Topological Approach to Analgesia

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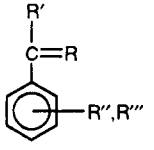
In this study we show that by making use of the molecular connectivity indices, including a new index, which we denominate "σ_t" and which is obtained from a linear combination of the indices, as well as from an "E" form index, it is possible to discriminate minor (nonnarcotic) analgesic character with great efficiency, as well as forseeing the analgesic potency of the analyzed compounds, which represents, without a doubt, a powerful tool for the rational design of new analgesic drugs.

1. INTRODUCTION

Connectivity indices have shown their usefulness in the prediction of diverse physical, chemical, and biological properties of an extensive group of compounds.[1-4] Our research team has applied connectivity indices to the computer assisted design of new drugs, combining them with other indices of our own.[5-7] In this study, we apply different topological indices including connectivity as well as others derived from them, for the analgesic character discrimination of an extensive group of compounds, as well as for the prediction of its relative potency if the considered compound is analgesic. The format of this paper is as follows. Definitions and an outline of our procedures are described in section 2. The obtained results are described and discussed in section 3. Finally, the practical conclusions of the work are summarized in the last section.

2. METHODOLOGY

With the objective of reaching a discriminant function of the analgesic character using connectivity indices, we proceeded with the selection of groups of simple molecules (phenyl derivatives), with the greatest resemblance (including isomeric position), one being analgesic and the other/s not. All of these compounds are derived from the basic structure.



On the one hand, different structural and physicochemical parameters, among which we can emphasize the charge on atoms, dihedral angles, interatomic distances, formation enthalpy, ionization potentials, and the dipolar moments, were calculated by mechanoquantical procedures (AM1 method).[8] Of all of these properties, only the last, i.e. the dipolar moment, showed that it kept some kind of relation, as we shall see further on. On the other hand, with the objective of evaluating the inductive and mesomeric effects, which are clearly related to the properties of electrons "π" and "n", the differences between nonvalence and valence indices ($^1\chi - {}^1\chi^v$, $^2\chi - {}^2\chi^v$, etc.) were calculated, since these differences seem to evaluate said properties.[9] From these differences, the most significant ones were $^4\chi_p - {}^4\chi^v_p$ and $^4\chi_{pc} - {}^4\chi^v_{pc}$.

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Table 1. Values of Different Physicochemical and Topological Parameters for Sets of Analogous Compounds with and without Analgesic Activity

compound	activity	$\Delta^4\chi_p$	μ (D)	$\Delta^4\chi_{pc}$	σ_t
p-methylpropiophenone	yes[10]	0.050	2.601	0.139	–0.049
p-chloropropiophenone	no[10]	0.016	2.164	0.099	0.043
2,4-dimethylacetophenone	yes[10]	0.084	2.602	0.102	0.022
3,4-dimethylacetophenone	no[10]	0.046	2.704	0.111	–0.020
2-(1-propenyl)phenol	yes[11]	0.1453	0.96	0.1843	0.0011
2-(2-propenyl)phenol	no[12]	0.1557	1.140	0.2050	–0.009
o-hydroxybenzoic acid	yes[14]	0.397	1.474	0.375	0.053
m-hydroxybenzoic acid	no[14]	0.271	1.373	0.321	–0.010
p-hydroxybenzoic acid	no[14]	0.234	1.400	0.329	–0.054
o-hydroxybenzamide	yes[14]	0.370	2.920	0.351	0.058
m-hydroxybenzamide	no[14]	0.251	3.980	0.295	–0.004
p-hydroxybenzamide	no[14]	0.212	3.270	0.303	–0.050
3-chlorosalicyclic acid	yes[10]	0.335	2.378	0.450	–0.075
5-chlorosalicyclic acid	no[10]	0.328	1.371	0.338	0.030

Table 2. Potency, P, (Relative to ASA = 1), IC_{50}, E, σ_t, and log IC_{50} Values of a Group of Analgesics

compound	P^a	$IC_{50}{}^b$ (μM)	σ_t	E	log $IC_{50}{}^c$
ASA	1	700	0.1682	2.15	2.97
salicyclic acid	0.8	1000	0.0626	2.46	2.83
flufenamic acid	1	6	0.443	1.59	0.53
meclofenamic acid	1	15	0.139	1.89	0.57
mefenamic acid	2	4	0.144	1.86	1.16
alclofenac	1.5	18	0.2146	0.90	1.71
aminopyrine	1.5	10000	0.372	1.34	3.68
diclofenac	40	4.6	0.109	1.57	0.80
etodolac	1.5	–	0.77	1.81	1.69
fenclofenac	1	–	0.016	1.39	1.52
phenylbutazone	0.7	169	0.401	1.45	1.88
fenoprofen	3.0	100	0.0028	1.29	1.34
flurbiprofen	20	0.34	–0.109	1.25	1.21
acetaminophen	1.2	–	0.109	1.42	2.45
indomethacin	40	10.5	0.242	1.08	1.08
ketoprofen	30	6	–0.207	1.33	0.68
naproxen	10	32	–0.107	1.29	1.01
piroxicam	50	120	–0.415	1.44	2.54
tolmetin	15	11.7	0.165	0.82	1.44
sulindac	40	28	0.086	1.08	0.95
ibuprofen	28	45.2	–0.170	1.13	1.24

[a] Data obtained from refs 13 and 15. [b] Inhibition concentration-50 (IC_{50}) in bovine seminal vesicle (data obtained from ref 13). [c] Resulting values from eq 5.

3. RESULTS AND DISCUSSION

Table 1 shows the values of said differences together with the theoretically determined dipolar moments for the chosen molecular groups.

Several facts stand out: On the one hand, the difference $^4\chi_p - {}^4\chi_p{}^v$, $\Delta^4\chi_p$ seems to be more sensitive to the modification

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Table 3. Results Obtained by the Discriminant Analysis, Carried Out on a Group of 82 Molecules (40 with Analgesic Activity (+) 42 Inactives (–))[a]

compounds with analgesic activity				compounds without analgesic activity			
molecule	Y_1	log IC	classification	molecule	Y_1	log IC	classification
AAS	0.42	2.97	+	aciclovir	–2.00	4.22	–
acetanilide	0.41	2.26	+	desciclovir	–2.67	3.95	–
flufenamic acid	0.47	0.53	+	ebastatine	–36.65	–3.43	–
alclofenac	0.20	1.71	+	acenocoumarol	0.46	1.86	+
meclofenamic acid	0.42	0.57	+	afloqualone	0.14	2.29	+
mefenamic acid	0.47	1.16	+	amaranth (dye)	=1.59	–4.08	–
aminopyrine	0.42	3.68	–	ascorbic acid	–3.18	5.30	–
4-hydroxyisophthalic	0.32	3.00	+	benziodarone	–2.16	–3.22	–
aminopropylon	–0.72	3.00	–	bromindione	0.38	0.01	+
benorylate	0.46	2.47	+	bromazine	–1.02	–0.06	–
benoxaprofen	–0.04	1.05	–	carisoprodol	–56.45	2.49	–
benzpiperylon	0.3	0.84	+	α-carotene	–121.50	–7.07	–
carprofen	0.23	0.91	+	β-carotene	–104.52	–6.79	–
clopirac	0.46	1.60	+	γ-carotene	–27.73	–5.56	–
diclofenac	0.43	0.80	+	carteolol	–27.04	–0.72	–
diflunisal	0.22	2.73	+	cloranolol	–28.49	–1.47	–
droxicam	0.47	3.22	–	erythritol	0.03	3.93	–
phenylbutazone	0.47	1.88	+	histapyrodine	0.23	0.17	+
fenoprofen	0.42	1.34	+	isopromethazine	–0.63	0.81	–
feprazone	0.41	1.22	+	khellin	0.03	4.49	–
flurbiprofen	0.37	1.21	+	oxazidione	–6.66	1.33	–
ibuprofen	0.46	1.24	+	tricromyl	0.45	2.22	+
idomethacin	0.47	1.08	+	bamipine	0.43	0.31	+
isonixin	0.47	1.89	+	ursolic acid	–303.58	–2.33	–
isoxicam	0.37	3.37	–	carnitine	–52.26	0.89	–
ketoprofen	0.40	0.68	+	EPA	–1.45	–1.03	–
ketoprolac	0.45	2.07	+	oxatomine	–0.11	0.68	–
naproxen	0.36	1.01	+	promethazine	0.44	–0.30	–
niflumic acid	0.46	0.89	+	terfen	–47.67	–3.33	–
oxaprozin	0.47	1.23	+	vidarabine	–1.22	6.61	–
oxyphenbutazone	0.28	2.08	+	rimantadine	–10.82	1.55	–
acetaminophen	0.42	2.45	+	AzddU	0.46	4.79	–
piroxacam	0.46	2.54	+	$AzddCF_3U$	0.47	4.06	–
propylphenazone	0.35	3.14	–	AzddFU	0.06	5.38	–
salicyclic acid	0.47	2.83	+	AzddIU	0.35	2.51	+
salsalate	0.47	2.59	+	AzddOEtU	–1.78	5.31	–
sulindac	0.44	0.95	+	tertatolol	–27.44	–3.02	–
tenoxicam	0.44	1.82	+	timolol	–41.23	0.01	–
tiaprofenic	0.47	–0.44	–	δ-tocopherol	–2.80	–2.72	–
tolmetin	0.40	1.44	+	toliprolol	–0.03	2.29	–
				triamterene	0.47	2.94	+
				xibenolol	–27.55	–1.35	–

[a] False actives 7/40 = 17.5%; false inactives 8/42 = 19.05: overall accuracy 67/82 = 81.7%.

of the positions of the aromatic ring's substituents (compare the values for the *o*-, *m*-, and *p*-hydroxybenzoic acids). Likewise, said difference seemed to be more sensitive to the inductive effect of the ring's substituents. Thus, *p*-methylpropiophenone, possessor of a weak positive inductor group ($-CH_3$) shows a value of $\Delta^4\chi_p$ (0.050) much greater than that of *p*-chloropropiophenone (0.016), which in the same position possesses a strong negative inductive group (–Cl). On the other hand, the difference $\Delta^4\chi_{pc}$ seemed to be related more to the effect of aromaticity and the conjugation of electrons π and n, which conditions the value of the dipolar moment. Thus, the difference is greater for the 3,4-dimethylacetophenone than for the 2,4-dimethylacetophenone in concordance with the dipolar moments values, also being greater in the 2-(2-propenyl)phenol (where the π of the propenyl electrons are not conjugated with those of the aromatic ring) than in the 2-(1-propenyl)phenol, where the π electrons are conjugated. Another fact concerns the analgesic character; the existence of negative inductive substituents (–Cl, –OH) in the "para" position of the aromatic ring hinder the analgesic action (see the cases of 5-chlorosalicylic and *p*-hydroxybenzoic acids and of *p*-chloropropiophenone). Moreover, the existence of "meta" substituents, with respect to the carbonilic group, either hinder (for example in the case of 3,4-dimethylacetophenone) or make difficult (3-chlorosalicylic acid) the analgesic activity. On the contrary, the existence of "ortho" substituents assure it. Since the presence of negative inductive groups in the para position implies a notable fall in the molecular dipole moments (see Table 1), the influence of this physicochemical parameter on the analgesic character seems reasonable. Nevertheless, although the dipolar moment changes within each test group in a manner parallel to the differences ($^4\chi_{pc} - {}^4\chi^v_{po}$), it does not seem to be the determinant factor for analgesic character. Moreover, the differences ($^4\chi_p - {}^4\chi^v_p$) act, inside each group, as the discriminant. In fact, with only the exception of the phenolic derivatives, in all other cases such differences are higher for those molecules showing analgesic activity. However the foresaid differences are not useful by themselves as discriminant functions, given their high variability from one group to another. Thus, the analgesic character seems to be related to both the substituent's position in the aromatic ring and the molecular dipole moments, which may, in turn, be related to the inductive and resonant effects. This is a reason why the cases of 2-(1-propenyl)phenol and 2-(2-propenyl)-phenol are significant; the first product possesses analgesic activity;[11] the second, showing only antiinflammatory activity,[12] does not. This suggests that this combination effect must play an important role in the analgesic action. In fact,

Table 4. Results Obtained To Apply the Discriminant Functions (eqs 5 and 6) on a Group of 171 Molecules (29 with Analgesic Activity (+) and 142 Inactives (–))[a]

molecule	Y_1	log IC	classification	molecule	Y_1	log IC	classification
			Compounds with Analgesic Activity				
2,4-acetophenone	0.43	1.82	+	etersalate	–0.3	2.46	–
2-amino-4-picoline	0.41	2.48	+	etodolac	–27.76	1.69	–
2-(1-propenyl)phenol	0.24	1.98	+	phenacetin	–2.32	2.43	–
acemetacin	0.34	1.32	+	fenbufen	0.47	0.37	+
alminoprofen	0.11	1.39	+	fenclofenac	0.42	1.52	+
amino-C1-thenoxazole	0.33	2.92	+	fenol	0.46	2.26	+
2-amino-4-picoline	0.14	2.91	+	ibufenac	0.30	1.52	+
diplosal acetate	0.38	2.74	+	indoprofen	0.21	1.17	+
aniline	0.45	2.15	+	morazone	0.46	2.54	+
antipyrine	0.37	2.78	+	pirprofen	0.42	1.17	+
apazone	0.31	3.95	–	methyl salicyclate	0.17	2.62	+
bumadizon	0.46	1.46	+	sulfadiazine	0.14	1.18	+
cinmetacin	–0.53	1.10	–	viminol	–0.30	0.24	–
1-(4-chlorophenyl)propanol	0.47	1.17	+	zomepirac	0.47	1.61	+
chlorthenoxazine	0.47	2.74	+				
			Compounds without Analgesic Activity				
(4-hydroxybutyl)guanine	–0.20	3.40	–	cryptoxanthin	–107.57	–5.28	–
acicloguanosine	–2.26	4.30	–	curcumin	–0.19	1.31	–
almitrine	–0.40	1.64	–	epanolol	0.47	1.34	+
astemizole	0.45	–0.10	–	epithiazide	0.44	–3.67	–
azatadine	–0.42	–0.52	–	esmolol	0.20	1.57	+
brovincamine	–0.62	4.74	–	fenofibrate	–1.20	0.61	–
bucyclovir	0.25	3.83	–	fenquizone	–0.23	0.10	–
cetirizine	–0.84	0.65	–	flavoxanthin	–150.79	–2.67	–
cinnarizine	–1.36	–0.68	–	flumetramide	0.27	1.15	+
cyproheptadine	–0.34	–0.94	–	glutamic acid	–1.82	2.99	–
cytarabine	–2.23	6.43	–	glycerol	0.47	3.18	–
clemastine	–2.35	–0.51	–	indenolol	0.12	1.78	+
chlorcyclizine	0.12	0.21	+	indigo carmine	0.47	–1.05	–
chlorfenac	–0.10	–0.01	–	C.I. acid green 5	–11.69	–8.08	–
chlorothen	–1.81	–0.90	–	malic acid	–0.78	3.76	–
deptropine	0.18	0.68	+	maltol	–0.09	3.19	–
6-desoxiaciclovir	–2.94	3.54	–	mephenesin	0.39	2.51	+
diphenhydramine	–1.03	1.09	–	mepindolol	–0.29	2.60	–
diphenpyramide	0.44	0.63	+	metipranolol	–1.03	2.74	–
dimethindene	–1.28	–0.11	–	metroprolol	0.32	1.65	+
doxylamine	–6.55	0.99	–	moprolol	0.45	2.79	+
phenindamine	–0.68	0.18	–	nadolol	–17.05	–0.36	–
ganciclovir	–0.04	4.77	–	nadoxolol	0.46	2.24	+
3HM-HBG	–0.25	3.69	–	neohesperidin DHC	–22.95	9.48	–
9-(3-ohetoxy)guanine	–1.18	4.52	–	nicofibrate	–4.71	0.69	–
idoxuridine	0.16	3.13	–	nipradilol	0.05	4.44	–
acebutolol	0.32	2.36	+	oxprenolol	0.47	2.68	+
acetic acid	0.43	3.06	–	pentrinitrol	–15.04	5.13	–
alprenolol	0.40	2.05	+	pindolol	0.33	2.47	+
amantadine	–6.81	1.34	–	ponceau 3R	0.32	–2.54	–
amosulalol	–3.85	0.03	–	practolol	–0.29	2.53	–
amotriphene	–9.49	–0.33	–	pronethalol	0.37	1.17	+
arotinolol	–23.96	–5.45	–	propionic acid	0.46	2.57	+
atenolol	–0.27	2.20	–	propranolol	0.32	1.77	+
befunolol	0.45	3.17	–	rhodoxanthin	–109.13	–5.03	–
beclobrate	–11.17	–0.24	–	riboflavine	–4.47	4.39	–
bendrofluazide	–0.36	–1.55	–	rubixanthin	–29.32	–4.06	–
bevantolol	–1.94	1.62	–	saccharin	0.36	1.77	+
bisoprolol	0.41	2.30	+	sorbic acid	–0.17	2.37	–
bixin	–1.04	–2.00	–	sorbitol	–4.35	5.34	–
bopindolol	–33.04	–1.20	–	sotalol	–0.03	–0.87	–
brilliant blue FCF	–14.41	–7.81	–	styramate	0.47	2.49	+
brontripelenamine	–0.39	–0.12	–	succinic acid	0.12	2.80	+
bucumolol	–27.79	–0.56	–	sulfinalol	0.47	0.71	+
bufetolol	–27.50	–0.38	–	tartaric acid	–5.13	4.59	–
bufuralol	–38.62	–0.94	–	tartrazine	0.46	–0.94	–
bunitrolol	–32.95	–0.93	–	xipamide	–1.51	0.16	–
bupranolol	–27.96	–1.30	–	isothipendyl	0.43	0.15	+
butofilolol	–32.35	–0.81	–	clomestrone	–15.68	–0.35	–
canthaxanthin	–88.01	–6.71	–	eritadenine	–2.22	4.73	–
carazolol	0.27	2.11	+	meglutol	–9.35	2.10	–
carminic acid	–9.61	7.31	–	melinamide	0.42	–2.67	–
carvedilol	–1.69	1.93	–	*m*-aminobenzoic acid	0.46	2.47	+
celiprolol	–54.86	–0.57	–	mequitazine	0.28	–0.14	–
cetamolol	–35.91	–0.51	–	nebularine	–0.35	6.21	–
chlorothiazide	–1.48	–0.48	–	methaphenilene	0.24	–0.08	–
citric acid	0.24	3.97	–	methyl gallate	–0.37	3.51	–
clofibric acid	–0.98	1.27	–	DHPG	–0.04	4.77	–
clonitrate	–0.07	4.41	–	PABA	0.42	2.30	+

Table 4 (Continued)

molecule	Y_1	log IC	classification	molecule	Y_1	log IC	classification
			Compounds without Analgesic Activity				
pyrathiazine	0.06	−0.55	−	AzddPropenyloxyU	0.25	5.14	−
ribavirin	−2.09	6.63	−	AzddCyanoMeOxyU	0.15	5.22	−
pyrilamine	−1.53	1.05	−	AzddtiocyanoU	0.47	4.08	−
talastine	0.17	0.91	+	AzddSMeU	−0.38	3.86	−
thonzylamine	−0.12	2.12	−	AzddC	0.44	4.64	−
trifluridine	−0.40	4.68	−	AzddFC	0.00	5.23	−
tripelennamide	−0.40	1.04	−	AzddMeC	0.28	4.60	−
aryldone	−1.84	−0.26	−	Azdd3-(3oxopropenyl)T	0.43	4.78	−
AzddBrU	0.46	3.87	−	Azdd6azatimidine	0.17	5.24	−
AzddOHU	0.09	5.31	−	ddC	0.11	4.06	−
AzddOMeU	0.04	5.27	−	merocianine	−1.21	−0.81	−
AzddPropinyloxyU	0.27	5.17	−	zidovudine	0.28	4.79	−

[a] Falses active 6/29 = 20.7%; falses inactive 28/142 = 19.7%; overall accuracy 137/171 = 80.1%.

nearly all the nonnarcotic analgesics show a high relative percentage of the conjugated π and n electrons.

Since Hammet's σ function takes into consideration these effects, we thought of the possibility of introducing something like a topological Hammet function, which would include the aforementioned differences of the connectivity indices, in the form

$$\sigma_t = a({}^4\chi_p - {}^4\chi^v_p) + b({}^4\chi_{pc} - {}^4\chi^v_{pc}) + c \qquad (1)$$

In this equation, σ_t represents a normalized value of the function, taking into consideration that the *o*- and *p*-hydroxybenzoic acids would have symmetrical values, that is to say, the same magnitude but with an opposite sign. The results for coefficients "*a*", "*b*", and "*c*" were

$$a = 1 \qquad b = -1 \qquad c = 0.04$$

As can be seen in Table 1, although the σ_t function, in various cases, takes on positive values for the molecules with analgesic activity and negative values for those with nonanalgesic activity, there are exceptions such as 3- and 5-chlorosalicylic acids or 4′-methyl- and 4′-chloropropiophenone. Moreover, the parameter σ_t does not act as a *general* discriminant function, demonstrated by the fact that multiple nonanalgesic compounds display very diverse σ_t values (from −0.6 to +0.4).

It is, therefore, necessary to find a general discriminant function for all the analgesics. Since the nonnarcotic analgesic action is related to the inhibition of cyclooxigenase,[13] we can use the obtained connectivity function with this property as a starting point for the discriminant analysis.

$$\log IC_{50} = (-2.64\,{}^3\chi^v_p) + (1.8\,{}^4\chi_p) - (10.28\,{}^4\chi_c) + (1.24\,{}^4\chi_{pc}) + 3.056 \qquad (2)$$

$$N = 20 \qquad R = 0.8457 \qquad SE = 0.6281$$

$$F = 9.42 \qquad p < 0.0005$$

Where IC_{50} = Inhibition Concentration-50 (μM) in bovine seminal vesicle[13]. As illustrated in Table 2, the majority of the analgesics shows theoretical log IC_{50} values between 0 and 3, which is why it was chosen as the first discriminant function. Although many nonanalgesics possess values in this interval, few analgesics have them outside it, which is why this function can be considered as a necessary but not sufficient condition.

With the objective of finding an efficient discriminant function, able to identify the nonanalgesic molecules, we selected an extensive group of compounds (40 with contrasted analgesic activity and 42 with no analgesic activity) and we obtained the linear discriminant function using the connectivity indices up to the fourth order as independent variables. The chosen discriminant function was

$$Y = (-1.325\,{}^0\chi) + (4.67\,{}^1\chi) + (1.96\,{}^1\chi^v) - (6.56\,{}^2\chi^v) - (4.25\,{}^3\chi_p) - (4.11\,{}^3\chi_c) + (2.68\,{}^3\chi^v_p) + (13.31\,{}^3\chi^v_c) + (1.28\,{}^4\chi_p) + (11.75\,{}^4\chi_c) + (1.22\,{}^4\chi_{pc}) - 0.04 \qquad (3)$$

$$N = 82 \qquad F = 9.32 \qquad U\text{-statistics (Wilks' } \lambda) = 0.7976$$

If we use $Y_1 = 0.47 - Y^2$, the value that Y_1 takes on for a certain compound will indicate to us its analgesic character; thus, if $Y_1 > 0$, the compound will have theoretical analgesic activity, and if $Y_1 < 0$, the compound will be inactive.

In this manner, and working with both equations, a molecule will be selected as active if $3 > \log IC_{50} > 0$ and $Y_1 > 0$ or as inactive if $Y_1 < 0$.

Table 3 contains the classification results obtained after the discriminant log IC_{50} and Y_1 functions with their respective discriminant functions were applied to each molecule. As can be observed, the average degree of success is superior to 80% (80.8%).

The validity of the obtained discriminant function was confirmed when it was applied to a test group, meaning an extensive group of compounds not used in the discriminant function. Table 4 shows the results. The percent of success is similar to that obtained with the group used in the discrimination, which vouches for said discriminant functions.

To extend the study, we widened the σ_t calculation for a group of analgesics whose common action mechanism is the inhibition of the cyclooxygenase.[13] Since the molecule's form should have played an important part in the fixation of the enzyme, we used an *E* form factor, introduced by us,[6] and which we define as

$$E = S/L^2 \qquad (4)$$

where "*S*" represents the "molecular surface parameter" and "*L*" the "topological molecular length", that is, the counted distance in the number of edges or links, between the molecule's two most separate atoms by the shortest means. *S* is calculated as the sum of the contributions for each molecular fragment, according to the values illustrated in Table 5.

It is important to point out that, only in relation to their contribution to the surface parameter, *S*, the double bonds are considered as simple.

It is evident that, despite the simplicity of its calculation, the *E* index gives a measure of the molecular form; thus, molecules with high *E* values, like ASA or salicylic acid, show

Table 5. Contribution by Different Molecular Fragments to the Value of S [6]

group	contribution	group	contribution
	2		28
	6		14
	12		36
	20		18
	10		49.5
	18		
	24		

a similar circular symmetry form, whereas those with a low value, such as tolmetin, show a form with greater excentricity.

Table 2 illustrates the values for the potency, P (relative to ASA = 1), IC_{50}, the E form factor, and σ_t for a wide group of analgesics, including compounds from different families: Aril–acetic, aril–propionic, and antranilic derivatives, as well as antipirines, salicylates, and oxicams.

One point to be made is that there do not exist potent analgesics ($P > 10$) with values of $E > 1.60$. This result is logical since the union to the enzyme should be conditioned by the form, in such a way that the molecules close to a circular symmetry do not "fit" in the enzyme's union site. The form would be, therefore, a necessary but not sufficient condition (see the fenclofenac and alclofenac cases or the aminopirine case in which the low E value does not imply high potency).

If we analyze the results by chemical families, we observe that the potency does not depend on that of the value of σ_t in the case of the aril–acetic derivatives, for those which, save for the two aforementioned exceptions (alcofenac and fenclofenac), the form seems to be decisive. Thus, all of them show values of $E < 1.60$ and high potencies, except etodolac with $E = 1.81$ and low potency.

For the rest of the chemical families the analgesic potency is clearly influenced by σ_t. Figure 1 illustrates the representation of potency versus σ_t for the rest of the studied analgesics. As can be seen, two regions are clearly distinguished: the first, comprised between $\sigma_t = 0$ and $\sigma_t = 0.8$, for which no potent analgesics appear; the second, between $\sigma_t = 0$ and $\sigma_t = -0.6$ approximately, for which the potency increases with the absolute value of σ_t.

Empirical equations which led to good adjustments were

$$\text{(a) for } -0.6 < \sigma_t < 0$$

$$P = K[1 - e^{\beta\sigma_t}] + K'/(1 + e^{\gamma\sigma_t}) \quad (5)$$

$$\text{(b) for } 0 < \sigma_t < 0.8$$

$$P = K'/(1 + e^{\gamma\sigma_t}) \quad (6)$$

with parameter values, $K = 80$, $\beta = 2.35$, $K' = 2.5$, and $\gamma = -1962$.

If the representation potency (P) versus σ_t is made for analgesics that only include one benzenic ring (i.e. phenyl derivatives), the parameter σ_t seems to have a discriminant action. Thus, for these kinds of compounds the σ_t values between 0 and –0.1 imply nule (or very low) analgesic activity (Figure 1). All the values between –0.1 and +0.8 adjust reasonably well to eq 6.

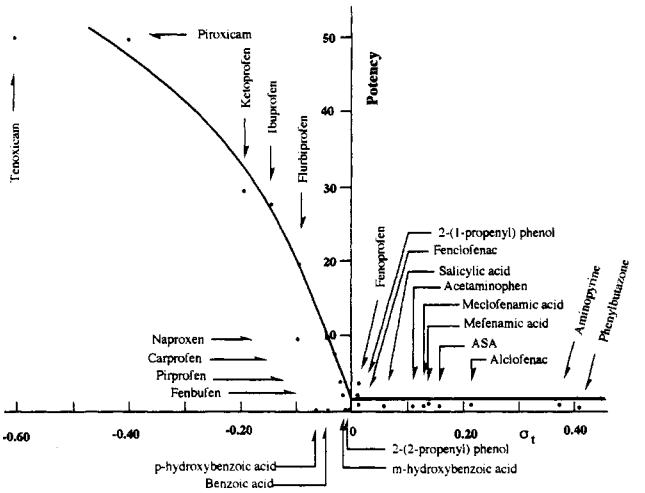

Figure 1. Plot of potency, P, vs σ_t, for a wide group of analgesics, excepting aril–acetic derivatives.

4. CONCLUSIONS

The preceeding results clearly demonstrate that by adequate choice of topological indices it is possible to discriminate, with good efficiency, the minor (AINA) analgesic activity. Among these descriptors we may emphasize the connectivity ones, as well as the shape factor E. Moreover, it is also possible to predict the analgesic potency through the parameter σ_t, which is obtained as a linear combination of the differences $({}^4\chi_p - {}^4\chi^v_p)$ and $({}^4\chi_{pc} - {}^4\chi^v_{pc})$. Those results illustrate the amazing ability of the topological descriptors in the rational discrimination of the analgesic character and, therefore, in the design of new drugs.[16]

Consequently, the rational design of new analgesics demands the following conditions:

(A) Analgesic activity

$$3 > \log IC_{50} > 0 \quad \text{and} \quad Y_1 > 0$$

(B) Potency (ASA = 1)

(B1) Aril acetic derivatives: only shape factor's influence; $E < 1.60$ implies high potency ($P > 10$) (B2) Other groups

(B2.1) Phenyl derivatives: $\sigma_t > 0$, potency similar to ASA ($P = 1$); $-0.1 < \sigma_t < 0$, low potency ($P < 0.5$); $-0.6 < \sigma_t < -0.1$, high potency ($P > 10$) (B2.2) The rest: $\sigma_t > 0$, potency similar to ASA (P = 1); $\sigma_t < 0$, potency increases with $-\sigma_t$

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