 2H, Ar-H); 8.54 (d, *J*= 6.1 Hz, 1H, -C=CH); 10.92 (bs, 3H, NH, D_2O exchangeable). Anal. Calcd for $C_{11}H_8BrN_3O_3$ (310.10): C, 42.60; H, 2.60; N, 13.55. Found: C, 42.87; H, 2.29; N, 13.36.

2.2.2.3. 5-[(4-Chlorophenylamino)methylene]pyrimidine-2,4,6-trione(17)

Yield: 76%, mp: > 300°C .IR (cm^{-1}): 3399 (NH); 3058 (=C-H); 1699 (C=O); 1597(C=N); 1496 (C=C); 1H-NMR (δ ppm): 7.25 (d, *J*=6.1 Hz, 2H, Ar-H); 7.43 (d, *J*=6.2 Hz, 2H, Ar-H); 8.53 (d, *J*=6.1Hz, 1H, -C=CH); 10.89 (bs, 3H, NH,

D_2O exchangeable). Anal. Calcd for $C_{11}H_8ClN_3O_3$ (265.65): C, 49.73; H, 3.04; N, 15.82. Found: C, 49.49; H, 3.25; N, 15.60.

2.2.2.4. 5-[(2-Methoxyphenylamino)methylene]pyrimidine-2,4,6-trione (18)

Yield: 43%, mp: > 300°C. IR (cm^{-1}): 3420 (NH); 3070 (=C-H); 1701 (C=O); 1596(C=N); 1521(C=C); 1H-NMR (δ ppm): 3.64 (s, 3H, OCH_3); 7.26 (d, *J*=14.1Hz, 1H, Ar-H); 7.31 (t, *J*=6.2 Hz, 2H, Ar-H); 7.38 (d, *J*= 6.1Hz, 1H, Ar-H); 8.51 (d, *J*= 6.1Hz, 1H, -C=CH); 10.76 (s, 1H, -NH D_2O exchangeable), 10.87 (s, 1H, -NH D_2O exchangeable); 11.83(d, 1H, -NH D_2O exchangeable *J*=14.1),. Anal. Calcd for $C_{12}H_{11}N_3O_4$ (261.23): C, 55.17; H, 4.24; N, 16.09. Found: C, 54.88; H, 4.37; N, 15.78.

2.2.2.5. 5-[(4-Methoxyphenylamino)methylene]pyrimidine-2,4,6-trione (19)

Yield: 56%, mp: > 300°C. IR (cm^{-1}): 3418 (NH); 3067 (=C-H); 1705 (C=O); 1581(C=N); 1513 (C=C); 1H-NMR (δ ppm): 3.71 (s, 3H, OCH_3); 7.22 (d, *J*=6.1,2H, Ar-H); 7.48 (d, *J*=6.2Hz, 1H, Ar-H); 8.51 (d, *J*=6.1Hz, 1H, -C=CH); 10.82 (s, 1H, -NH D_2O exchangeable), 10.96 (s, 1H, -NH D_2O exchangeable); 11.88 (d, 1H, -NH D_2O exchangeable *J*=14.1),. Anal. Calcd for $C_{12}H_{11}N_3O_4$ (261.23): C, 55.17; H, 4.24; N, 16.09. Found: C, 55.50; H, 3.95; N, 16.21.

2.2.2.6. 5-[(Phenylamino)methylene]pyrimidine-2,4,6-trione (20)

Yield: 63%, mp: 301-302 °C. IR (cm^{-1}): 3428 (NH); 3054 (=C-H); 1687 (C=O); 1594(C=N); 1521 (C=C); 1H-NMR (δ ppm): 7.28 (d, *J*=6.3Hz, 2H, Ar-H); 7.31(t, *J*=6.3Hz, 1H, Ar-H); 7.36 (t, *J*=6.3Hz, 2H,Ar-H); 8.24 (d, *J*=6.2Hz,1H, -C=CH); 10.26 (bs, 3H, NH, D_2O exchangeable). Anal. Calcd for $C_{11}H_9N_3O_3$ (231.21): C, 57.14; H, 3.92; N, 18.17. Found: C, 57.14; H, 3.92; N, 18.17.

2.2.2.7. 5-[(p-Tolylamino)methylene]pyrimidine-2,4,6-trione(21)

Yield: 59%, mp: 305-307 °C .IR (cm^{-1}): 3434 (NH); 3086 (=C-H); 1699(C=O); 1597(C=N); 1H-NMR (δ ppm): 2.47 (s, 3H, CH_3); 7.24 (d, *J*=6.1Hz, 2H, Ar-H); 7.26 (d, *J*=6.2 Hz, 1H,Ar-H); 8.51 (d, *J*=6.1Hz,1H, -C=CH); 10.90 (bs, 3H, NH, D_2O exchangeable). Anal. Calcd for $C_{12}H_{11}N_3O_3$ (245.23): C, 58.77; H, 4.52; N, 17.13. Found: C, 58.87; H, 4.38; N, 17.02.

2.3. Pharmacology

Investigation of the antihistaminic activity for representatives of the newly synthesized compounds has been assessed through the process of histamine-induced spasms in isolated segments of guinea pig ileum. Acrivastine (**22**) has been utilized as reference drug (Fig. **5**). The investigation conformed to the guide for the Care and Use of Laboratory Animals published by US National Institute of Health (NIH Publication No. 83-23, revised 1996). The Local Ethics Committee approved this study.

All new compounds **15- 20 and 21** were tested for their antihistaminic activity. Acrivastine (**22**) was donated by Glaxo-Welcome pharmaceutical company, Elsalam City, Cairo, Egypt. All test agents were directly solubilized in distilled water.

Male Hartley guinea pigs (6 weeks of age, 250 ± 50g body weight) were of local breed and obtained from the animal house located at the Medical Research Institute, University of Alexandria, Egypt.

Male guinea pigs were sacrificed by a blow to the base of the skull and cervical dislocation. Clean ileal segments of 2–3 cm long were prepared from the guinea pigs. One end was fixed to a glass aerating tube and the other to isotonic transducer (Bioscience, England). The whole preparation was set up in 10-mL organ bath containing aerated Tyrode solution (NaCl: 1.0; $CaCl_2$:0.2; KCl: 0.2; $MgCl_2.6H_2O$: 0.2; NaH_2PO_4: 0.05; $NaHCO_3$: 1, and glucose: 2.0 g/dL). The Tyrode solution was maintained at 37 °C.

The submaximal dose of histamine was estimated to be 2.63×10^{-3} M and taken as control (100% agonist effect).

The maximum % inhibition of histamine induced contractions (I_{max}), for acrivastine and the test new compounds were measured at the submaximal dose level of 10^{-3} M.

The % inhibition, for each agent was calculated from the difference in heights induced by histamine in absence and presence of the test agent. Each assigned submaximal dose was added into the organ bath two min prior to histamine challenge.

The partition coefficient [C log P] for the newly synthesized compounds compared with the anti-histaminic acrivastine **22** was calculated by applying the procedure described by Leo [10] in 1993, where log P values of the compounds could be computed using a routine method "calculated log P" included in pc-soft ware package (Mac log P 2.0. Bio Byte Corp. CA, USA). A representation of the molecular structure, where hydrogens would be omitted or suppressed (SMILES notation) could be introduced into the program, which would compute the log P based on the fragment method.

3. RESULTS AND DISCUSSION

3.1. Molecular Modeling

3.1.1. Generation of the Pharmacophore Model

The pharmacophore model was generated derived from a training set containing 5 H_1-antagonists (Fig. **2**) and then validated using a validation set containing 6 H_1-antagonists (Fig. **3**) [12]. This model was made up of an aromatic or π-ring system (Aro|PiR), a hydrophobic group (Hyd), a H-bond donor (Don2) and a H-bond acceptor (Acc2) (Fig. **4**). In the derived model, the aromatic or π-ring system is associated with the pyrimidine core of the H_1-antagonists, the H-bond donor corresponding to the pyrimidine N1 Hydrogen, the H-bond acceptor corresponding to the pyrimidine C4 Oxygen and a hydrophobic moiety which is attached to the pyrimidine C5.

Using this pharmacophore model, the designed compounds (**15-21**) (Fig. **5**) were mapped in order to confirm that these compounds are capable of binding to the H_1-receptor with a similar set of interactions. Mapping of com-

Table 1. RMSD Values of Compounds 15-21

Compound	RMSD (Å)
15	0.6350
16	0.6302
17	0.6302
18	0.6306
19	0.6299
20	0.6310
21	0.6328

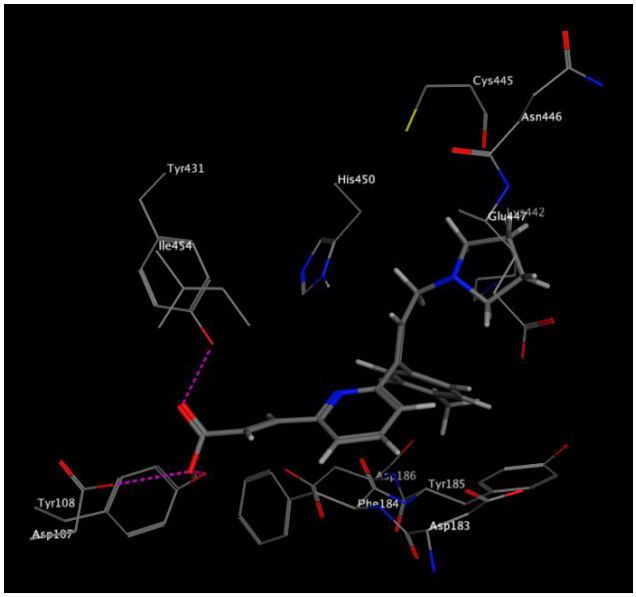
Table 2. MolDock Score and H-bond Score of the Docked Compounds

Compound	MolDock Score	H-bond score
1	-83.23	-2.72
2	-89.43	-1.15
3	-108.67	-1.69
4	-92.24	-5.79
5	-94.61	-0.13
6	-75.91	-11.75
7	-86.82	-4.64
8	-97.12	-4.51
9	-88.24	-3.34
10	-88.96	-2.69
11	-87.42	-1.17
15	-107.98	-3.15
16	-101.81	-2.59
17	-101.67	-2.92
18	-102.15	-2.79
19	-106.31	-2.90
20	-95.78	-2.94
21	-106.57	-3.77
Acrivastine (**22**)	-150.21	-2.71

pounds **15-21** on the pharmacophore model showed good fitting with low RMSD between the model feature and their matching ligand target points (Table **1**). Afterwards, the interactions between compounds **1-11**, **15-21** and H_1-receptor were studied using molecular docking.

3.1.2. Molecular Docking Study

In the present study, an attempt was made to investigate the ligand-receptor interactions of compounds **1-11**, **15-21** against H_1-receptor homology model, by performing docking studies using Molegro Virtual Docker (MVD) version 2010.4.0.2 [12].



Acrivastine (22)

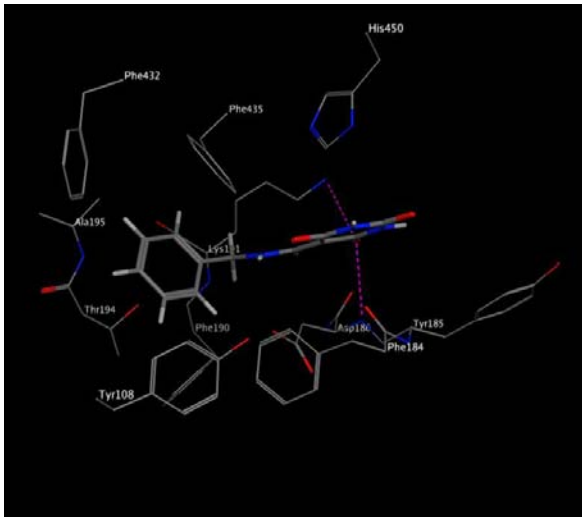


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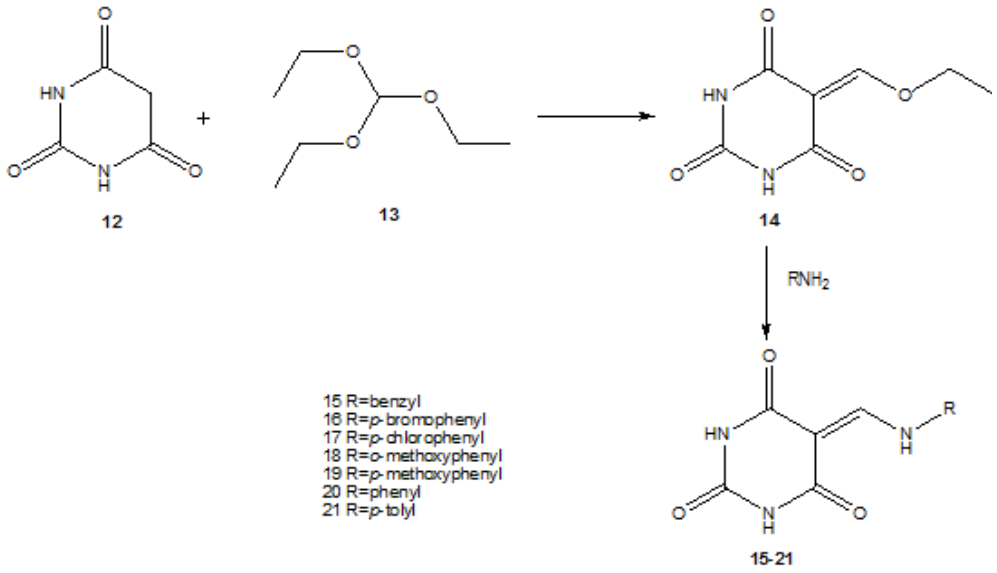
Fig. (6). Binding of Acrivastine (**22**) and compound **15** to the H_1-receptor homology model.

The H_1-receptor homology model was built by submitting the amino acids sequence of H_1-receptor obtained from GenBank [13, 14] (protein code: EAW64092.1) was submitted to SWISS-MODEL server [15, 16].

Compounds **1-11**, **15-21** and Acrivastine (**22**) were then docked inside the binding site of the H_1-receptor homology model. The MolDock score and H-bond scores of the docked compounds are presented in (Table **2**). The results showed that compounds **15-21** had good docking scores with H-bond scores comparable to or higher than Acrivastine. The binding of Acrivastine (**22**) and compounds **15** to the H_1-receptor homology model are shown in (Fig. **6**).



Scheme 1.

Table 3. Establishment of the Submaximal Inhibitory Dose for Acrivastine (22) in Relevance to the Effects Obtained for the Test Newly Synthesized Compounds [a, b]

M / Cpd	10^{-6}	10^{-5}	10^{-4}	10^{-3}	10^{-2}
15	33.3±0.33	75.5±0.57	81.9±0.57	90.0±0.57	100.0±0.57
16	6.6±0.33	26.0±0.33	54.2±0.57	66.0±0.33	88.0±0.33
17	5.0±0.57	10.0±0.33	28.9±0.57	55.5±0	77.8±0
18	0.0±0.00	22.2±0.33	55.5±0.57	75.0±0.57	95.1±0.33
19	25.0±0.33	45.0±0.57	64.3±0.33	75.5±0.57	100.0±0.57
20	17.2±0.33	18.0±0.57	20.7±0.33	25.0±0.57	29.1±0.57
21	20.0±0.33	44.4±0.57	66.0±0.33	80.0±0.57	100. 0±0.57
Acrivastine	16.6±0.57	27.0±0.33	55.0±0.57	100.0±0	100. 0±0

[a] Data are presented as molar concentrations (M) and are average of five replicates ± standard error of the mean.
[b] Histamine effect was produced using the histamine submaximal dose-agonist response.

3.2. Chemistry

The general synthetic strategy employed to obtain the target compounds is depicted in Scheme **1**.

It describes the synthesis of 5-substituted aminomethylenepyrimidine-2,4,6-triones (**15-21**) through amination of the key intermediate 5-ethoxymethylene-2,4,6-trione (**14**), obtained from the condensation of pyrimidine-2,4,6-trione (barbituric acid) (**12**) with triethyl orthoformate (**13**) [9].

The IR spectra for all compounds **15-21** displayed stretching absorption bands at the expected regions of NH, and C=O groups.

The ^{1}H-NMR spectra for compounds **15-21** lacked the triplet and quartet of the ethyl group present in the parent compound **14** [9], but exhibited signals corresponding to the existing CH_3, CH_2, methylene CH and / or regular CH groups as well as for the D_2O exchangeable proton of the NH functions.

The structures for all new compounds have been substantiated by elemental analyses, IR and by ^{1}H-NMR spectra. Both analytical and spectral data of all the compounds are in full agreement with the proposed structures. Moreover, comparison of the spectroscopic data of the new compounds with those of the previously reported analogs further confirmed the above structures.

3.3. Biological Screening

Investigation of the antihistaminic activity for representatives of the newly synthesized compounds has been assessed through the process of histamine-induced spasms in isolated segments of guinea pig ileum [17-19]. Acrivastine (**22**) has been utilized as reference drug.

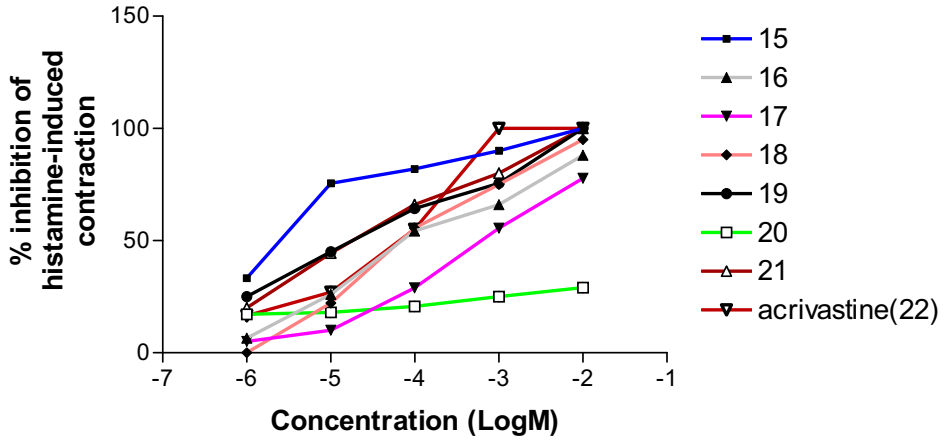


Fig. (7). The log dose-response curve of the tested newly synthesized pyrimidine -2,4,6-trions (**15-21**) in relevance to acrivastine (**22**).

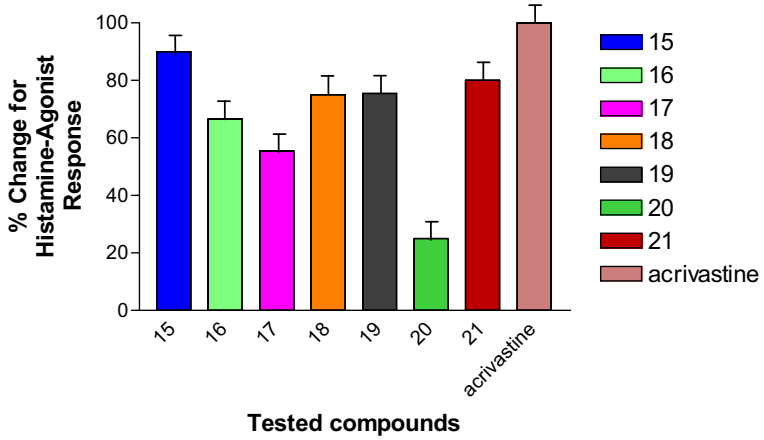


Fig. (8). Histogram illustrating the blocking effects of acrivastine and the test newly synthesized compounds; upon using the histamine – submaximal dose agonist - response.

Table 4. Comparison between the Maximum % Inhibition of Histamine Induced Contractions (I_{max}) for Acrivastine [a, b, c] and the Test Newly Synthesized Compounds; Together with Comparative Study for the Data of C log P[d] Computed Values

Cpd	I_{max} ± SEM	C log P[d]
Acrivastine	100.0±0	4.34
15	90.0±0.57	0.86
16	66.0±0.33	2.10
17	55.5±0	1.95
18	75.0±0.57	1.04
19	75.5±0.57	1.04
20	25.0±0.57	0.94
21	80.0±0.57	1.44

[a]doses used were the submaximal concentrations obtained from (Table **4**).
[b]data were presented as mean value of five replicates ± standard error of the mean(SEM).
[c]Histamine effect was produced using the histamine submaximal dose-agonist response.
[d]calculated log partition coefficient.

Compounds **15- 19**, and **21** showed promising activity among the newly synthesized compounds.

Different dose levels (10^{-6}-10^{-2} M) of acrivastine and the test new compounds were used for establishement of submaximal inhibitory doses (Table **3**) and for construction of log dose-response curves (Fig. **7**).

The maximum % inhibition of histamine induced contractions (I_{max}), for acrivastine and the new compounds were measured at the submaximal dose level of 10^{-3} M (Table **4**). The C log P values, for each, are also listed in (Table **4**); in order to validate the new assumption within the present investigation concerning the ability for crossing the blood brain barrier (BBB) [20]. The % change of histamine agonist responses for acrivastine and the test new compounds at the assigned submaximal dose levels are also represented as histogram (Fig. **8**).

All test new compounds displayed lower C log P values when compared with the reference drug acrivastine.

The applied *in vitro* investigation revealed decrement responses, for histaminergic (H_1) activity, at submaximal dose levels of 10^{-3} M, in the order of acrivastine **22**(100%) > **15** (90.0%) > **21** (80.0%) > **19** (75.5%) > **18** (75.0%) > **16** (66.0%) >**17** (55.5%) >**20** (25.0%) (Table **4**).

CONCLUSION

The aim of the present study was to synthesize and investigate the H_1-blocking activity of 5-substituted aminomethylenepyrimidine-2,4,6-triones with the hope of discovery new structural leads serving as anti-histaminics. MOE based molecular docking results showed that compounds **15-21** had better docking scores with H-bond scores comparable to or higher than acrivastine. Also, the obtained *in-vitro* testing results revealed that compounds **15, 18, 19,** and **21** exhibited moderate to considerable antihistaminic activity when using isolated segments from guinea pig ileum. In addition, their C log P values were lower than the reference drug. These facts would suggest that such compounds might be effective in blocking H_1 receptors with less liability to cross the BBB.

Consequently, 5-substituted aminomethylenepyrimidine-2,4,6-triones would represent a promising template for the design of new class of non-sedating H_1 antihistaminic agents.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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