Pharmacophore Modeling of N^1-alkyltheobromine as Histamine-H1 Receptor Antagonist

Maywan Hariono and Habibah A. Wahab

***Abstract*—Previous studies worked on the evaluation a few alkylxanthine derivatives synthesized from theobromine, exhibiting micromolar activities of the compounds against histamine *in vitro*. The structure-activity relationships study showed that the elongation of alkyl group at N^1 of xanthine ring increased the tracheospasmolytic activity. This result opened the opportunity for alkylxanthine to be developed as antihistamine. Presently, we elucidate the mechanism of N^1-alkylxanthine derivatives as antihistamine at a molecular level using pharmacophore modeling. The pharmacophore model was generated from a series of Histamine-H1 antagonists employing hydrogen bond acceptor (HBA), hydrogen bond donor (HBD) and two hydrophobic features and used as a search queries to map the N^1-alkylxanthine derivatives as Histamine-H1 antagonist. The results showed that all the designed ligands can adopt the pharmacophore features model providing the insight understanding about the opportunities of the N^1-alkylxanthine as Histamine-H1 antagonists.**

***Index Terms*—Histamine, N^1-alkylxanthine, pharmacophore, antagonist.**

I. Introduction

Asthma is a complex disease involving the concerted actions of multiple inflammatory and immune cells, spasmogens, inflammatory mediators, cytokines and growth factors [1], [2]. In individual who are susceptible, this inflammation can cause recurrent status of wheezing, breathlessness, chest tightness and coughing [3], [4]. World Health Organization estimated 300 million people worldwide suffer from asthma and 250 thousands death attributed to this disease. It was noted that 70% of asthma also had allergies [5], [6].

The first study of theophylline and theobromine derivatives as antihistamine was done by Pascal *et al*. (1985) showed that substitution with piperazine moiety at C4 of xanthine ring demonstrated a bronchorelaxant effect of tracheal bronchospasm induced by histamine in guinea pig [7]. Later on, some N^1-alkyltheobromine derivatives which showed tracheospasmolytic activities against histamine as the spasmogen had been synthesized [8]-[11]. The structure-activity relationships study showed that the elongation of alkyl group in the N^1 of xanthine ring increased the tracheospasmolytic activity.

Computer methodologies have become a crucial part of drug discovery projects from hit identification to lead optimization and approaches such as ligand- or structure based virtual screening techniques are widely used in many discovery efforts. A computational method in ligand-based drug design, pharmacophore modeling was developed to be an effective and rapid virtual screening which uses the architecture and physicochemical texture of the binding pocket to perform the virtual screening experiments [12]. One of the software which is widely used in Pharmacophore Modeling is catalyst, has been re-engineered for improvement of usability in Discovery Studio® [13].

In this present study, we elucidate the mechanism of N^1-alkylxanthine derivatives as an antihistamine at the molecular level using pharmacophore modeling. The designed ligands were then mapped into the pharmacophore model generated from a series of Histamine-H1 antagonists based on indole scaffold to support the insight understanding of N^1-alkyltheobromine mechanism as Histamine-H1 antagonist.

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II. Methods

A. Data Collection and Generation

The ligands set were collected from published papers [14]-[16] and then splitted into two different sets (training set and test set). The biological activities with the same methods on an isolated ileum of guinea pig were expressed in the negative logarithm of the concentration antagonist needed to shift the dose response curve by b-factor of 2 (pA2 (M)).

B. 3D-QSAR Pharmacophore Generation

The training set containing 14 ligands were used as an input ligand in the setting parameters. Three features including HBA, HBD and Hydrophobic were selected and then followed by setting all parameters using these values: Maximum Pharmacophores (10), Minimum Features (4), Maximum Features (5), Minimum Interfeature Distance (3), Maximum Excluded Volumes (0), Minimum Feature Points (4), Minimum Subset Points (4), Conformation Generation (BEST), Weight Variation (0.302), Variable Weight (False), Variable Tolerances (False), Scale Feature Blob Size (1.0), Explore Exhaustive HBond Geometry (True), Align Ligands to Hypothesis (True), Fischer Validation (90%) and Browse (False). The Hypogen model were generated and then statistically selected as described in Catalyst user guide in term of Fixed Cost, Null Cost, Total Cost and other statistical parameters (Discovery Studio) [17].

C. Model Validation

The test set containing 12 ligands were used as an input ligand in the setting parameters and the selected pharmacopore model was used as 3D-Query Search. The parameters in the ligand pharmacophore mapping protocol were set as follow: Best Mapping Only (True), Maximum Omitted Feature (1), Fitting Method (Flexible),

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Conformation Generation (BEST) and Parallel Processing (True) [18]. The valid model was defined when the ligands in the test set gave the FitValue after mapping them into the pharmacophore model.

D. Ligand Pharmacophore Mapping

This mapping procedure was employed using the same ligand pharmacophore mapping procedure as described in Model Validation (Sub Chapter C). The ligands used in this work are all ligands which previously synthesized by Ismail *et al* and Hariono *et al*. [8]-[11].

III. Results and Discussions

The predictive pharmacophores can be generated using the 3D Quantitative Structure-Activity Relationships (QSAR) Pharmacophore. In this work, Catalyst Hypogen algorithm [19] was utilised to construct the SAR hypothesis models (pharmacophores) from a set of ligands with known bioactivity values. This is different with a typical QSAR in which the descriptors are derived from the ligand alignments rather than molecular features. Therefore, the descriptors are concerned more into the whole structure than a single substituent [20]. The 3D QSAR Pharmacophore generates the models based on how fit the ligand mapped into the pharmacophore. The more or less active compound can be predicted by correlating that the better a ligands fits a pharmacophore, the more active it is predicted to be, and vice versa.

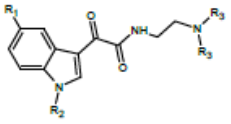
The parameter to measure how good the designed ligand fits to pharmacophore was named by FitValue which was calculated by using this following formula:

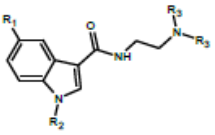
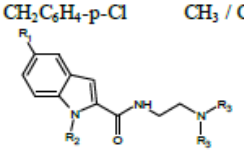
$$\text{Fit} = \sum \text{mapped hypothesis features } x\ W\left[-\sum\left(\frac{\text{disp}}{\text{tol}}\right)^2\right] \quad (1)$$

where ∑mapped hypothesis features represents the number of pharmacophore features that successfully map onto the corresponding chemical moieties within the fitted compound. W is the weight of corresponding hypothesis feature spheres. This value is fixed to 1.0 in catalyst-generated models. Disp is the distance betwen the center of particular pharmacophore sphere and the center of the corresponding overlapped chemical moiety of the fitted compound. tol is the radius of the pharmacophoric feature sphere (stand for tolerance, equal to 1.6 Å by default). $\sum(\text{disp/tol})^2$ is the sum of $(\text{disp/tol})^2$ values for entire pharmacophoric features that successfully map onto the corresponding chemical functionalities in the fitted compound [21].

In the training set, the hydrogen bond acceptor was represented by carbonyl group and tertiary amine while the hydrogen bond donor was represented by the amine moieties. Furthermore, the hydrophobic features were represented by benzyl group, halogen, dimethyl, ethylene as well as the modified alkyl group at terminal nitrogen. As well studied, the classical H_1-antagonists follows the basic structure consisting of a basic nitrogen atom, predominantly protonated at physiological pH, and two aromatic groups connected via linking group, which can be different chemical natures [22]. Although the indole ring used as the scaffold in this training considered as a non-classical H_1-antagonists but it presents elements of the general structure. Table I listed down the indole derivatives used as the training set in this pharmacophore model generation.

TABLE I: The Indole Derivatives Used as the Training Set



Compound	R_1	R_2	R_3-N-R_3	pA_2
12	H	$CH_2C_6H_5$	CH_3 / CH_3	6.01 ± 0.25
				
32	H	$CH_2C_6H_5$	CH_3 / CH_3	7.03 ± 0.22
33	H	$CH_2C_6H_5$	piperidine	8.23 ± 0.34
34	H	$CH_2C_6H_5$	N-methyl piperazine	6.36 ± 0.21
36	Cl	$CH_2C_6H_5$	CH_3 / CH_3	6.23 ± 0.53
38	H	$CH_2C_6H_4$-p-F	CH_3 / CH_3	7.05 ± 0.13
39	H	$CH_2C_6H_4$-p-F	piperidine	8.00 ± 0.27
40	H	$CH_2C_6H_4$-p-F	CH_3 / CH_3	7.75 ± 0.37
41	H	$CH_2C_6H_4$-p-Cl	piperidine	7.13 ± 0.20
42	Cl	$CH_2C_6H_4$-p-Cl	CH_3 / CH_3	5.94 ± 0.21
				
51	Cl	H	piperidine	6.53 ± 0.22
52	Cl	H	pyrollidine	5.90 ± 0.33
54	H	$CH_2C_6H_5$	piperidine	6.42 ± 0.28
55	Cl	$CH_2C_6H_5$	CH_3 / CH_3	6.50 ± 0.31
56	Cl	$CH_2C_6H_5$	piperidine	6.50 ± 0.31

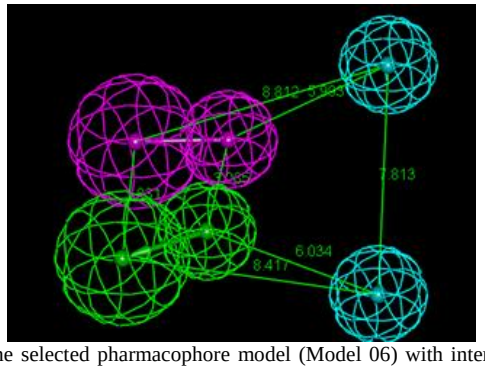


Fig. 1. The selected pharmacophore model (Model 06) with inter-features distance as stated in Angstrom unit. The green spheres represent HBA feature, the magenta spheres are HBD feature while the blue spheres represent hydrophobic features.

Nine pharmacophore models were generated employing one HBA, one HBD and two hydrophobics feature (see Fig. 1). The model definitions such as weight, tolerance and coordinate values were detail listed down in Table I. The models were selected to approach the ideal statistical criteria such as the lowest total cost, the highest difference between the total cost and null cost ($), the lowest RMSD and the highest correlation (see Table II). Among those nine hypothesis model, Model 06 was found having criterion in such a way that will be able to predict the bioactivity of unknown ligand. The pharmacophoric features was separated

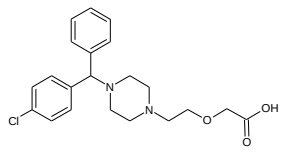
by its distance as seen in Fig. 1.

TABLE II: THE STATISTICAL VALUES OF HYPOGEN MODELS OF HISTAMINE-H1 RECEPTOR ANTAGONISTS

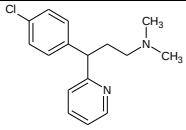
Model	Total Cost	Cost Difference $	RMSD	Correlation	Features
2	53.2494	6.0854	0.24604	0.0550	ADHH
3	56.3972	9.2332	0.55335	0.0667	ADHH
4	58.0064	10.8424	0.59332	0.2628	ADHH
5	60.2294	13.0654	0.62202	0.2021	ADHH
6	60.4581	13.2941	0.61368	0.3747	ADHH
7	60.5695	13.4055	0.62255	0.2132	ADHH
8	61.1849	14.0209	0.61407	0.3749	ADHH
9	61.6687	14.5047	0.62243	0.2039	ADHH
10	61.7368	14.5728	0.61307	0.3667	ADHH

RMSD = Root Mean Square Difference; *A* = Hydrogen Bond Acceptor; *D* = Hydrogen Bond Donor; *H* = Hydrophobic

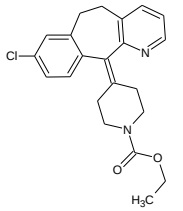
TABLE III: THE TEST SET CHEMICAL STRUCTURES



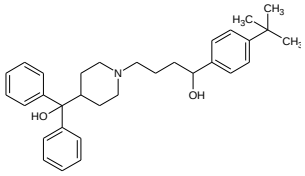
Cetirizine (pA_2 7.96 M)



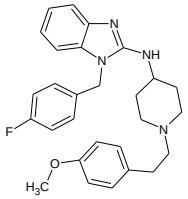
Chlorpheniramine (pA_2 9.38 M)



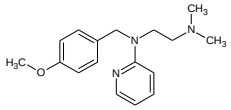
Loratadine (pA_2 7.63 M)



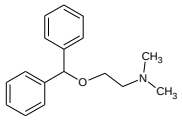
Terfenadine (pA_2 9.06 M)



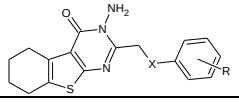
Astemizole (pA_2 8.61 M)



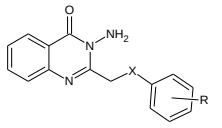
Mepyramine (pA_2 9.50 M)



Diphenhydramine (pA_2 7.61 M)



Compound	R	X	pA_2 (M)
10c	-3-CH_3	-O-	7.94
10e	-3-CH_3 -4-Cl	-O-	8.17
10g	H	$NHSO_2$	8.73



10r	-3-CH_3	-O-	8.26
10t	-4-Cl	-O-	8.63

This selected model has 1.04295 in a weight and 4.58496 in configuration for all features. The weight means a value that increases in a Gaussian form as the feature weight deviates from an ideal value (2.0), thus it deviates about 0.95705 points from its ideal value. Although it is not the nearest value to the ideal one, but it still makes a sense to be appointed as a relative good model. The configuration component is a constant cost, which depends on the complexity of the hypothesis space being optimized. In standard HypoGen mode, the configuration should not be greater than 17.00 [23], thus, the configuration value of this model is well considered.

The validation of the hypothesis model was carried out by mapping the active ligands in test set (see Table III) into the selected pharmacophore model. In the test set, several commercial antihistamines H1 such as cetirizine, loratadine, terfenadine, mepyramine and chlorpheniramine were included and the results showed that 11 of 12 H1 antagonists were successfully mapped into the corresponding pharmacophore model (see Table IV).

In Shishoo's compounds, most of methoxy groups fit into the HBA feature whereas the amine group fits into the HBD feature. On the other hands, the hydrophobic features were commonly fitted by halogen, methyl and benzyl group. The same patterns were also shown by some commercial antihistamine H1 reflecting that the tested ligand possessed its activity as H_1-Antagonist as predicted having pharmacophoric features similar to that of training set. The top eight mapped ligands of the test set can be seen at Fig. 2. As we can see in Table V-Table VII, the series of xanthine derivatives were able to fit to the pharmacophore model. This is not surprising since the xanthine is quite similar with the indole scaffold, however, the most important thing is the spatial arrangement of functional group modification in xanthine derivatives dealt with the pharmacophore features predicted as the active site. Theophylline was considerably having a lower FitValue than theobromine pharmacophore pose gaining more preference to utilize theobromine as the lead compound in further structural modification.

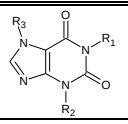
TABLE IV: THE FITVALUE OF TEST SET

No	Compound	FitValue
1	Shishoo_10e	3.98854
2	Shishoo_10g	3.89869
3	Shishoo_10c	3.81446
4	Christophe_terfenadine	3.51648
5	Shishoo_10t	3.4682
6	Shishoo_10r	3.35904
7	Christophe_cetirizine	3.12554
8	Battaglia_astemizole	3.12179
9	Christophe_loratadine	3.05615
10	Battaglia_mepyramine	0.77003
11	Christophe_chlorpheniramine	0.742774

In the pharmacophore pose (see Fig. 3), theophylline and theobromine accommodated the HBD feature at the NH of imidazole ring. In this particular functional group, the nitrogen was predicted donating proton to the essential amino acid residue at the pocket side which acted as the HBA. Meanwhile, on one hand, this pharmacopore feature was accommodated by N^9 of N^1-*n*-propyl, isopropyl and

sec-buyltheobromine while on the other hand, no HBD feature could be accommodated by N^1-*n*-butyltheobromine. Next, the HBA features were only fitted by carbonyl oxygen group which could be at C^2 or C^9 of N^1-*n*-propyl, *n*-butyl and *sec*-buyltheobromine. Here, in contrast with N^9 and NH imidazole, the carbonyl oxygen accepted proton from the corresponding amino acid residue at the active pocket of the receptor. The two hydrophobic features were solely accommodated by all N^1-alkyltheobromine derivatives providing van der waals interaction with the hydrophobic amino acid residues (see Fig. 4).

TABLE V: THE FITVALUE OF N^{1-}ALKYKXANTHINE DERIVATIVES MAPPED INTO PHARMACOPOHORE MODEL



Compound	R_1	R_2	R_3	FitValue
Theophylline	CH_3	CH_3	*H*	1.9313
Theobromine	H	CH_3	CH_3	2.3333
N^1-*n*-propyltheobromine	H_3C-CH_2-CH_2	CH_3	CH_3	2.5687
N^1-*n*-butyltheobromine	H_3C-$(CH_2)_2$-CH_2	CH_3	CH_3	2.8442
N^1-isopropyltheobromine	$(H_3C)_2$-CH	CH_3	CH_3	1.7017
N^1-sec-butyltheobromine	$(H_3C)_2$-CH-CH_2	CH_3	CH_3	2.6030

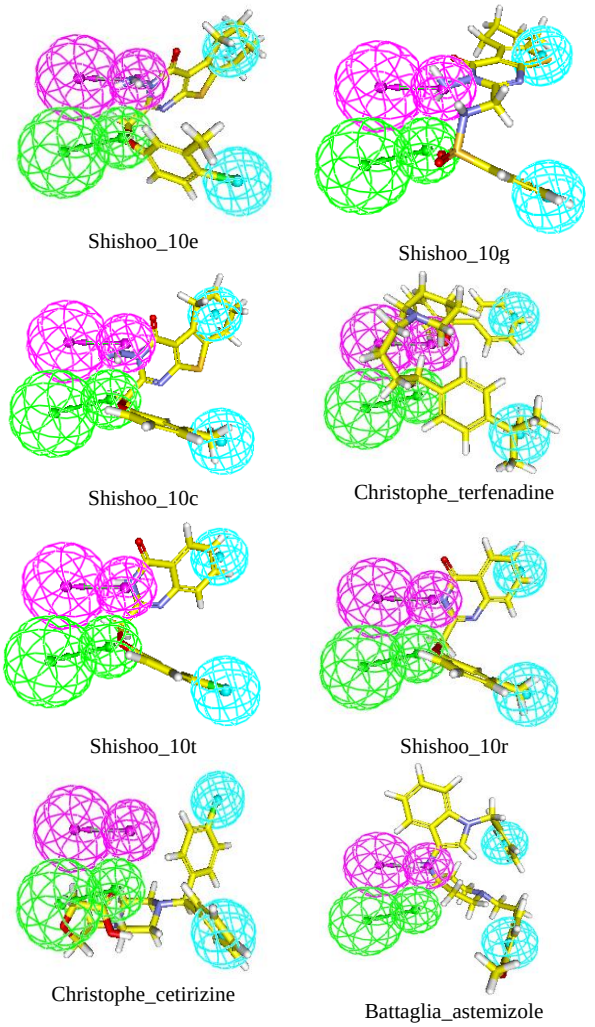


Fig. 2. The top eight mapped ligands of the set set.

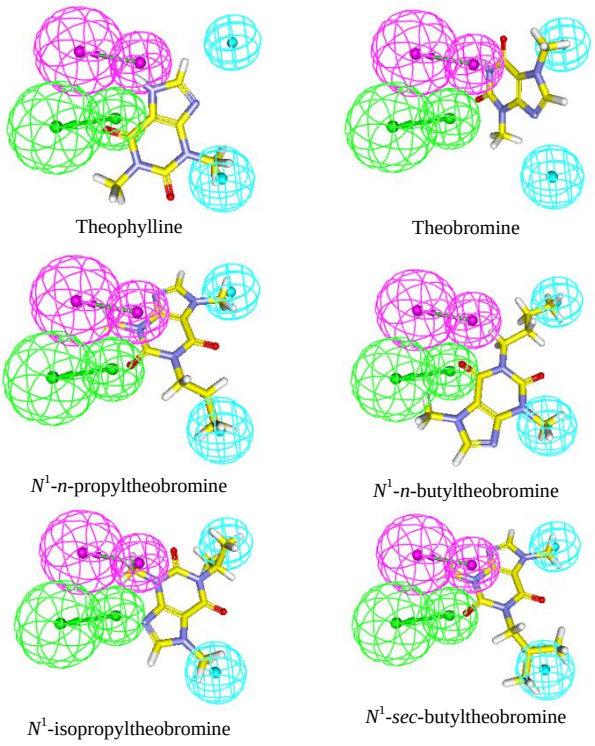


Fig. 3. The alkylxanthine derivatives mapped ligand.

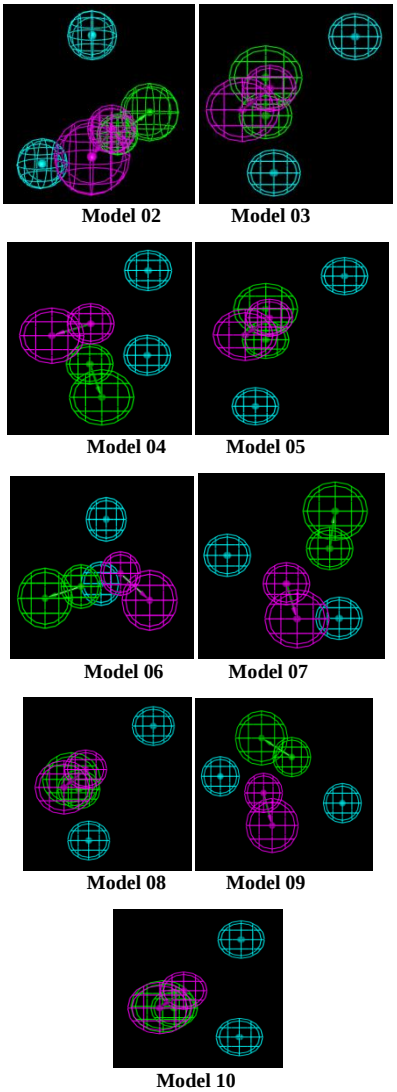


Fig. 4. The ninth Hypogen model of Histamine-H1 receptor antagonist generated form indole derivatives by Catalyst embedded in Discovery Studio Client 2.5.

TABLE VI: THE EXPERIMENTAL EC_{50} OF N^1-ALKYKXANTHINE DERIVATIVES

No	Compound	EC_{50}
1	Theophylline	112. μM
2	Theobromine	n. a.
3	N^1-*n*-propyltheobromine	58 μM
4	N^1-*n*-butyltheobromine	19 μM
5	N^1-isopropyltheobromine	65 mM
6	N^1-sec-butyltheobromine	7 μM

EC_{50} = 50% of Effective Concentration

TABLE VII: THE PROPERTIES OF HYPOGEN MODELS OF HISTAMINE-H1 RECEPTOR ANTAGONIST

Model	Definitic		Chemical features					
			HBD		HBA		Hydro phobic	Hydro phobic
02	W		1.99		1.99		1.99	1.99
	T		1.60	2.20	1.60	2.20	1.60	1.60
	C	X	-0.37	2.12	-0.28	-0.52	-4.02	-0.94
		Y	2.21	3.84	1.49	-0.71	-1.22	7.16
		Z	-1.65	-1.30	1.81	3.83	2.38	4.74
03	W		1.48509		1.48509		1.48509	1.48509
	T		1.60	2.20	1.60	2.20	1.60	1.60
	C	X	-0.75	-1.96	-1.84	-3.27	-0.24	1.76
		Y	0.82	3.55	2.06	0.89	-3.10	7.08
		Z	-2.17	-2.61	1.29	3.65	-0.04	2.46
04	W		1.29281		1.29281		1.29281	1.29281
	T		1.60	2.20	1.60	2.20	1.60	1.60
	C	X	-0.27	2.53	-0.80	-3.47	-4.51	2.10
		Y	-1.23	-0.25	1.03	1.67	-4.73	6.30
		Z	2.64	2.20	0.02	-1.19	4.27	2.16
05	W		1.07206		1.07206		1.07206	1.07206
	T		1.60	2.20	1.60	2.20	1.60	1.60
	C	X	0.37	2.99	0.53	-0.53	-2.42	-0.94
		Y	1.49	2.96	2.21	0.18	-3.46	7.96
		Z	-1.07	-1.08	2.65	4.59	0.12	2.14
06	W		1.04295		1.04295		1.04295	1.04295
	T		1.60	2.20	1.60	2.20	1.60	1.60
	C	X	-3.54	-5.78	-1.99	-4.56	1.23	2.45
		Y	0.43	-0.84	2.72	2.52	-1.78	5.75
		Z	0.97	2.58	2.36	3.96	-1.99	-0.29
07	W		1.03965		1.03965		1.03965	1.03965
	T		1.60	2.20	1.60	2.20	1.60	1.60
	C	X	-2.36	-5.06	0.66	2.55	0.21	-0.40
		Y	0.79	1.44	2.21	-0.14	-0.03	6.06
		Z	-1.36	-2.48	1.01	1.03	-6.94	4.58
08	W		0.97632		0.97632		0.97632	0.97632
	T		1.60	2.20	1.60	2.20	1.60	1.60
	C	X	-1.36	-0.98	-4.31	-3.58	-0.72	-8.34
		Y	0.95	3.77	-1.70	-4.34	-4.30	0.44
		Z	0.10	1.06	-0.36	0.88	-1.63	-4.80
09	W		0.94030		0.94030		0.94030	0.94030
	T		1.60	2.20	1.60	2.20	1.60	1.60
	C	X	0.64	0.51	-1.09	-1.75	3.69	-0.10
		Y	1.10	2.34	1.86	-0.82	-2.00	7.14
		Z	-2.19	-4.92	1.47	2.70	-0.18	3.38
10	W		0.92755		0.92755		0.92755	0.92755
	T		1.60	2.20	1.60	2.20	1.60	1.60
	C	X	-1.03	-1.12	-1.84	-3.27	3.18	1.76
		Y	0.46	1.24	2.06	0.89	-1.53	7.08
		Z	-1.67	-4.56	1.29	3.65	-1.33	2.46

Among those xanthine ligands, N^1-*n*-butyltheobromine and N^1-*sec*-butyltheobromine which are predicted as two most active ligands, succesfully demonstrating an agreement in both *in silico* as well as *in vitro* experiments. The FitValue of N^1-*n*-butyltheobromine (2.8442) was slightly higher than N^1-*sec*-butyltheobromine (2.6030), respectively predicting that the normal alkyl have a higher chance to fit the active pocket of the Histamine-H1 receptor rather than the more steric one. In contrast, the experimental EC_{50} of N^1-*sec*-butyltheobromine is lower than of N^1-*n*-butyltheobromine defining that the more steric alkyltheobromine is more potent than the normal one. However, instead of this inverse result, both compounds have high chances to be optimized as the lead compounds in designing Histamine-H1 antagonists (see Table VII).

IV. CONCLUSION

Four number of N^1-alkylxanthine derivatives with theobromine as the major scaffold had been mapped into the pharmacophore model generated from the series of histamine-H1 antagonist bearing indole scaffold. The N^1-alkylation of theobromine had proven to increase the FitValue of corresponding ligands from the parent compounds i.e. theophylline and theobromine. The longer alkylation of terminal N^1-alkyltheobromine provided an extra hydrophobic characters that might contribute to Histamine-H1 receptor upon agonist recognition. It is worth to pursue the research in design and synthesis for more N^1-alkylxanthine derivatives to be the next generation of H1-antihistaminic agent.

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