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Investigation of Antisecretory activities of Imidazo[1,2,a]pyridinylethylbenzoxazoles with the Electron Topological Method (ETM)

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Abstract

Relationship structure-antisecretory of a series of Imidazo[1,2,a]pyridinylethyl benzoxazole derivatives which is known to be either active-inactive or their activity which is known quantitatively are investigated theoretically with Electron Topological Method (ETM). This technique can identify active fragment, related activity, belongs to the series of compounds and can quantitatively give the values of some compounds whose secretion activities cannot be measured experimentally. For 47 compounds, conformational analysis and quantum chemical calculations were done, and unit matrix representing electronic character was calculated, and active fragment in the active compounds were extracted.

Introduction

Investigation of the antisecretory and antiulcer mechanism of new compounds previously reported to inhibit gastric acid secretion to prevent gastric ulcerations induced by indomethacin or ethanol has been given in an intense research effort[(1-5)]. Barocelli and co-workers tested the new compound on the acid hypersecretion induced

by histamine *in vivo* and *in vitro* experimental models. Furthermore, its influence on the mucosal layer adhering the gastric wall in indomethacin-treated rats was considered. Ranitidine was selected as a reference drug[6]. In order to study structure-activity relationship of dual histamine H2 and gastrin receptor antagonists as well as to improve their low oral absorbability, their prototype benzodiazepine gastrin receptor antagonistic moieties were altered to a conformationally flexible noncyclic dipeptite equivalent [7]. Gastric acid is of central importance in the pathogenesis of duodenal ulcer, gastric ulcer, and gastroesophageal reflux disease. Pharmacological reduction of acid secretion is, therefore, the mainstay of current treatment, but the optimal degree of acid suppression remains incompletely understood[8]. This paper consider the ideal ways relating from experimental antisecretory data belongs to imidazo[1,2,a]pyridinylethylbenzoxazoles' derivatives to theoretical Electron Topological Method (ETM) [9,10]. This technique can identify active fragment, related activity, belongs to the series of compounds and can quantitatively give the values of some compounds whose secretion activities cannot be measured experimentally.

Methodology

The set of compounds investigated is a series of compounds tested on antagonist activity known to be either active-inactive or their activity which is known quantitatively. For each molecule its geometric and electronic properties are determined and arranged as a set of m matrices of the order n, where n is the number of atoms in the molecule, and m is the number of different electronic characteristic, which may be applied for the same atom (m is fixed for all compounds within the given series). So, we have multidimensional matrices called electron-topological matrices of conjunction (ETMC), which may be viewed as weighted graphs with a few values prescribed to every vertex edge, and serve as a language for the description of the molecular structure and properties of chemical substance.

As a rule, all diagonal elements, a_{ii}, correspond to the calculated charge[11] on atoms, and non-diagonal elements a_{ij}, to Wiberg's indices[12] (bond strength) between the bonded atoms and the distance between non-bonding atoms. When forming an order

n*n ETMC, one may choose m (1,2,3...) representing the values for diagonal and non-diagonal elements among different layers of the multidimensional matrix. Science ETMC is a symmetric matrix; only its upper triangle is stored in the memory of the computer for the computational process.

The following main classes of calculations present the computational part of the method:

(1) Conformational analyses[13] (using Molecular Mechanics-MMFF)

(2) Quantum-chemical calculation[11] (using Semi-Empirical-AM1)

(3) ETMC formation;

(4) ETMC processing and activity features selection.

The firs two steps are traditional enough[10] ; others reflect particularities of the ETM-method. The last two steps are unified in a single cyclic process. Two sets of logical conditions are governed this process. Firstly, after appropriate layer of multidimensional matrix elements have been chosen, the ordinary matrices for all compounds have been formed. Secondly, the initial (examined) conditions are given values representing the limits deviation admitted for varying matrix elements (diagonal and non-diagonal). One of the compounds (usually, the most active one) is taken as the template compound for comparison with the rest of compounds. If the initial deviation, d1 for diagonal and d2 for non-diagonal, are chosen to appropriate, the best statistical results can be obtained.

When the comparison process is completed, some fragments common for the active compounds are found as the sub matrices of the template matrix. The resulting conditions representing the probabilities of encountering these fragments in the classes of active and inactive compounds are evaluated. If defined fragments belong to the active compounds only and are not found in the inactive ones, then they are considered as features of activity, i.e., as the fragments responsible for this kind of activity.

If the results of the final conditions elevated are not satisfactory, then the cyclic process may be repeated with one of the following changes;

1. Matrix elements may be given in another way (i.e. E_{bond} can be used instead of bond length)
2. Template compound may be changed with another one (i.e. an other active compound can be used as a template compound)
3. Changing of deviation values of the d1 and d2 for the limits entering into initial condition (d1 and d2 values can be changed from 0.05 Å up to 0.25 Å)

The same procedure may be repeated until satisfactory fragments are found with the template compound, then the fragment which is responsible from the activity will be used in the following steps of the process. Once the activity is known quantitatively, electron topological contiguity matrices (ETC) should be compared within each group of molecules, which have the some value of activity. After obtaining the appropriate fragments to the training set of compounds, they form a part of a system predicting activity for any other series of compounds. Two parameters, α_a and β_a (see below) showing the probabilities of the feature realization are used for this purpose. As an example, ETC for relatively small compound N49 is given in Fig.1. It is formed of effective charges on atoms (Q_{ii}), the Wiberg's indices (W_{ij}) and optimized distances between atoms in the molecule (D_{ij}) (H-atoms are not given here for short). The electronic characteristics are given in electron charge units (e), the distances are given in Å.

C1 C2 C3 C4 C5 O1 C6 C7 C8 C9 C10 C11 C12 N1 O2 C13 C14 N2 C15 C16 C17 C18 C19 C20 N3 C21 C22 N4

-0.165 1.432 2.429 2.797 1.373 2.380 4.145 4.556 3.730 6.024 6.820 8.258 11.00 9.016 9.017 10.35 10.37 11.40 12.55 12.37 2.500 13.71 13.68 15.00 15.90 15.38 16.69 15.66

-0.061 1.371 2.424 2.442 2.798 3.738 4.565 4.165 6.030 6.668 8.133 10.89 8.766 9.035 10.35 10.15 11.50 12.58 12.29 1.480 13.81 13.84 15.07 16.03 15.36 16.71 15.51

-0.095 1.433 2.828 2.468 2.546 3.614 3.617 5.006 5.546 6.994 9.736 7.542 7.990 9.281 8.930 10.48 11.50 11.14 2.490 12.76 12.85 14.00 14.99 14.22 15.58 14.30

-0.005 2.445 1.437 1.365 2.198 2.270 3.629 4.303 5.743 8.488 6.364 6.704 7.995 7.746 9.183 10.21 9.889 3.800 11.46 11.54 12.70 13.68 12.95 14.29 13.11

-0.046 1.375 3.593 3.607 2.532 5.007 5.914 7.290 9.976 8.115 7.963 9.278 9.438 10.28 11.44 11.31 3.772 12.57 12.52 13.86 14.74 14.28 15.55 14.64

-0.060 2.302 2.244 1.391 3.678 4.588 5.970 8.671 6.754 6.729 8.034 8.088 9.111 10.21 10.02 4.277 11.39 11.40 12.66 13.58 13.02 14.32 13.34

-0.145 1.391 2.315 2.539 3.105 4.501 7.212 5.030 5.576 6.815 6.416 8.065 9.016 8.621 5.030 10.30 10.45 11.50 12.52 11.69 13.04 11.81

-0.074 1.418 1.480 2.485 3.800 6.479 4.512 4.717 5.964 5.845 7.146 8.147 7.854 5.985 9.391 9.498 10.61 11.59 10.88 12.19 11.15

-0.202 2.568 3.639 4.889 7.492 5.732 5.562 6.827 7.002 7.871 8.966 8.812 5.645 10.12 10.13 11.38 12.29 11.76 13.03 12.16

-0.082 1.520 2.483 5.041 3.170 3.450 4.597 4.443 5.820 6.739 6.403 7.429 8.004 8.174 9.194 10.20 9.420 10.72 9.727

-0.122 1.489 4.291 2.501 2.500 3.742 3.802 4.992 5.961 5.679 7.985 7.235 7.387 8.462 9.465 8.742 10.13 8.876

-0.059 2.802 1.406 1.401 2.366 2.455 3.710 4.536 4.190 9.452 5.849 6.098 7.028 8.071 7.257 8.657 7.408

-0.062 2.388 2.486 1.436 1.396 2.296 2.187 1.412 12.21 3.558 4.151 4.484 5.644 4.492 5.894 4.686

-0.135 2.442 2.737 1.393 4.116 4.510 3.763 10.03 5.887 6.352 6.872 8.022 6.803 8.162 6.862

-0.106 1.383 2.876 2.499 3.594 3.646 10.38 4.790 4.888 6.079 7.016 6.555 7.961 6.814

-0.017 2.438 1.396 2.233 2.321 11.70 3.495 3.744 4.731 5.724 5.172 6.583 5.474
-0.079 3.604 3.567 2.567 11.41 4.922 5.547 5.738 6.938 5.508 6.843 5.558
-0.153 1.444 2.338 12.86 2.348 2.398 3.712 4.549 4.492 5.853 4.942
0.180 1.344 13.93 1.378 2.019 2.501 3.549 3.068 4.467 3.574
-0.177 13.62 2.501 3.315 3.172 4.381 3.080 4.499 3.375
-0.179 15.17 15.21 16.43 17.39 16.69 18.06 16.77
-0.311 1.002 1.403 2.230 2.557 3.766 3.275
0.262 2.059 2.386 3.440 4.498 4.129
0.328 1.242 1.517 2.472 2.474
-0.331 2.429 2.772 3.271
-0.108 1.517 1.515
-0.210 2.494
-0.207

Figure 1. ETC for N-49 molecule

Result and discussion

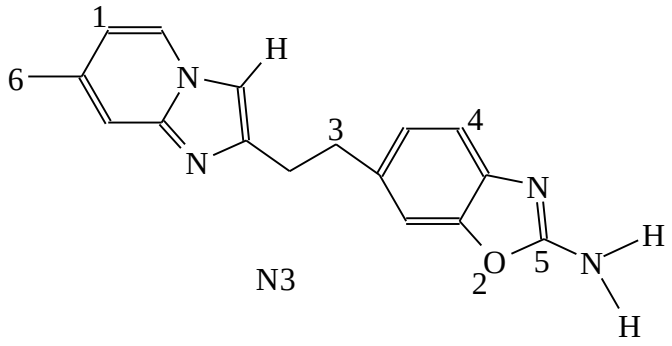


Fig.2. Reference molecule and active atoms within the structure

Table 1.ETC values of reference active fragment

1	2	3	4	5	6
-0.0120	11.3390	6.6230	10.0210	12.3260	2.4700
	-0.2410	4.9170	3.4690	1.0470	13.2910
		0.0300	3.7340	5.8060	7.76400
			-0.0120	3.4140	11.4440
				0.3340	13.2910
					-0.0100

Series of molecules including ETC or not as pointing out (+) and (-) respectively are given in Table 2.

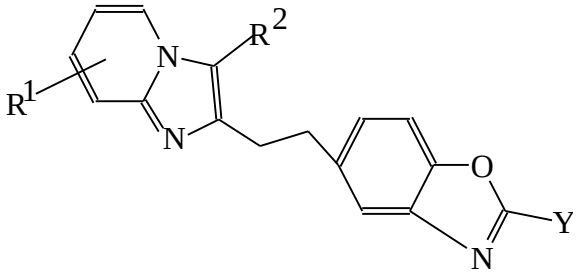


Table 2. The values of antisecretory activity (AA), dummy parameter (Io) and active-fragment (AF), for investigated compounds.

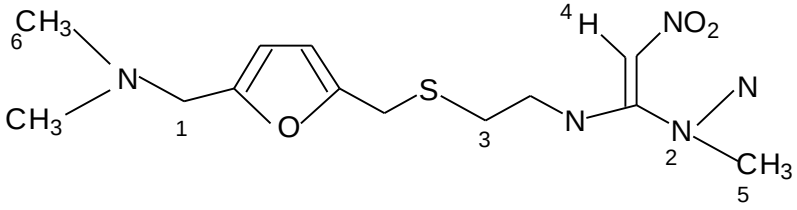
No	No	R^1	R^2	Y	AA	Io	AF
N1	N1	H	CH_3	NH_2	0	0	-
N2	N2	6- CH_3	CH_3	NH_2	0	0	-
N3	N3	7- CH_3	H	NH_2	73	1	+
N4	N4	7- CH_3	CH_3	NH_2	65	1	+
N5	N5	7- CH_3	Cl	NH_2	88	1	+
N8	N6	7-C_2H_5	CH_3	NH_2	27	0	-
N9	N7	7-OH	CH_3	NH_2	91	1	-
N10	N8	7-OCH_3	H	NH_2	67	0	+
N11	N9	7-OCH_3	CH_3	NH_2	59	1	-
N12	N10	7-OCH_3	Cl	NH_2	0	0	-
N13	N11	7-OC_2H_5	CH_3	NH_2	59	1	-
N14	N12	7-$OCOCH_3$	CH_3	NH_2	25	0	-
N16	N13	7-CH_2OCH3	CH_3	NH_2	0	0	-
N17	N14	7-NH_2	CH_3	NH_2	70	1	+
N22	N15	8-CH_3	CH_3	NH_2	67	1	-
N23	N16	8-OH	CH_3	NH_2	0	0	-
N25	N17	8-NH_2	CH_3	NH_2	0	0	-
N27	N18	7-CH_3	CH_3	$NHCH_3$	48	1	+

N28	N19	7-OCH_3	CH_3	$NHCH_3$	0	0	-
N29	N20	H	CH_3	NHC_2H_5	15	0	-
N30	N21	7-CH_3	H	NHC_2H_5	67	1	+
N31	N22	7-CH_3	CH_3	NHC_2H_5	59	1	+
N32	N23	7-CH_3	Br	NHC_2H_5	0	0	-
N33	N24	7-OCH_3	CH_3	NHC_2H_5	35	0	-
N34	N25	7-CH_3	CH_3	NH-iso-C_3H_7	45	1	+
N35	N26	7-OCH_3	CH_3	NH-iso-C_3H_7	23	0	-
N36	N27	7-CH_3	CH_3	$NHCH_2CH=CH_2$	62	1	+
N37	N28	7-OCH_3	CH_3	$NHCH_2CH=CH_2$	41	0	-
N38	N29	7-CH_3	H	$NHCOCH_3$	53	1	+
N39	N30	7-CH_3	CH_3	$NHCOCH_3$	57	1	+
N40	N31	7-CH_3	Cl	$NHCOCH_3$	28	0	-
N43	N32	7-OCH_3	H	$NHCOCH_3$	57	1	-
N44	N33	7-OCH_3	CH_3	$NHCOCH_3$	44	1	-
N45	N34	7-$OCOCH_3$	CH_3	$NHCOCH_3$	0	0	-
N46	N35	8-CH_3	CH_3	$NHCOCH_3$	22	0	-
N47	N36	7-CH_3	H	$NHCOC_2H_5$	68	1	+
N48	N37	7-CH_3	H	NHCO-n-C_3H_7	41	0	+
N49	N38	7-CH_3	H	NHCO-iso-C_3H_7	82	1	+
N50	N39	7-CH_3	H	NHCO-tert-C_4H_9	58	1	-
N51	N40	7-OCH_3	H	NHCO-tert-C_4H_9	40	0	-
N52	N41	7-CH_3	H	$NHCOCH(C_2H_5)_2$	14	0	-
N53	N42	7-OCH_3	H	NH-L-$COCH(CH_3)$-$OCOCH_3$	65	1	-
N55	N43	7-CH_3	H	NHCO-cyclo-C_6H_{11}	0	0	+
N57	N44	7-CH_3	H	$N=CH-N(CH_3)_2$	56	1	+
N60	N45	7-CH_3	CH_3	C_2H_5	0	0	-
N68	N46	Cimetidin			53	1	-
N69	N47	Ranitidine			72	1	+

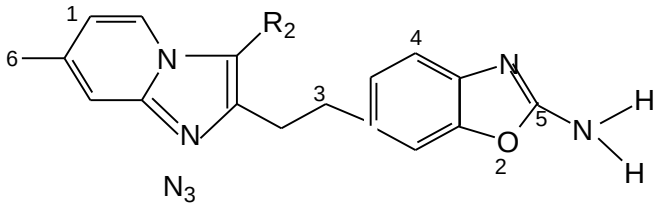
As an antisecretory activity inhibition % of the 6-[2-(Imidazo[1,2-a]pyridin-2-yl) benzoxazoles can be divided into two classes which are active and inactive compounds. The active compounds (23 molecules bigger than 44% inhibition) and inactive ones (24 smaller than it) were shown to be Io (dummy parameter) = 1 and 0, respectively, in Table 1. Number of active compounds and inactive compounds are selected to be equal, approximately each other for statistically accurate. Compounds possessing weak antagonist activity were inactive and strong ones active. Cimitidine, ranitidine, N3 and N38, which are structurally different compounds as skeleton are held independently as a control compound, either rather active or ones used as a drug. These matrixes reduced to a common matrix for template. After the process was done; in the last two steps, a better electron topological contiguity matrix (ETC) which represents the considered molecules was formed. ETC's electronic and geometric characteristics, which were charge and distance, belong to the active compounds were found. To get a better ETC, it was necessary to extract the biggest n1 and the smallest n3. If so, αa and Pa were to be maximum values and received as the best statistical* parameters.

In the calculation of αa and Pa it was taken d1 (Diagonal deviation), d2 (Non-diagonal deviation) being ± 0.06 and ± 0.01, respectively. The extracted ETC having C, O, H atoms of 6*6 diagonal matrix was shown in Fig.1.

*Pa=(n1+1)/(n1+n3+1); αa = (n1*n4-n2*n3)/m1*m2*m3*m4)/2, where n1 and n2 are the numbers of molecules possessing and not possessing the features of activity (predicted by ET) in class of inactive compounds, respectively; n3 and n4 have the analogous meaning for the class of inactive compounds; m1 and m2 are the numbers of molecules in the classes of active and inactive compound, (m1/m2 = 23/24) respectively; m3=m1+m3; m4 = n2 + n2 (n1/n3 = 15/3), αa = 80, Pa = 0.64.



Ranitidine



Cimetidine

Both the basic series of 6-[2-(Imidazol[1,2-a]pyridin-2-yl) benzoxazoles and ranitidine and cimitidine contain ETC however they have different molecular skeleton. For example, ETC is signed on N3 and ranitidine, one across to other, as following with (1-6).

The effects of substutients, as defined R1, R2 and Y, on the activity are given. The basic skeleton and two of three substituents are same and other substituent is different as it can be seen in Tables 2.,3, and 4. Each active molecule is compared within other inactive ones in the same colon.

When R' in the 7-position is CH_3 donating electron as inductively, the activity of molecule is increased or in R', if there are OCH_3 acceptor electron, the activity decreased (Table 2). Comparison of the molecules number and their activity is given in Table 2.This increase is due to the hydrofobisty of O in the OCH_3 group which inturn provides hydrofobisty and in this way it increases the activity.

Table 2. The effect of R' on the activity.

CH_3	N3	N4	N5	N27	N36	N38	N39
OCH_3	N10	N11	N12	N28	N37	N43	N44

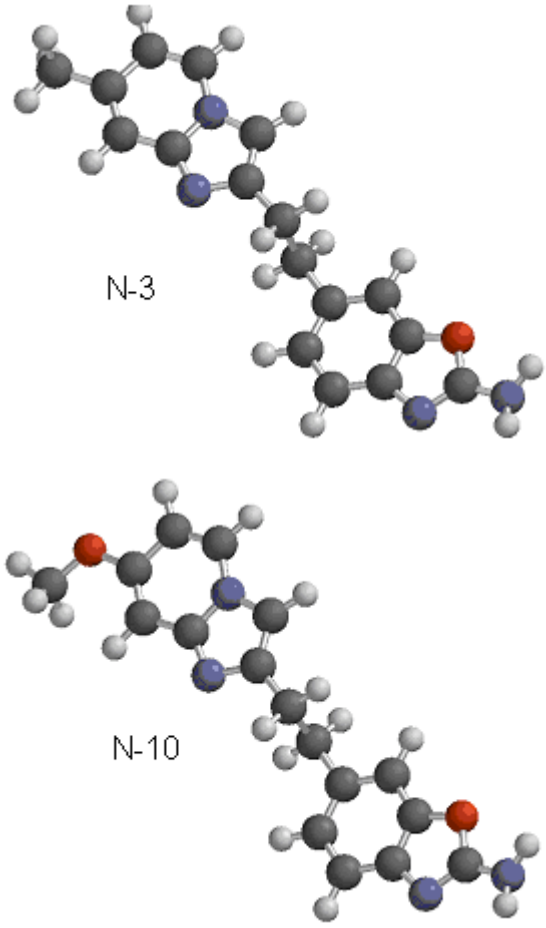
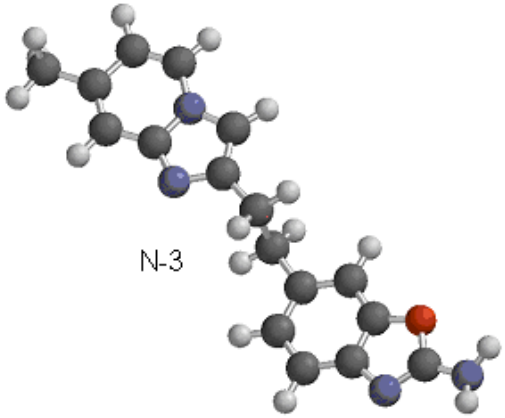


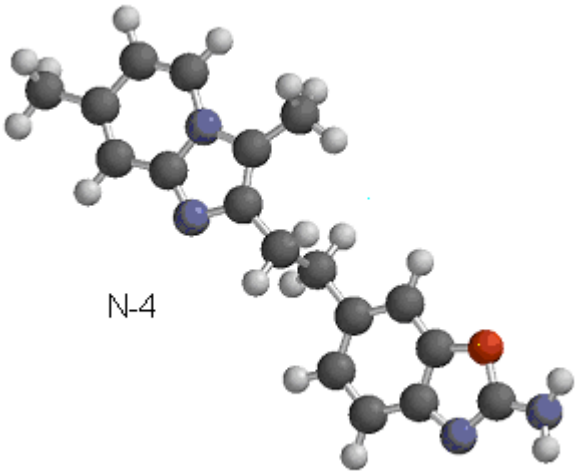
Figure 3 N-3 compound and N-10 compound were shown. When the CH_3 group present as a substituent N-3 compound's activity found to be as 73 however when OCH_3 group takes place as a substituent the reactivity of N-10 reduces to 67.

To compare each molecule whether including hydrogen or not, the numbers of molecules along with their reactivities were given in Table 3. When R^2 is being considered the precence of h-atom increases and conversally the precence of halogen atom decreases the reactivity.

Table 3. The effect of R^2 on the activity.

H	N3	N10	N30	N38	N43
C	N4	N11	N31	N39	N44
X	N5	N12	N32	N40	





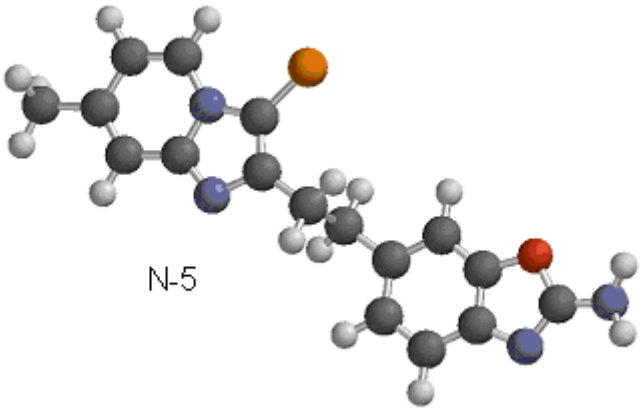


Figure 4 N-3 compound, N-4 compound and N-5 compound are seen. N-3 compound's activity is 73, N-4 compound's activity is 65 and N-5 compound's activity is 88.This shows that the activity depends on the substituents in this region.

In the series of molecule under investigated, Y-substituent is generally -NHR^3- group. If R^3-substituent contains an acceptor group, the molecules activity is enhanced as shown in Table 4.

Table 4. The effect of group-Y on the activity

NH_2	N2	N3	N5	N10	N11
NHR	N27,31,37	N30	N40	N43,51	N33

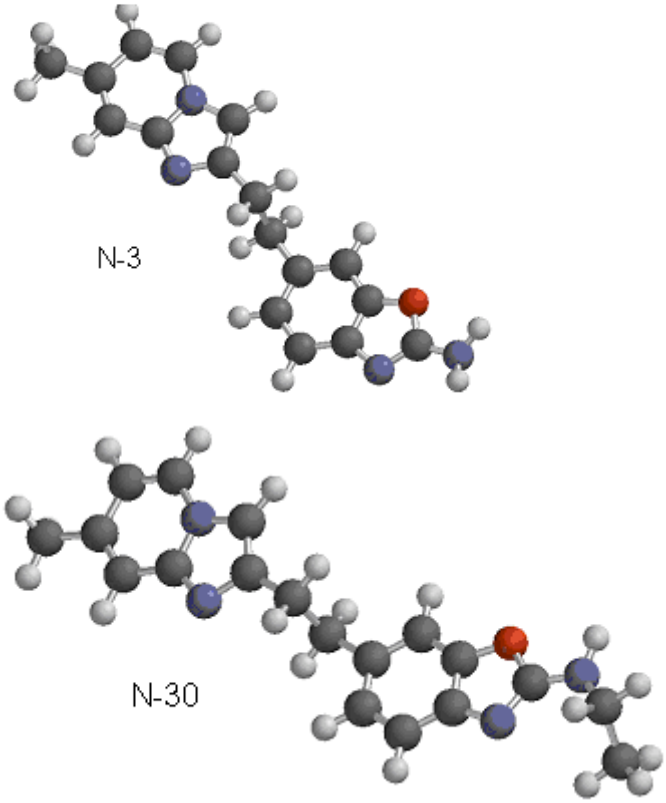


Figure 5 N-3 compound and N-30 compound are seen. N-3 compound's activity is 73 and N-30 compound's activity is 67.This shows the effect of Y substituents.

As a result, it seems that it will be possible to predict the activities of compounds, which their activities are unknown, providing that they pocess pharmacophore and will save the time and money of researchers.

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