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Bicyclic [*b*]-Heteroannulated Pyridazine Derivatives—II. Structure–Activity Relationships in the 6-Aryltriazolo-[4,3-*b*]Pyridazine Ligands of the Benzodiazepine Receptor

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Abstract—Electronic parameters (molecular electrostatic potential MEP, charge distribution on the nitrogen atoms, dipole moment μ and ionization potential IP) were calculated by semiempirical quantum chemistry methods for 2 sets (X = H and *m*-CF_3, the *syn*- and *anti*-rotamers of the latter being considered separately) of the 6-aryl-3-substituted-triazolo[4,3-*b*]pyridazine ligands of the benzodiazepine receptors (Figure 1; for X and Y c.f. Table 1). The calculations located the deepest MEP minimum near the =N–N= fragment of the triazole ring (Figure 2). Activity of the investigated compounds (1 μM), expressed as % inhibition of *in vitro* ^{3}H-diazepam (1.5 nM) binding, revealed a significant dependence on IP, which combined in correlation studies with the hydrophobic constants π_X and π_Y and the Swain–Lupton field constant $\mathcal{F}_Y$ gave a 100 % explanation of variance (Equations 1–3). However, extrapolation pointed to a compound with excessive hydrophobicity. The dipole moment orientation, roughly consistent with the C(6)-aryl main molecular axis, was considered as another factor controlling the docking of the investigated triazolopyridazine ligands to the benzodiazepine receptor (Figure 3). A model of the triazolopyridazine-benzodiazepine receptor interaction was proposed (Figure 4).

Introduction

The biological activity of the derivatives of triazolo[4,3-*b*]pyridazine was first reported[1] in 1979 and the compounds have become the focus of pharmacological research. According to the original paradigms,[1-3] the most active member of the series, 3-methyl-6-(3-trifluoromethylphenyl)triazolo[4,3-*b*]pyridazine (Figure 1, X = CF_3, Y = CH_3), usually referred to as CL 218,872, prevented both pentylenetetrazole-induced convulsions and behavior reinforced by punishment in experimental animals at doses comparable to those of diazepam. These early tests were also highly predictive of interesting anxiolytic activity, especially as the compound appeared at that time to be, unlike benzodiazepines, relatively free of the ataxic and depressant effects and considerably less interactive with alcohol. However, later *in vivo* investigations[4,5] have accumulated evidence that CL 218,872 is actually inferior to benzodiazepines in the anxiolytic activity; they also failed to confirm its non-sedative properties. On the other hand, results of utmost importance have been obtained in the early radioligand[1,6,7] and radiohistochemical[8] experiments which have supplied the first dependable evidence for recognizing heterogeneity of the benzodiazepine receptor. With high affinity to the BZ_1 receptor subtype, CL 218,872 made a crucial contribution in delineating the existence and biological specifity of the BZ_1/BZ_2 receptor subtypes.[6] It is recognized at present as a partial benzodiazepine agonist at both α_1- and α_3-containing subunits of the $GABA_A$ receptor with highest affinity for the $\alpha_1\beta_1\gamma_2$ isoform.[9-11]

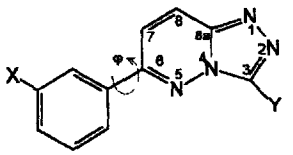

Figure 1. Free rotation in 6-aryl-3-substituted-triazolo[4,3-*b*]-pyridazines
(c.f. Table 1 for listing of X and Y substituents).

More than 50 6-aryl-3-substituted-triazolo[4,3-*b*]pyridazine derivatives (Figure 1) have been reported in a synthetic paper[12] published in 1981, which also included the data on their antipentylenetetrazole activity in rats, and *in vitro* ^{3}H-diazepam binding inhibition (c.f. Table 1). Depending on the nature of the 3- and 6-substituents, the results of the latter tests varied across a very wide range. The triazolopyridazine series may be considered, therefore, as a convenient model for studying the ligand–receptor interactions and searching for geometric and electronic parameters of the molecules and of the particular substituents responsible for binding efficacy. The results of such a study are reported in this paper.

Methods and Results

The data on % competitive inhibition of ^{3}H-diazepam (1.5 nM) binding *in vitro* by 1 μM concentration of the

investigated compounds (Table 1) were taken from literature.[12] The starting 3-D models of all selected compounds were based on earlier crystallographic studies.[13] Geometry of the molecules was estimated first in the global minimum by molecular mechanics methods[14] and its more precise optimization has been done with the PM3 method[15] from MOPAC.[16] The final geometric parameters were obtained by minimizing the energy with respect to all variables. The molecular electrostatic potentials (MEP) were calculated using the VMNDO program.[17]

Ligands with high affinity to the benzodiazepine receptor are in most cases capable of assuming a planar or pseudoplanar topography; their main molecular framework is for the most part plainly planar or nearly planar. The "planarity hypothesis", originally advanced for β-carbolines upon comparing their affinities with those of the non-planar tetrahydro-analogs,[18] has been recently found to fit well for other polycyclic ligands including the nearly-planar benzodiazepines.[19-27] In the title compounds, the bicyclic moiety is also nearly planar and thus essentially rigid according to both crystallography[13] and present geometry optimization. The conformational flexibility of the molecules is therefore associated with rotation of the aryl substituent at C(6) and, to a lesser degree, of the substituent at C(3). The barrier to rotation about the C(6)-aryl group bond in CL 218,872 (X = CF_3, Y = CH_3), calculated by molecular mechanics methods (MMX program, full turn in 10 ° steps), was found to be as low as ~1.5 kcal/mol, yet coplanarity with the bicyclic moiety is certainly favoured owing to the conjugation effects and steric preferences of the *m*-substituent. With reference to the CH_3 substituent at C(3), the periplanar CF_3 group may be either *anti* (the torsional angle φ = 4.5 °, c.f. Figure 1) or *syn* (φ = 170 °); the former rotamer has been shown to occur in crystals.[13] An analogous conformational pattern has to be assumed for all congeners with asymmetrically (*ortho* or *meta*) substituted aryl groups.

In our research we have selected two sets of the title compounds: with X = H and X = *m*-CF_3. Other substituents X appear in the investigated series only in very few, mostly untested compounds which, therefore, are of little value in correlation studies. For the selected compounds, the ionization potential (IP in eV), the deepest molecular electrostatic potential (MEP) minimum (V_M in kcal/mol), the dipole moment (μ in D) and the angle φ characterizing the aryl group out-of-plane distortion have been calculated. A map of MEP distribution in the *syn*-rotamer of CL 218,872 (compound **9**) is shown in Figure 2 as an illustrative example of the calculation results. The numeric data are listed in Table 2 and the dipole moment vectors are presented in Figure 3. In all calculations, the *syn* and *anti* rotamers of the compounds with X = CF_3 have been considered separately.

Discussion

The torsional angle φ values (Table 2) give unequivocal evidence for practical coplanarity of all cyclic elements of the molecules. Some minor departures are noted only in compounds with relatively bulky Y substituents (C_2H_5 and C_3H_7). It is therefore legitimate to use that main molecular plane in studying MEP distribution throughout the molecules. In allcompounds of the investigated sets,

Table 1. Benzodiazepine receptor affinity of 6-aryl-3-substituted-triazolo[4,3-*b*]pyridazines

No.	X	Y	% Inhibition of ^{3}H-diazepam (1.5 nM) binding		
			Observed[b] (1 μM)	Calculated from Eq.3	Difference obsd./calcd.
1	H	C_6H_5	74	73.00	-1.00
2	H	CH_3	55[c]	53.74	-1.26
3	H	C_2H_5	not tested	48.62	---
4	H	CH_2Cl	45	43.86	-1.14
5	H	C_3H_7	38	40.08	2.08
6	H	CF_3	not tested	40.00	---
7	H	H	23	23.91	0.91
8	H	CH_2OCH_3	<10[d]	5.45	0.45
9[a]	CF_3	CH_3	77[c]	79.61	2.61
10	CF_3	C_2H_5	73[c]	71.18	-1.82
11	CF_3	CH_2Cl	67[c]	69.73	2.73
12	CF_3	C_3H_7	not tested	63.52	---
13	CF_3	CF_3	60	60.02	0.02
14	CF_3	H	55[c]	51.42	-3.58
15	CF_3	CH_2OCH_3	23	23.08	0.08
16	CF_3	C_6H_5	66	92.11	26.11

Notes: [a]CL 218,872; [b]data for compounds **1**–**15** from ref. 12, for **16** from ref. 29; [c]ID_{50} values (ref. 12): **2** - 633 nM; **9** - 116 nM; **10** - 280 nM; **11** - 391 nM; **14** - 905 nM; [d]the value of 5 was arbitrarily used in the correlation analysis.

Table 2. Rotational conformation and electronic parameters after geometry optimization by PM3

	Y (compd.no.)							
	CH_3	C_2H_5	CH_2Cl	C_3H_7	CF_3	H	CH_2OCH_3	C_6H_5
X = H	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**1**
φ[°][a]	-1.1	0.6	1.2	5.5	7.5	4.5	1.8	-10.4
V_M [kcal/mol][b]	-24.3	-24.4	-21.7	-24.3	-18.9	-24.3	-24.2	-24.1
μ [D][c]	5.77	5.72	6.08	5.65	7.65	5.80	5.48	5.69
IP [eV][d]	9.30	9.35	9.52	9.32	10.01	9.58	9.39	8.91
X = CF_3 (*syn*)	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
φ[°][a]	0.1	25.2	0.4	-26.3	-1.3	-0.6	-1.23	0.7
V_M [kcal/mol][b]	-21.6	-21.7	-19.2	-21.9	-16.6	-21.8	-22.5	-21.4
μ [D][c]	5.05	4.99	5.84	5.02	8.14	5.55	6.64	4.88
IP [eV][d]	9.49	9.54	9.71	9.53	10.27	9.75	9.68	8.98
X = CF_3 (*anti*)	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
φ[°][a]	1.17	-0.1	27.6	-0.7	-26.2	29.1	-26.8	-27.0
V_M [kcal/mol][b]	-21.5	-21.5	-18.9	-21.5	-16.1	-21.6	-21.4	-21.4
μ [D][c]	3.78	3.74	3.48	3.77	4.51	4.11	4.71	3.75
IP [eV][d]	9.50	9.55	9.74	9.54	10.29	9.78	9.70	9.09

Notes: [a]torsional angle (c.f. Figure 1); [b]molecular electrostatic potential (MEP) minimum depth; [c]dipole moment; [d]ionizaton potential (IP).

the deepest MEP minimum M (in **9**, V_M = −21.6 kcal/mol) is localized in proximity to the =N–N= fragment in the triazole ring (Figure 2). The corresponding V_M values show only slight changes with the substituent Y, though strongly electronegative Y, such as CH_2Cl and CF_3, make them shift upward by approximately 3 and 5 kcal/mol, respectively. In the set with X = CF_3, slightly lower V_M values characterize the *syn* rotamers. As far as position of the main minimum is concerned, there is a full consistency with the results of Bertolasi *et al.*,[13] who located it using the INDO method and a slightly different calculation algorithm than ours.

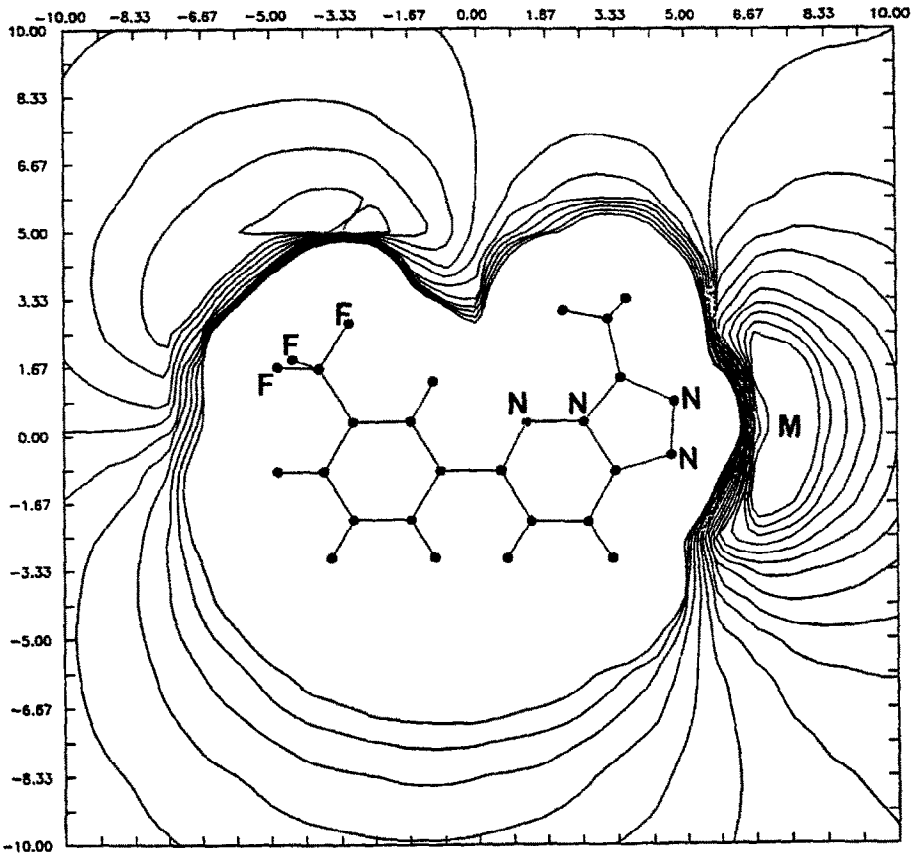

Figure 2. Molecular Electrostatic Potential (MEP) distribution in 3-methyl-6-(3-trifluoromethylphenyl)-triazolo[4,3-*b*]pyridazine. Equipotential lines are shown in the −6 to −22 kcal/mol range at intervals of 2. The deepest minimum is marked M.

The map produced for **9** (Figure 2) also shows a second potential depression which appears near the nitrogen atom N(5) and manifests itself as an inflection on the –6 kcal/mol equipotential line. Some still shallower minima are associated mostly with the *m*-CF_3 substituent and, in a few cases, also with the Y substituent.

The charge distribution on the nitrogen atoms, with the mean values of –0.05, -0.04, 0.4, and –0.18 for N(1), N(2), N(4), and N(5) atoms, respectively, is closely similar in all investigated compounds. It is noteworthy that a MEP depression coincides with the negative charge on the N(5) atom which thus may act as a proton acceptor in the formation of a hydrogen bond. Therefore, participation of both MEP minimum sites in bonding the compounds to the BZ receptor, either by coulombic attraction or by means of hydrogen bonds, seems to be rather unquestionable.

The order of ionization potential (IP) values is roughly consistent with that of receptor affinity (RA) of the compounds expressed as % inhibition of ^{3}H-diazepam binding.[12] This makes the IP parameter a *prima facie* plausible candidate for application in quantitative structure–activity analysis. Combining the calculated values of IP (Table 2) with the standard values[28] of the Hansch hydrophobic constant π in its 1st and 2nd power and the Swain–Lupton field constant $\mathcal{F}$ for the substituent Y, we have obtained the following correlation equations:

In the group with X = CF_3 (compounds **9–11**, **13–15**, *anti*-rotamers):

$$RA = 31.57\ (\pm 1.30)\ \pi_Y + 45.44\ (\pm 2.36)\ \mathcal{F}_Y - 47.91\ (\pm 1.42)\ IP - 19.81\ (\pm 0.79)\ \pi^2_Y + 522.35\ (\pm 13.68) \quad (1)$$

n = 6 r = 1.000 s = 0.6505 F = 1120 Table F (4,1,0.05) = 225

In the group with X = H (compounds **1**, **2**, **4**, **5**, **7** and **8**):

$$RA = 28.10\ (\pm 0.72)\ \pi_Y + 110.98\ (\pm 6.19)\ \mathcal{F}_Y - 94.74\ (\pm 3.66)\ IP - 19.88\ (— 0.68)\ \pi^2_Y + 931.24\ (\pm 34.80) \quad (2)$$

n = 6 r = 1.000 s = 0.8544 F = 910 Table F (4,1,0.05) = 225

When both groups are combined and the Hansch hydrophobic constant of the substituent X is added, the correlation analysis gives the equation:

$$RA = 46.52\ (\pm 2.56)\ \pi_X + 28.64\ (\pm 1.46)\ \pi_Y + 103.98\ (\pm 11.04)\ \mathcal{F}_Y - 81.85\ (\pm 6.25)\ IP - 18.38\ (\pm 1.37)\ \pi^2_Y + 808.89\ (\pm 59.23) \quad (3)$$

n = 12 r = 0.996 s = 2.6137 F = 162 Table F (5,6,0.01) = 8.75

This excellent correlation depends to a considerable extent on the IP parameter as its elimination makes the correlation coefficient (r) drop to 0.85. Extrapolation of the results to include compounds with higher π values, what the equation outwardly suggests, calls however for important limitations. Thus, when calculating predictions for compounds with other combinations of the X and Y substituents listed in Table 1, Equation 3 highlighted the congener with X=CF_3 and Y=C_6H_5 (predicted > 90 % inhibition of ^{3}H-diazepam binding). The radioligand test revealed only a 66 % inhibition.[29] There is every reason to assume that high hydrophobicity and consequent very poor solubility of this compound makes the ligand–receptor contact difficult. In our judgment, the sum of the Hansch hydrophobic constants for substituents in the triazole and benzene rings (in our case X and Y) should not be much higher than two.

The experimental and calculated values of the receptor affinity (RA) are compared in Table 1 which also includes predictions for some compounds not tested earlier.

According to the calculations, the dipole moment vectors of all investigated molecules point to the aryl moiety though, depending on the substituents X and Y and the rotational conformer, they diverge from the C(6)-aryl main molecular axis within a rather substantial range (Figure 3a-c). Attempts at correlating the dipole moment magnitude and direction (the angle formed with the C(6)-aryl axis) with receptor affinity of the particular compounds were unsuccessful. Moreover, analysis of the dipole vector orientation in the *syn*- and *anti*-rotamers of the CF_3-substituted compounds gave no information on the receptor's conformational preferences. Nevertheless, as polarity certainly ranks among the most significant factors acting to orientate the molecule towards the complementary polar sites of the receptor, what is a prerequisite to possible subsequent bonding, the general direction of the dipole moment, has to be considered as another important feature of the triazolopyridazine ligands.

The results of the present research correlate well with recent concepts of the structural requirements for benzodiazepine receptor ligands with agonist and inverse agonist activity.[19,21,24–27,30-33] A size-limited lipophilic region with a π–π interaction capacity, at least one hydrogen bond donor or a coulombic interaction site and a bulk tolerance region of the receptor must have their counterparts in the ligands. This image may be readily adopted in delineating the pharmacophore elements of the investigated compounds (Figure 4). Thus, the aryl group may act as the hydrophobic π-electron fragment, the N(5) atom and the main MEP minimum M, as the hydrogen bond acceptor and/or coulombic attraction site, and the substituent Y, as the bulky group.

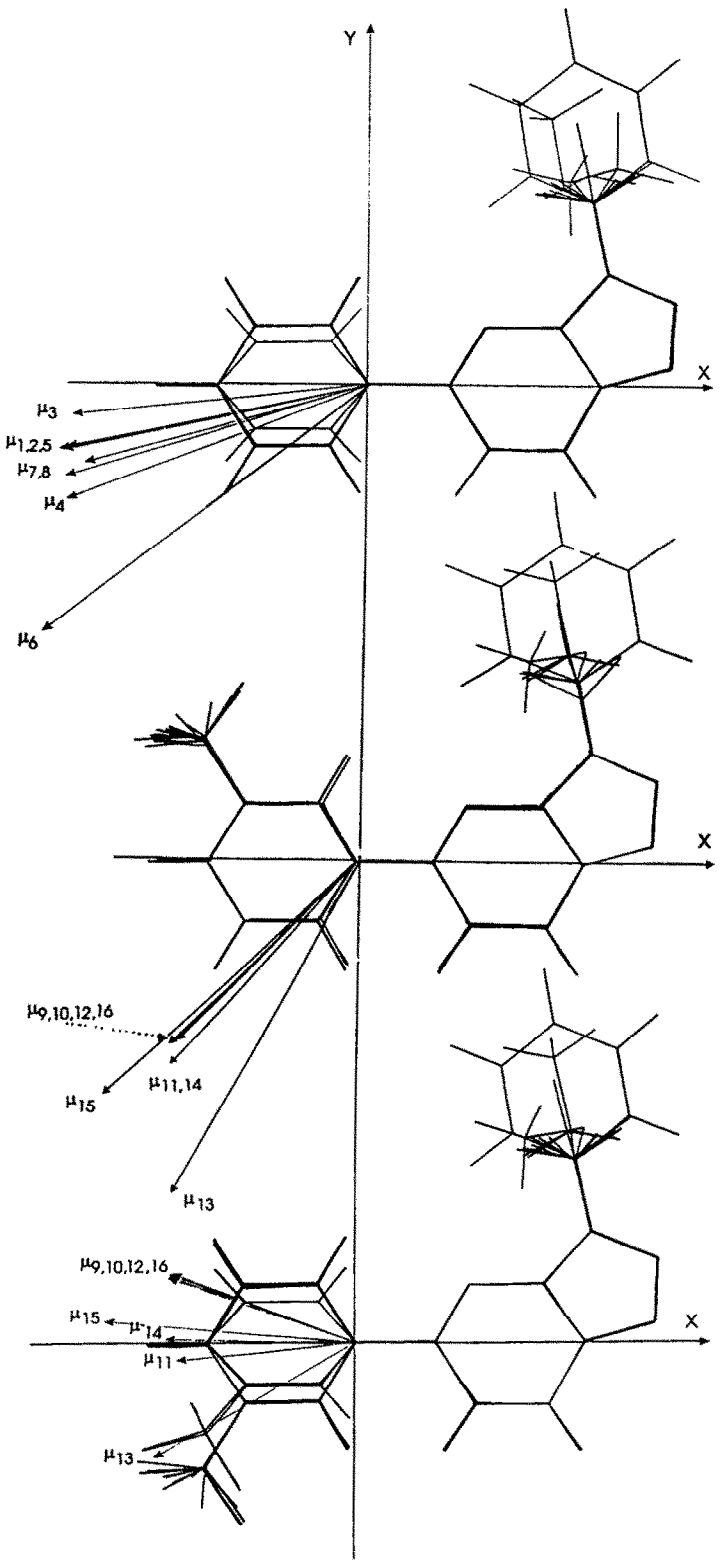

Figure 3. Superimpositions along the aryl–pyridazine axis showing the dipole moment vectors of:
compounds **1–8** (top);
syn-rotamers of compounds **9–16** (center);
anti-rotamers of compounds **9–16** (bottom).

Since the partial agonist properties of the triazolopyridazines are presumably related to their preferential binding with the α_1 receptor subunit, corresponding to the 51 kDa protein,[7,34,35] the proposed model may be particularly representative of this domain. This can explain the problems encountered by authors attempting to fit CL 218,872 in with models intended to depict the pharmacophoric descriptive points of agonist ligands with no distinction of the apparent specifity of full and partial agonists. Thus, Borea *et al.*,[27] who, in accord

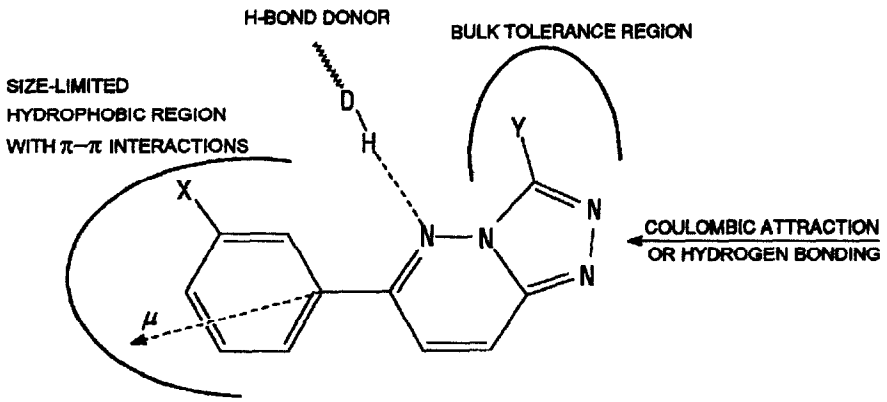

Figure 4. The proposed model of the triazolopyridazine–benzodiazepine receptor fit.

with contemporary knowledge, treated CL 218,872 as a full agonist, considered this compound of little use in determining the receptor geometry. Moreover, superimposing it to oxazepam, zopiclone and CGS 9896 they assumed that only the N(5) lone pair was acting as a hydrogen bond acceptor and entirely disregarded the N(1) and N(2) lone pairs which practically merge into one zone with highest negative potential, the most characteristic electronic feature of the molecule.[13] Similarly, Tebib *et al.*,[25] who developed a multi-parameter model accomodating many ligands and distinguishing requirements for agonist and non-agonist activity profiles, found CL 218,872 meeting only some of these parameters.The most recent "triangle" models of the benzodiazepine agonist pharmacophore, published by Cook and co-workers, were built mostly on superimposing the diindole, thienylpyrazoloquinoline, pyrazoloquinoline and β-carboline agonists and inverse agonists to the classical benzodiazepines.[26,30–33] Although the triazolopyridazines were not considered therein, the points of electrostatic interactions shown in Figure 4 seem to correspond well with the sites marked H_1 and H_2 in these models. The distance determined by the two highest electronegativity centers in CL 218,872 amounts to 7.2 Å and is comparable with that between H_1 and H_2 (6.5 Å in the model of Diaz-Arauzo *et al.*,[26] and 5.0–7.5 Å in that of Hollinshead *et al.*[31]). However, there is no such consistency in the case of the lipophilic center which, in accord with the dipole moment orientation and with the results of Borea *et al.*,[27] and Villar *et al.*,[36] is associated with the phenyl ring. Superimposition of the MNDO-optimized[37] structure of CL 218,872 to that of CGS 9896 (Figure 5) shows, with reference to the model of Diaz-Arauzo *et al.*,[26] a possible interaction of its lipophilic fragment only with the L_3 area, the L_1 and L_2 lipophilic pockets being left unoccupied. Further studies are required to answer the question whether this difference may be responsible for the agonist vs partial agonist activity of some benzodiazepine receptor ligands.

The results presented show that a synthetic work on congeners or analogs of the investigated series should consider the criterion of possibly low ionization potential and moderate hydrophobicity. With constant substituent X, the electron-withdrawing substituents Y have to be avoided. The orientation of the dipole moment may serve as another criterion, yet of only qualitative significance. If the molecule is seen as a dipole, its negative pole is associated with the MEP minimum M close to the =N–N= fragment of the triazole ring, whereas the positive one points to the aryl moiety. With reference to molecule positioning as in Figure 3, the dipole vector localization in the lower left quadrant of the *x*–*y* co-ordinates seems to be preferred.

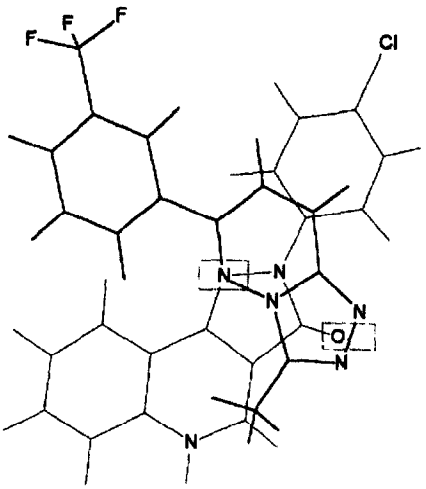

Figure 5. Superimposition of CL 218,872 (solid line) to the pyrazoloquinoline ligand CGS 9896 (thin line) with aligning the hydrogen bond acceptor sites (boxes).

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