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ORIGINAL PAPER

Molecular electrostatic potentials in aromatic substituted 4-hydroxyquino-2-lones: Glycine/NMDA receptor antagonists

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Abstract Hydroxyquinolone derivatives have proven to be useful for inhibition at the glycine binding site of N-methyl-D-aspartate (NMDA) receptor. In this work the electronic structure, molecular electrostatic potential (MESP) and vibrational characteristics of a set of C_3 substituted 4-hydroxyquino-2-lone (HQ) derivatives, which act as Glycine/NMDA receptor antagonists, have been investigated using the density functional calculations. In the optimized structures a substituent at the C_3 site of HQ tends to adopt a helical structure. MESP investigations reveal that the ligands showing better inhibition activity should possess electron-rich regions extending over the substituent and carbonyl group of HQ. A correlation of inhibitory activity to the molecular electrostatic potential topography at the carbonyl oxygen as well as to the molecular electron density topography turns out to be a significant output of the investigation.

Keywords 4-hydroxyquino-2-lone (HQ) · Glycine/NMDA receptors · Hybrid density functional · Molecular electrostatic potential topography

Introduction

Binding of ligands to proteins and enzymatic moieties possessing multi-functional binding sites has been of considerable interest. N-methyl-D-aspartate receptor [1–4] is one interesting system which offers multifunctional sites for ligand binding, viz., glutamate, polyamine, glycine and channel blocker site. Better side effect profile of glycine site over the glutamate and channel blocker sites has triggered a search for ligands antagonists, which bind to it [5–8]. Thus Kynurenic acid (4-oxo-1,4-dihydroquinoline-2-carboxylicacid), has been proposed [9] as a possible antagonist. Different glycine site directed NMDA receptor antagonists including kynurenic acid derivatives have subsequently been identified [10–30].

Quantitative structure activity relationship (QSAR) approach to get better insights for binding phenomenon has been explored in the literature [31–36]. QSAR investigations on kynurenic acid derivatives have shown that [28] their inhibition activity can be correlated to the hydrophobicity constants derived from the octanol/water partition coefficients. These investigations underline the importance of the structure of a ligand responsible for its biological activity. For this purpose, IC_{50} values of the ligands has been widely used as a measure of the response of the ligands towards biological activity. IC_{50}, or the half maximal inhibitory concentration, represents the concentration of an inhibitor required for 50% inhibition of its target (i.e. an enzyme, cell, cell receptor, protein). In simpler terms, it measures how much of a particular substance/molecule is needed to inhibit some biological process by 50%. The IC_{50} values for the hydroxyquinolone derived NMDA receptor antagonists studied in the present paper were evaluated by displacement of glycine site antagonist binding to rat cortex/hippocampus membranes [24–26].

It was further conjectured that weak hydrogen bonded interactions from carboxylate, amine or keto functional groups of kynurenic acid derivative are responsible for recognition at glycine/NMDA site. Investigations with

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topological and electronic descriptors related to hydrogen bonding have also been reported [36]. Electronic charge distribution from the topography of the molecular electrostatic potential (MESP) or the molecular electron density (MED) provide insights for ligand-receptor interactions at the molecular level.

In order to gain insights for the hydrogen bonded interaction in the C_{11}-substituted ligands, NMDA antagonists, we have employed the electrostatic potential topography as a tool [37]. Calculated vibrational frequency of the quinolinic carbonyl stretching has been correlated to the bond critical point in the MED topography in these antagonists. The present work focuses on the influence of C_3 substitution on the electronic structure, charge distribution and vibrational characteristics in a series of 4-hydroxyquino-2-lone (cf. Fig. 1) derivatives.

Computational method

Geometry optimizations using the hybrid density functional theory incorporating Becke's three parameter exchange with Lee Yang Parr's (B3LYP) correlation functional [38, 39] are performed on the C_3 substituted hydroxyquinolone derivatives using the GAUSSIAN03 [40] program by employing the internally stored 6-31G(d,p) basis set. Stationary point geometries were confirmed to be the local minima on the potential energy surface since all the vibrational frequencies turn out to be real. Normal vibrations were assigned by visualizing the displacements of atoms around their equilibrium (mean) positions [41].

The molecular electrostatic potential (MESP) $V(\mathbf{r})$ at a point $\mathbf{r}$ due to a molecular system with nuclear charges $\{Z_A\}$ located at $\{R_A\}$ and the electron density $\rho(\mathbf{r})$ is given by

$$V(\mathbf{r}) = \sum_{A=1}^{N} \frac{Z_A}{|\mathbf{r} - \mathrm{R}_A|} - \int \frac{\rho(\mathbf{r}')d^3\mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|}. \quad (1)$$

In Eq. (1) N denotes the total number of nuclei in the molecule and the two terms refer to the bare nuclear potential and the electronic contributions, respectively. The balance of these two terms brings about the effective localization of electron-rich regions in the molecular system.

MESP topography has been investigated. The most negative valued positions the (3, +3) minima, in the electrostatic potential near different electron rich atomic centers were located. UNIVIS-2000 [42–45] was used for visualization of the MESP topography. These (3, +3) minima represent the potential cation binding sites. The strength of different bonds in the system can be gauged in terms of bond critical points obtained in the molecular electron density (MED) topography [46, 47].

Results and Discussion

The atomic labeling scheme used for the 7-choloro-4-hydroxy-1H-quinolin-2-one (HQ) building block has been shown in Fig. 1. C_3 substituted HQ derivatives are shown in Table 1. These HQ derivatives were taken from the references [24–26] and considers the aromatic substitution at the C_3 position. These derivatives have been found to be active against the Glycine/NMDA receptor and possess Log (IC_{50}) values less than 1.

B3LYP calculations yield the C=O, OH or NH bond distances nearly insensitive to the aromatic substitution at the C_3 position. A nonplanar structure with the substituent orienting ~50° above the hydroxyquinolone plane has been predicted to be a local minimum on the potential energy surface. A substituent at the C_3 site emerge with a locally helix structure in these minima for large substituent as may be noticed in Fig. 2 which show a large inhibitory activity. It may therefore be conjectured that a (local) helix structure adopted by the HQ derivatives is partly responsible for inhibitory activity.

B3LYP calculated vibrational frequencies of selected vibrations in different HQ derivatives are reported in Table 2. The N_1H and the C-Cl frequencies are nearly insensitive to the aromatic substitutions at the C_3 position. The Hydroxyl $O_{14}H$ frequency normally appears at 3715 cm^{-1}. In case of benzophenone derivative (**1**), it shows an up shift to 3736 cm^{-1} where as for molecules (**10**), a downshift of 12 cm^{-1} has been predicted. The C_4O_{14} vibrational frequency appears normally at 1439 cm^{-1}

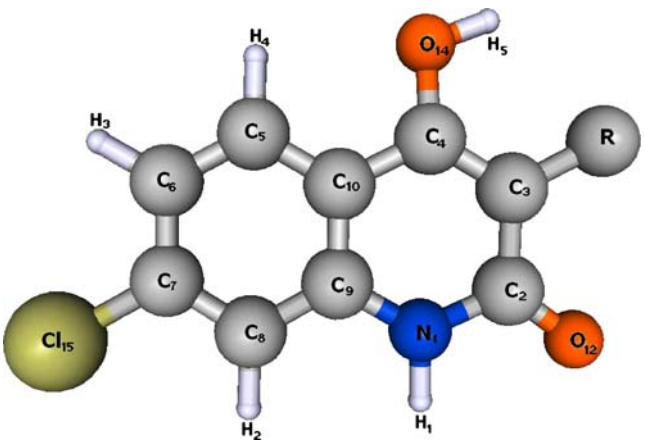
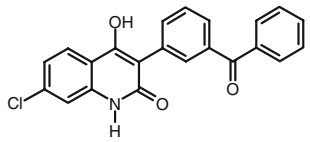
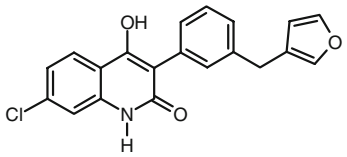
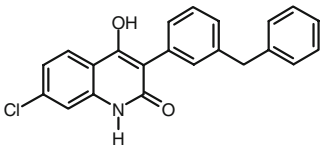
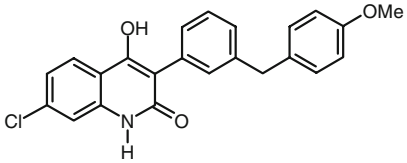
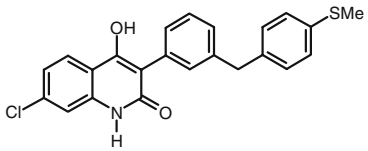
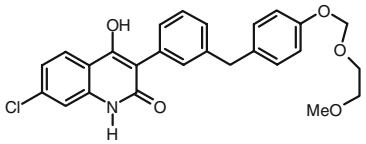
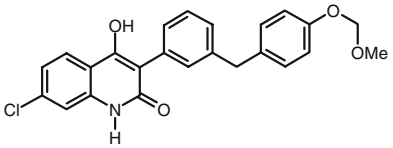
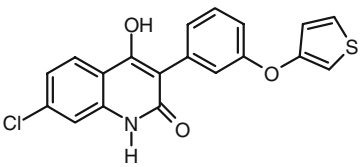
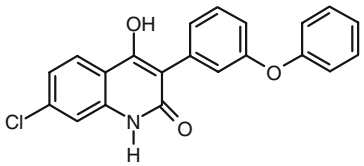
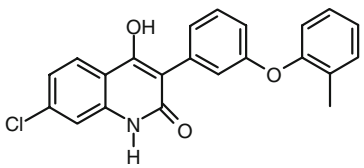


Fig. 1 Atomic numbering scheme in HQ skeleton

Table 1 C3 substituted HQ derivatives

	Structure	log(IC_{50})
1		0.556
2		0.949
3		0.602
4		0.653
5		0.380
6		0.556
7		0.342
8		0.146
9		0.301
10		0.114

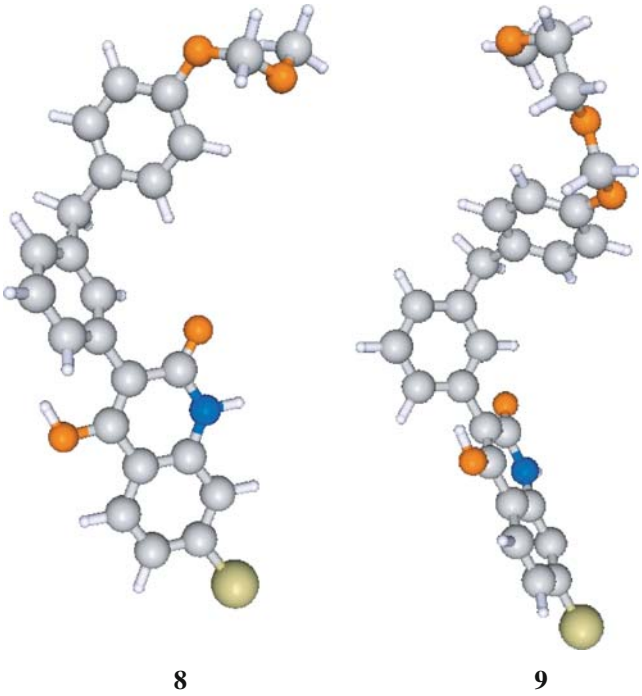


Fig. 2 Helical structure adopted by the hydroxyquinolone derivatives

showing minor effect of aromatic substitution at the adjacent carbon. Investigations on the carbonyl group C_2O_{12} turns out to be more significant. A linear variation of the inhibitory activity of these derivatives with the vibrational frequency of the carbonyl group can be noticed from Fig. 3.

It was pointed out earlier that the MESP (*cf.* Eq 1) brings about the effective localization of electron-rich regions in a molecular system. An isosurface of V=−65.6 kJ.mol^{-1} in different molecules has been depicted in Fig. 4. As is transparent the electron rich region in these ligands is localized near carbonyl oxygen O_{12}. Aromatic substitution at the C_3 position in these ligands engender large electron-

Table 2 Selected B3LYP frequencies for HQ derivatives

	$O_{14}H$	C_2O_{12}	C_4O_{14}
1	3736	1765	1436
2	3719	1753	1441
3	3713	1756	1440
4	3712	1755	1440
5	3718	1764	1439
6	3711	1761	1439
7	3719	1759	1437
8	3713	1763	1442
9	3708	1763	1439
10	3702	1763	1440

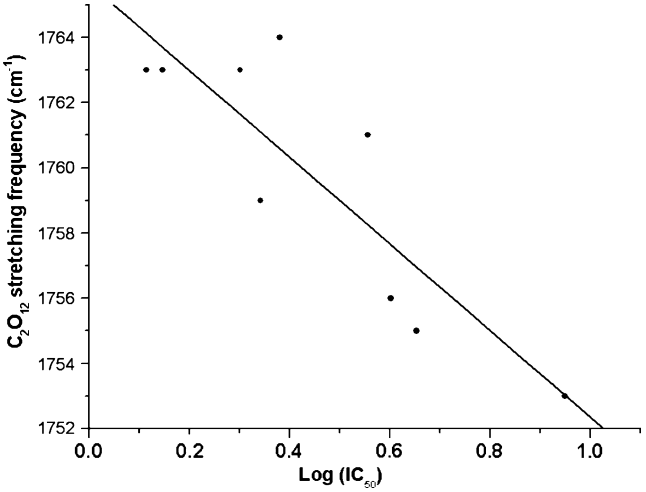


Fig. 3 C_2O_{12} streching frequency (in cm^{-1}) vs Log (IC50)

rich region, which can qualitatively be correlated to inhibition activity. For ligands with a large isosurface which engender greater number of sites for interaction with an electrophile engenders relatively small log(IC_{50}) values [24–26] implying larger inhibition activity.

Tables 3, 4 gives the (3, +3) MESP minima near the carbonyl oxygen O_{12}, hydroxyl oxygen O_{14} and the chloro group at C_7 position. As may be noted O_{12} exhibit deepest minimum in all the ligands. Furthermore the carbonyl oxygen and the chlorine atom in 10 revel deepest minima value in the given series. This may partly be responsible for the better activity profile of this HQ derivative over the other ligands. A plot of MESP minimum near O_{12} against the log(IC50) for the HQ derivatives has been shown in Fig. 5. The dependence of the inhibitory activity of HQ derivatives on MESP minima may be inferred from the plot shown in Fig. 5 and yields a correlation coefficient of 0.91. Variation of vibrational frequency of the carbonyl group with MESP minima as predicted earlier [37] for C_{11} derivatives of hydroxyquinolones has also been confirmed for the this series of C_3 substituted aromatic derivatives (cf. Fig. 6.).

The molecular electron density topography has also been investigated for these ligands. Active participation of the chloro substituent at the C_7 position in governing the inhibitory activity of hydroxyquinolone derivatives can be inferred from the topography of the electron density at the C-Cl bond. A linear variation of the bond critical point value (ρ_{bcp}) for the C_7-Cl bond with the inhibitory activity of these hydroxyquinolone derivatives in terms of Log (IC_{50}) with the correlation coefficient of 0.9 has been predicted (cf. Fig. 7.). Further it has been found that the ρ_{bcp} for different functional groups viz. C_2O_{12}, C_4O_{14} and $O_{14}H$ (also) show marked influence on the inhibitory activity. Hence to get a better understanding of how the

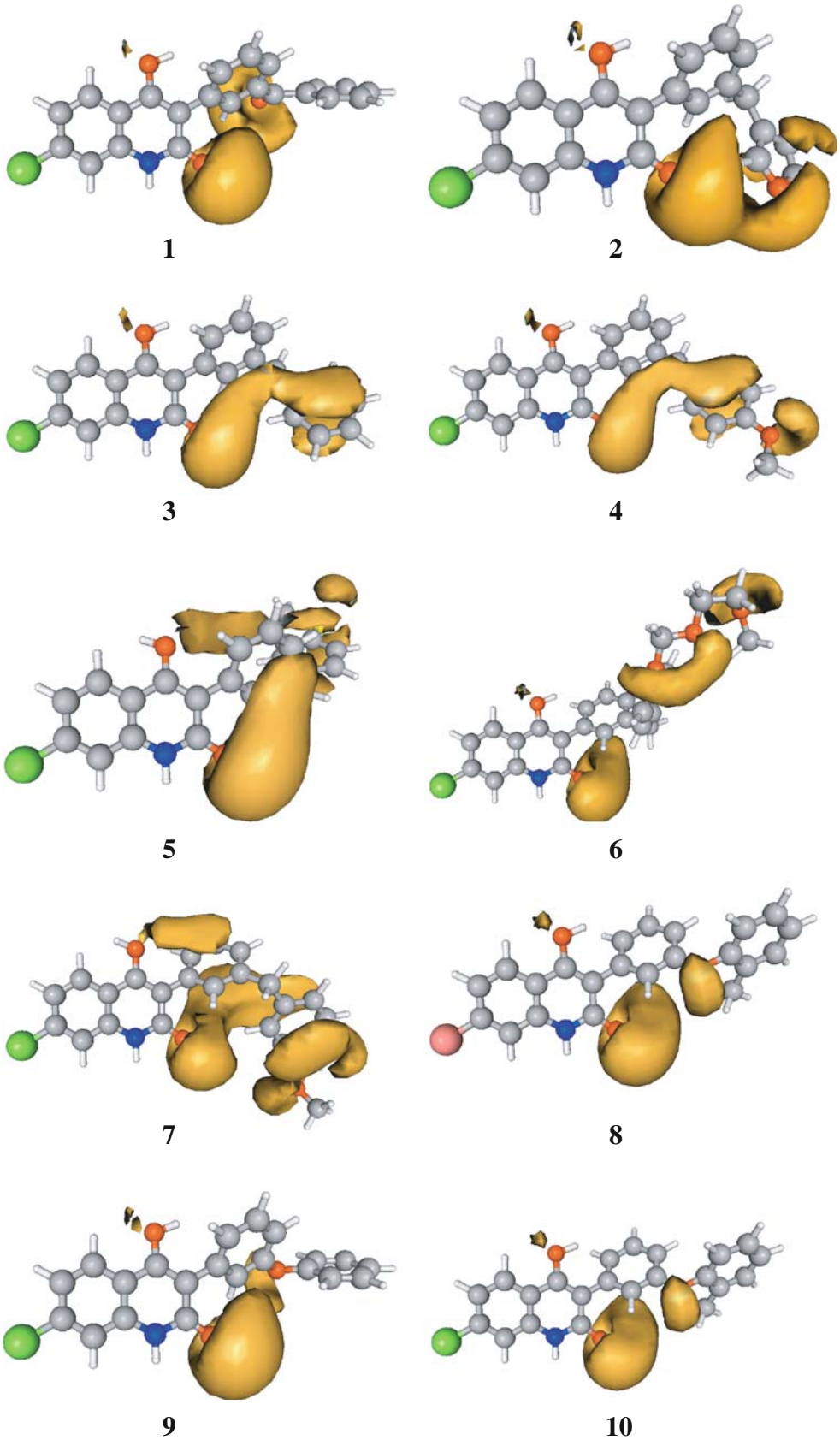


Fig. 4 MESP isosurface (V= – 65.6kJmol^{-1}) in C_3-substituted HQ derivatives

Table 3 MESP minima ($kJmol^{-1}$) fro C_3 substituted HQ derivatives

	O_{12}	Cl_{15}	O_{14}
1	-230.9	-42.3	-84.7
2	-206.9	-40.8	-86.1
3	-223.4	-42	-88.9
4	-224.0	-42	-90
5	-235.8	-29.3	-129
6	-236.6	-44.6	-91.5
7	-229.5	-30.2	-132.2
8	-239.1	-43.6	-72.9
9	-234.8	-43.3	-89.8
10	-245.9	-47.1	-79.1

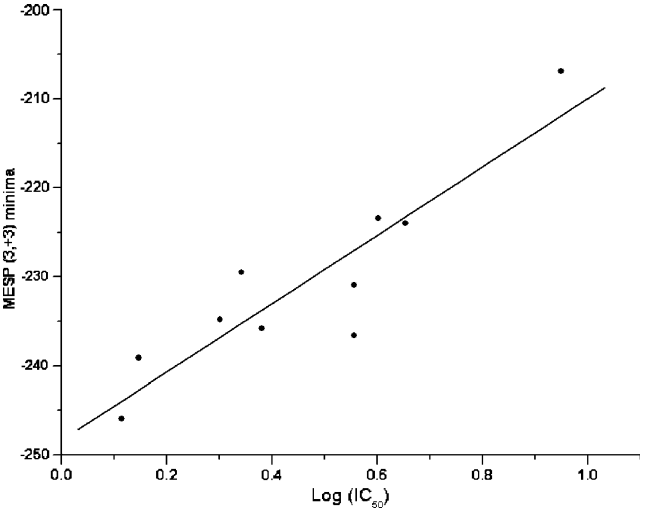


Fig. 5 MESP minima near O_{12} centre vs Log (IC_{50})

electron density topography influence the inhibitory nature of these ligands, we show here all the ρ_{bcp} for different bonds including C-C, C-N, C-Cl, C-O, O-H, N-H as well as C-H bonds of these ligands. As displayed in Fig. 8 these ρ_{bcp} together form an array of points which tends to adopt a helical structure with the increasing size of the ligand and supports the earlier conjectured relation of the helical nature of ligands render them larger biological activity.

Conclusions

The conclusions of this work can be summarized as follows. (i) Aromatic substitution at the C_3 position engenders a minimum on the potential energy surface with a helical structure (locally) for the substituent. (ii) A linear variation of the inhibitory activity of HQ derivatives with the C=O vibrational frequency has been noticed. (iii) Large electron-rich regions extending beyond carbonyl oxygen and the adjacent aromatic substituent yields a better profile towards inhibition. (iv) Inhibitory activity can be correlated linearly to the MESP minima near carbonyl oxygen as well to the bond critical points of the C-Cl bonds.

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Table 4 MED ρ_{bcp} in C_3 substituted HQ derivatives

	C_2O_{12}	C_4O_{14}	$O_{14}H$	C_7Cl
1	0.4027	0.2946	0.3582	0.2642
2	0.4002	0.2953	0.3571	0.2644
3	0.4009	0.2952	0.3569	0.2644
4	0.4008	0.2953	0.3568	0.2643
5	0.4030	0.2894	0.3647	0.2640
6	0.4019	0.2952	0.3567	0.2639
7	0.4021	0.2896	0.3647	0.2645
8	0.4016	0.2946	0.3564	0.2634
9	0.4023	0.2955	0.3566	0.2642
10	0.4017	0.2946	0.3556	0.2632

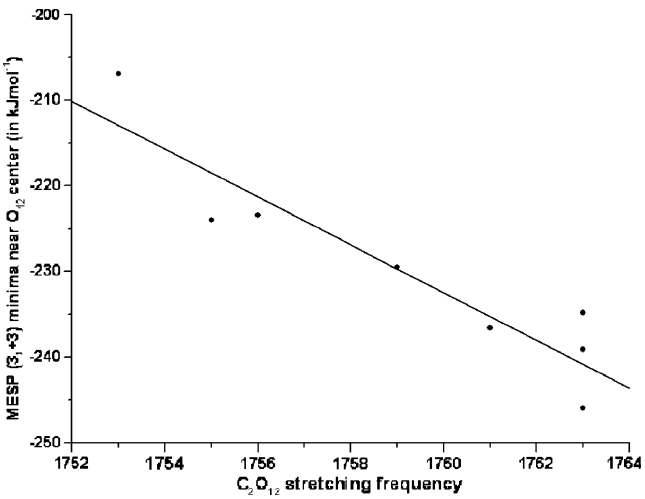

Fig. 6 MESP minima near O_{12} centre vs C_2O_{12} stretching frequency

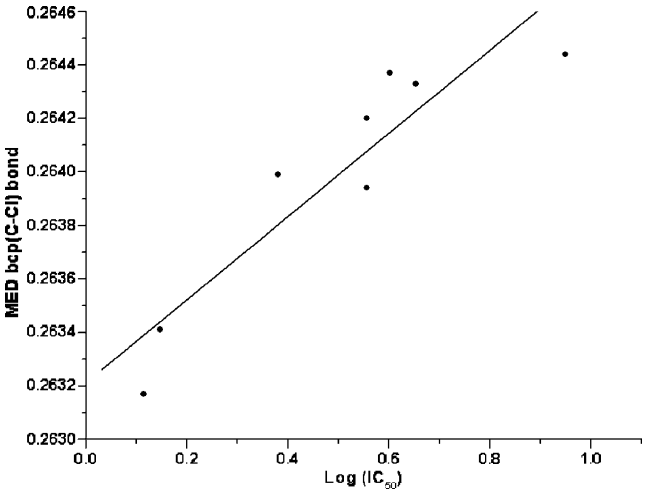

Fig. 7 Bond critical points in the C-Cl bond as a function of log (IC_{50}) value

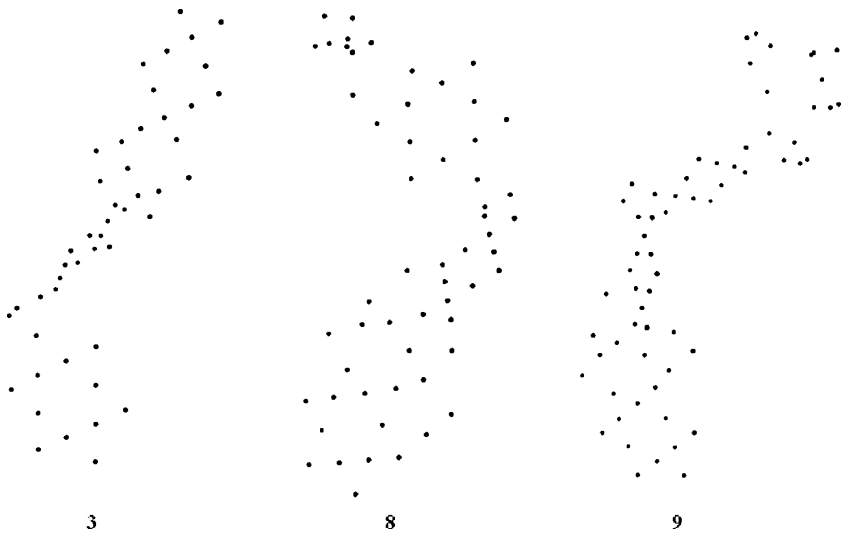

Fig. 8 MED critical points of HQ derivatives displaying the helical structure

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