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Five-membered heterocycles. Part IV: Impact of heteroatom on benzazole aromaticity

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Abstract

To complete a set of 3-D data for phenoxymethyl–benzazoles, molecular structures of respective benzothiazole and benzimidazole were determined using X-ray crystallography. Based on that, the structure and conformation of the benzazole bicycle (6 + 5) with various heteroatoms in position 3 – nitrogen, sulphur or oxygen – are discussed. Subsequently, aromaticity of (6 + 5) bicycles was analyzed on the basis of crystallographic data (our and from CSD) and HOMA index, quantitative estimation of heteroring aromaticity, was calculated. The rings aromaticity is amplified from oxygen to sulphur and nitrogen as the second heteroatom. The dependences between $HOMA_{av}$ indices and respective heteroatom electronegativity were roughly established as second-degree polynomial with maximum in the vicinity of nitrogen. Similar relationship was found between $HOMA_{av}$ and lipophilicity descriptor log *D* (at pH 7.4) for phenoxymethyl–benzoxazole, –benzothiazole, –benzimidazole. Both relationships explain the categorization of the species with various Y according to the location in periodic table of the elements.

Keywords: Aromaticity of heterorings; CSD; X-ray structure; HOMA index

1. Introduction

Our interest in title heterocycles has arisen from prior studies on structures of benzoxazole derivatives [1,2]. The very large set of synthesized analogous compounds contain a number of species [3–5] among which the families of benzoxazoles, benzothiazoles, and benzimidazoles have to be recognized (Scheme 1). Beside benzazole (here abbreviated as bicycle 6 + 5), all molecules comprise also the second ring (mostly substituted phenyl) joined to bicycle directly [6] or by aliphatic chain [1,2]. From practical viewpoint (it means – biological activity potency), the derivatives with diatomic heteroaliphatic spacer $–CH_2–X–$, where $X = O, S, NH$ or CH_2, are the most interesting compounds. That spacer conformation for X = O or S was the subject of previously published studies [2,7]. Therefore, recently our attention is focused on the bicycles with various Y-heteroatoms and identical spacer of $–CH_2–O–$. Thus, the derivatives under discussion fit the category of phenoxymethyl – benz-Y-azoles with Y = O, S or NH.

All species were synthesized and tested as potential antifungal drugs [3–5]. For structure description and for further application in SAR studies, bicyclic heteroring (6 + 5) seems to be essential. First of all, depending on Y-heteroatom, it could act as H-bond acceptor and/or donor not only in the crystal, but also during interactions with biological surroundings. Moreover, bicycle (6 + 5) might be stacked with another planar moiety in any environment. Stacking phenomenon is mostly connected with π–π association of the rings [8] and the involvement in such interactions is limited by rings planarity and aromaticity [9]. Nevertheless, until today, aromaticity of studied set

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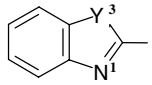
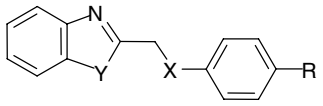


Where:
Y = O, S, NH

Scheme 1.



1	2
Y = S	Y = NH
X = O	X = O
R = Cl	R = Cl

Scheme 2.

of derivatives was rarely examined and only for benzoxazoles [2]. It encouraged us to complete study on bicycles with various second heteroatom, limiting the research to Y = O, S or N.

As it often happens in chemistry, aromaticity concept was born from practical viewpoint and no common interpretation exists as yet. During the last few years, the significant changes in aromaticity concept, newly accepted as a multidimensional phenomenon, were observed [10–14]. Aromaticity is frequently considered as a structural concept [15] but is almost always manifested by some chemical or physicochemical properties. Thus, aromatic systems are thermodynamically more stable than analogous aliphatic ones, which results from aromatic stabilization energy. Moreover, the endocyclic bond lengths tend to assume the intermediate values between the typical ones for single and double bond, which was quantitatively described by various geometrical indices of aromaticity. The majority of techniques for aromaticity estimation, either quantitative or qualitative, were limited to carbon rings and their adaptation to heterorings had led to confusing results for a long time. Last reinterpretation of theoretical basis for aromaticity phenomena and modification of aromaticity indices indicated their possible application to heterorings [16–19]. In this field, also our studies with five-membered heterorings aromaticity on the basis of crystallographic data, using HOMA index as a quantitative measure of aromaticity [20–22], should be mentioned. Until now, we have qualitatively established that the aromaticity of the five-membered heterorings decreases with an increase in heteroatom electronegativity [20]. The average HOMA indices ($HOMA_{av}$) for rings with one heteroatom are ordered as follows: furanes < pyrroles < thiophenes [21]. Furthermore, it have been established that the number of heteroatoms also influences heteroring aromaticity. The aromaticity increases significantly when nitrogen as the second heteroatom has been included to furan, pyrrole or thiophene rings [22].

Simple five-membered rings – oxazole, thiazole or imidazole – are combined with phenyl form (6 + 5) bicycles – benzoxazole, benzothiazole and benzimidazole. The aromaticity of these rings could be determined on the basis of crystallographic data (using HOMA index). The geometrical and conformational examinations of three alternative bicycles (6 + 5), based on our own X-ray studies, seem to be interesting. Moreover, we intended to complement the discussion on the conformational preferences of benzazoles substituted with phenoxymethyl group. Then, we choose to study the structures of benzothiazole and benzimidazole species, as supplement for previously published benzoxazoles [2]. On that ground, the 2-(4-Cl-phenoxymethyl)-benzothiazole **1** and 2-(4-Cl-phenoxymethyl)-benzimidazole **2** were selected for the X-ray structure analysis (Scheme 2).

2. Experimental

2.1. X-ray structure analysis

The compounds **1** and **2** were prepared at Ankara University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry [5]. Crystals of **1** and **2** were obtained by slow evaporation from ethanol solution.

The measurements for **1**–**2** were performed on a KM-4-CCD κ-axis diffractometer with graphite-monochromated MoKα radiation ($\lambda = 0.71073$ Å) [23] at room temperature. Crystallographic data and experimental details are gathered in Table 1. The structures were solved by direct methods using SHELXS [24] program and refined with SHELXTL [25]. E-map provided positions for all non-H-atoms. The full-matrix least-squares refinement was carried out on F^2's using anisotropic temperature factors for all non-H-atoms. The H-atoms were located from $\Delta\rho$-maps, and then their positions were refined in the riding model with isotropic displacement parameters.

Crystallographic data (excluding structural factors) for the structures reported in this paper are deposited in the Cambridge Crystallographic Data Centre and allocated under the deposition numbers: CCDC 623762 and 623763 for compounds **1** and **2**, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EW, UK (fax: Int. code +1223 336 033; e-mail:deposit@ccdc.cam.ac.uk).

2.2. Conformational calculations

The conformational calculations were performed with the application of molecular mechanics [26]. The calculations were carried out in the range of torsion angles from −180° to +180° with 10° increments. The crystallographically obtained structures were used as an initial conformation of studied molecules.

2.3. HOMA index calculations and data retrieval and arrangement

All calculations were performed using MS Excel®. Authors created suitable calculation sheet for Eq. (1):

$$HOMA = 1 - \alpha(R_{opt} - R_{av})^2 - \alpha/n \sum (R_{av} - R_i)^2 \qquad (1)$$

Table 1
Crystal data and structure refinement details for **1**–**2**

	1	**2**
Empirical formula	$C_{14}H_{10}N$–O–S–Cl	$C_{14}H_{11}N_2O$–Cl
Chemical name	2-(4-Cl-phenoxymethyl) benzothiazole	2-(4-Cl-phenoxymethyl) benzimidazole
Formula weight	275.75	258.70
Temperature		293 K
Radiation		Mo(Kα) = 0.71073 Å
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/c$
Unit cell dimensions	$a = 10.4121(16)$ Å	$a = 8.5168(19)$ Å
	$b = 3.9463(9)$ Å	$b = 16.575(4)$ Å
	$c = 30.730(5)$ Å	$c = 9.875(3)$ Å
	$\beta = 95.710(13)°$	$\beta = 113.11(2)°$
Volume (Å)^3	1256.4(4)	1282.2(6)
Z, calculated density (g/cm^3)	4, 1.458	4, 1.340
μ(mm^{-1})	0.455	0.286
$F(000)$	568	536
Crystal size (mm)	$0.2 \times 0.1 \times 0.1$	$0.2 \times 0.1 \times 0.06$
Theta range for data collection	2.7–25.0	2.5–25.0
Index ranges	$-12 \leqslant h \leqslant 12$; $-4 \leqslant k \leqslant 4 - 36 \leqslant l \leqslant 36$	$-10 \leqslant h \leqslant 10$; $-19 \leqslant k \leqslant 19$; $-10 \leqslant l \leqslant 11$
Diffractometer		KM-4 with CCD detector
Reflection collected/unique	12395/2232	10048/2243
	[$R_{int} = 0.039$]	[$R_{int} = 0.071$]
Data/parameters	2232/163	2243/164
Refinement method		Full-matrix-block least-squares on F^2
S (on F^2)	1.04	0.79
R_1, wR_2 [$I > 2\sigma(I)$]	0.0398, 0.0934	0.0391, 0.0707
Weighting scheme	$w = 1/[\backslash\sigma^2 (F_o^2) + (0.0432\ P)^2 + 0.3943\mathrm{P}]$ where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2 F_o^2) + (0.0270P)^2$ where $P = (F_o^2 + 2F_c^2)/3$
$\Delta\rho$ min i max (e Å^{-3})	−0.22, 0.22	−0.12, 0.14
Max. and av. shift/error	0.00, 0.00	0.00, 0.00

where n is the number of bonds taken into summation and α is an empirical constant fixed to give HOMA = 0 for the hypothetical Kekule structures of aromatic systems, and HOMA = 1 for the system with all bonds equal to the optimal value R_{opt}. R_{av} stands for the average bond length, while the individual bond length is represented by R_i [27,28].

General search constraints ensured that for all retrieved entries: (i) CSD checks showed no numerical errors; (ii) there was no disorder in the structure; (iii) the crystallographic R value is less than 0.075; (iv) entry was classified chemically as an organic compound; (v) no powder structures were taken into consideration. The search of CSD (CSD, version 5.27 of May 2006) [29] gave us 608 structures containing various bicycle (6 + 5) heterorings with N, O, and S atoms. Trial data sets were generated *via* the *QUEST* program [30]. The statistics of CSD studies is collected in Table 2.

3. Results and discussion

3.1. X-ray structures of *1* and *2*

An ORTEP plot of investigated molecules (with atoms numbering) is shown in Fig. 1. Selected geometrical data are collected in Table 3. Since subsequent examination is addressed to the set of benzoxazoles, benzothiazoles, and benzimidazoles, it was compulsory to include as well the geometrical data for previously published 6-methyl-2-(phenoxymethyl) benzoxazole [2] into Table 3. The basic skeleton of all molecules under discussion consists of two cyclic moieties – bicycle (6 + 5) and phenyl – linked together *via* diatomic spacer. In bicyclic (6 + 5), simple five-membered rings – oxazole, thiazole or imidazole – are combined with phenyl. The coupled rings are planar. The maximal random deviation from planes, which are fixed by the atoms of five-membered rings, is observed for benzoxazole

Table 2
Number of structures found in CSD for various bicyclic (6 + 5) (+structures from present studies) and descriptors used in aromaticity rationalization

(6 + 5) Bicycle	Y atom in the ring	No. of structures in CSD	Electronegativity of the hetero-element (Pauling's scale)	log D at pH 7.4 for phenoxymethyl-derivated [31]
Benzoxazole	O	71	3.44	3.11
Benzothiazole	S	178 + 1	2.58	3.52
Benzimidazole	N	341 + 1	3.04	3.03

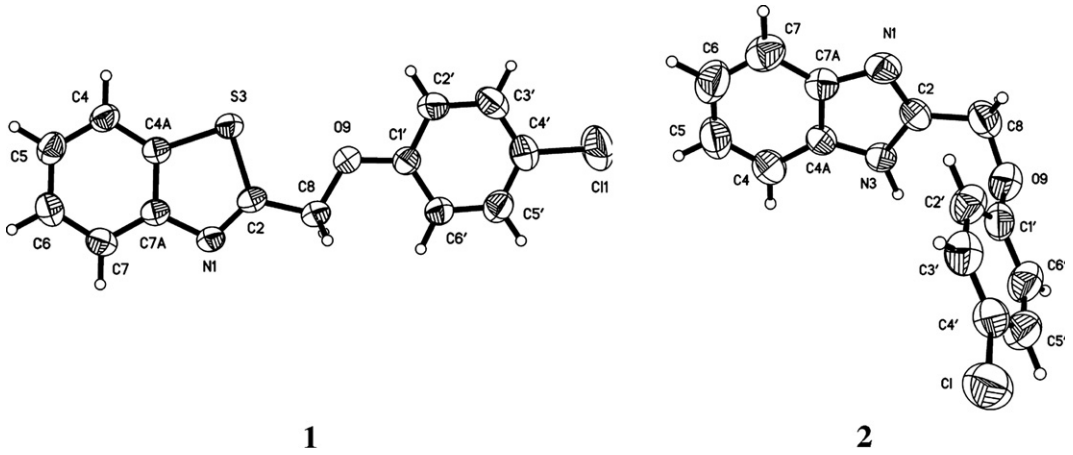


Fig. 1. ORTEP drawing of 1 and 2 molecules.

Table 3
Selected geometrical data for phenoxymethyl–benzoxazole [2], -benzothiazole (**1**) and -benzimidazole (**2**)

	Benzoxazole [2] Y = O	Benzothiazole (**1**) Y = S	Benzimidazole (**2**) Y = NH
(a) *Bicycle (6 + 5)*			
Random deviation from five-membered ring plane (Å)	0.0071	0.0011	0.0054
Dihedral angle between rings (6 + 5) (°)	0.88(2)	0.24(1)	2.50(2)
(b) *Bond lengths (Å) and angles (°) in five-membered heteroring*			
Y–C2	1.360(3)	1.733(2)	1.343(4)
Y–C4a	1.385(3)	1.726(2)	1.374(4)
N1–C2	1.296(3)	1.285(3)	1.316(4)
N1–C7a	1.400(3)	1.388(3)	1.385(4)
C4a–C7a	1.370(4)	1.394(3)	1.389(4)
C4a–Y–C2	101.1(2)	88.7(1)	107.3(3)
Y–C2–N1	115.6(2)	116.7(2)	113.0(3)
(c) *Molecule conformation*			
$\Phi 1$ = C2–C8–O9–C1′ [°]	175.8(2)	−175.2(2)	−70.8(2)
$\Phi 2$ = Y–C2–C8–O9 [°]	−58.4(4)	4.1(3)	−29.8(3)

(0.007 Å). The values of torsion angles in five-membered rings are flocculating from 1.96° to 1.62°. The impact of heteroatom Y on that ring geometry is visible, as it was expected, on the bonds lengths and angles values. Thus, the dimensions of the rings with Y = O, N (second period elements) are similar, while ring with sulphur (third period element) is significantly larger. Regardless of that, the sulphur atom stretches S–C bond, and thiazole is the most planar among the discussed rings (Table 3). All these differences are clearly visible from superimposition in Fig. 2. The insignificant inclinations of both saturated rings have proven the planarity of the bicycles (6 + 5). The bond lengths within the five-membered rings (Table 3) can be easy compared with average values of adequate bond lengths taken from the CSD and optimal values characterizing aromatic bonds (Table 4). Thus, those bonds are the conjugated ones.

The whole molecule conformation is controlled by the spacer and would be characterized by two torsion angles $\Phi 1$ = C2–C8–O9–C1′ and $\Phi 2$ = Y–C2–C8–O9. The angle $\Phi 1$ = C2–C8–O9–C1′ is responsible for –CH_2–O– chain conformation, while $\Phi 2$ = Y–C2–C8–O9 explains mutual

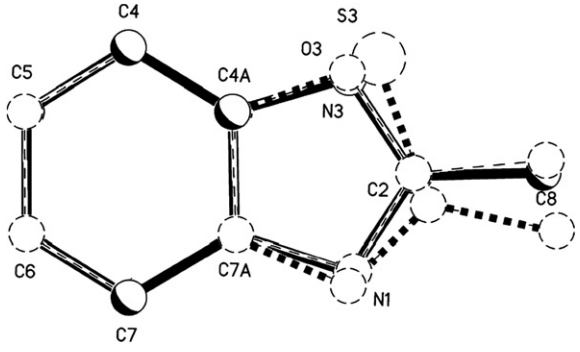


Fig. 2. Superimposition of benzoxazole, benzothiazole and benzimidazole moieties with respect to benzene ring atoms.

Table 4
Reference bond lengths used for HOMA calculations [28]

	Reference bond lengths (Å)		
	Double	Single	Optimal
N–C	1.269	1.465	1.388
O–C	1.217	1.367	1.265
S–C	1.611	1.807	1.677

position of both heteroatoms – Y and O9. If $Y = O$ or S, anti-periplanar (or extended) form of the molecule with $\Phi 1 \sim \pm 180°$ is promoted (Table 3). The syn-clinal position of O3 and O9 in benzoxazole is confirmed by the angle $\Phi 2 = O3–C2–C8–O9$ equaling $-58.4(4)°$. For **1**, $\Phi 2 = S3–C2–C8–O9$ of $4.1(3)°$ was found and it corresponds rather to syn-periplanar conformation. The molecule of **2** with $Y = NH$ adopts syn-clinal (or folded) form possessing $\Phi 1 = -70.8(2)°$. Both nitrogens (N1 and N3) in molecule **2** are syn-periplanar with $\Phi 2 = N3–C2–C8–O9 = -29.8(3)°$. In the last structure, H-bond employing N3 atom was identified. Thus, the intermolecular H-bonds of $N3–H3 \ldots N1(x, 3/2 - y, -1/2 + z)$ of 2.800(3) Å join molecules into infinitive chain.

To obtain the full set of all possible conformations, surface energy of the molecule has to be examined. Then, using crystallographic conformation as a starting one, energy changes with rotations of $\Phi 1$ and $\Phi 2$ angles were calculated (Fig. 3a–c). On the final maps, stars mark crystallographic forms and all of them are close to the one of the energy minimum. There is no global energy minimum on none of the three maps. However, independently of Y-heteroatom, four minima at $\Phi 1 \pm 180°$ and $\pm 60°$ are observed on all surfaces. Therefore, $–CH_2–O–$ chain is able to adopt either extended or folded form in all phenoxymethyl–benzazoles. Both forms are capable of setting various locations of two heteroatoms in the chains –Y–C2–C8–O9–, distinguished by the value of angle $\Phi 2$. Such angle on the maps for $Y = O$ or S (Figs. 3a and b) is restricted to syn-clinal forms with angles equaling $\pm 60°$. The impact of sulphur is visible in minima shallows and, consequently, smaller energy barriers between minima. For $Y = NH$, two wide minima at $\Phi 2 \sim 0°$ indicate the syn-periplanar conformation (Fig. 3c), either for folded or extended spacer $–CH_2–O–$. It should be mentioned that these minima are sufficiently wide to hold also more screw forms.

3.2. Aromaticity calculations

Considering that (6 + 5) skeletons in benzoxazoles, benzothiazoles and benzimidazoles are flat with coupled bonds, the calculations of HOMA indices for five-membered rings and for (6 + 5) bicycle were performed. For the bicyclic systems, the HOMA indices were calculated as global values (for whole molecule). The calculations for structures (our and found in CSD) were done tidily, separately for five-membered rings and for respective bicycles. The results of all HOMA value calculations were summarized graphically in Fig. 4. This diagram presents relationship between HOMA values and respective average endocyclic Y–C(sp^2) bonds lengths. After several trials that relationship was accepted as the most helpful in further discussion. The average HOMA values calculated separately for each group of the rings with studied heteroatoms are given in Scheme 3.

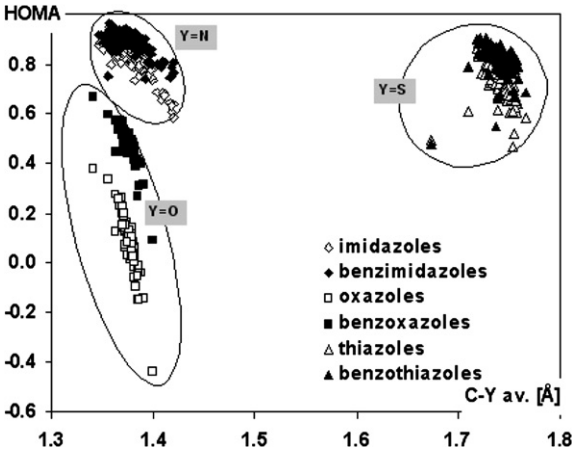
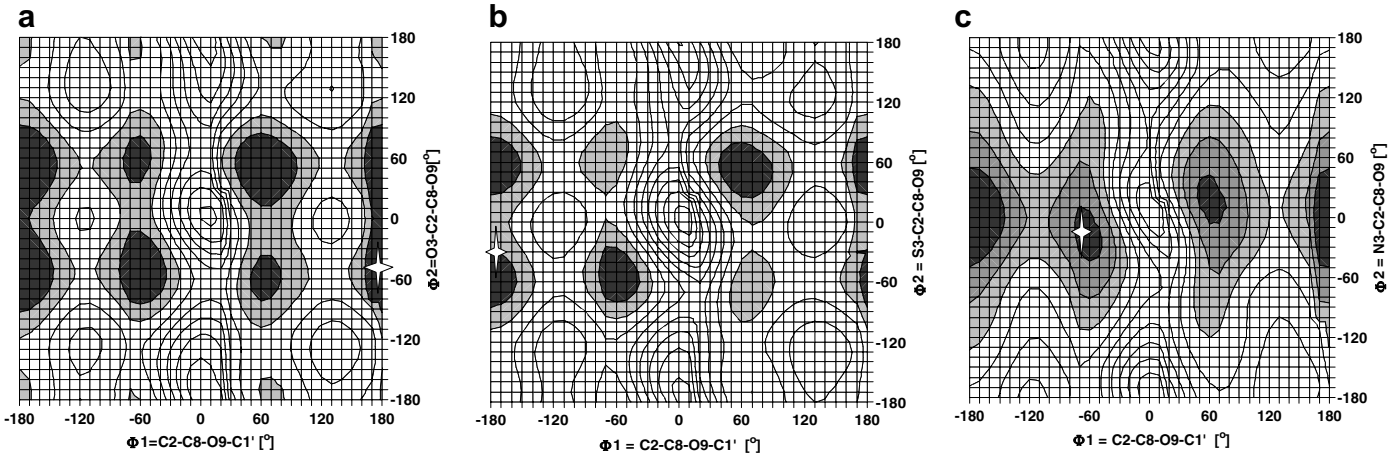
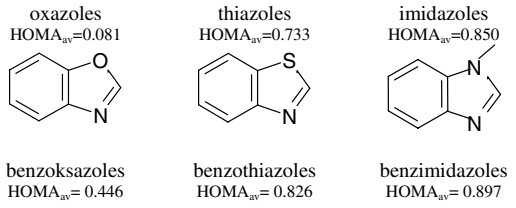


Fig. 4. Scattegram of HOMA values *vs.* average Y–C(sp^2) bond lengths.



Phenoxymethyl-benzoxazole Phenoxymethyl-benzothiazole Phenoxymethyl-benzimidazole

Fig. 3. Conformational energy surface. Equienergetic lines are drawn for every 0.5 kcal/mol.



Scheme 3.

The results of HOMA index calculation confirm our previous conclusions [22]. Regardless of the type of the ring system (single or fused), aromaticity increases with following order of Y – heteroatom: from oxygen through sulphur to nitrogen. However, the bicycle (6 + 5) aromaticity is always higher than that for the single five-membered ring. This is the consequence of the 5-membered ring fusion with fully aromatic phenyl. Even though the HOMA index is geometry-based parameter, the concept of aromaticity is multidimensional and selected carefully 'dimensions' have to be coupled in mathematically defined regression with HOMA index [31]. To find dependence between aromaticity and one of such 'dimensions' – electronic property of atom, in this case – electronegativity – was taken into consideration. The results are shown in Fig. 5a, where $HOMA_{av}$ indices for investigated five-membered rings and bicycles (6 + 5) *vs.* electronegativity of Y-heteroatom (according to Pauling's scale) are depicted. We concluded that too high (above 3.5 for oxygen) electronegativity of the heteroatom in the heteroaromatic ring systems cause the dramatic aromaticity decrease. Due to the fact, that only three kinds of heteroatoms were taken into consideration, we are able to discuss only the possible character of dependence between aromaticity and electronegativity. Nevertheless the points localization in the graph suggest that such dependence is not linear and can be roughly described by second-degree equation. It should be emphasized that it is a starting hypothesis, which will be a subject of our future investigation with expanded set of investigated objects. One must also remember also that however the value of electronegativity for nitrogen equals 3.04, this value is given for unsubstituted atom and every substituent can significantly change it.

The biological aspect of benzazole synthesis [3–5] has authorized us to search for the relationship between average aromaticity for bicycles (6 + 5) and the classical QSAR parameters as well. Hammett or Hansch's constants seem to be the most interesting [32,33]. Since lipophilicity – defined by log *P*, log *D* (at pH = 7.4 or 7), and pKa – is usually calculated from the partial π-constants of the molecule [34], the possible relationships between aromaticity and such descriptors are sensible. After several trials, the log *D* at physiological conditions, pH 7.4, was selected as the best descriptor. The values of log *D* at pH 7.4 for three phenoxymethyl–benzazoles were gathered in Table 2. The relation between $HOMA_{av}$ and log *D* (at pH 7.4) has also categorized Y-elements according to the location in periodic table (Fig. 5b) and can be roughly described by second-degree expression.

4. Conclusions

The impact of Y-heteroatom (where Y = O, S or N) on benzazole properties is drawing the inspiration for subsequent studies. Truthfully, the aromaticity – presented by HOMA indices – increases with order of Y – heteroatom: from oxygen through sulphur to nitrogen. But comparative geometrical data for respective rings and relationships between aromaticity HOMA indices and Y-heteroatom electronegativity or hydrophobic properties of the respective chemical species have categorized Y-elements according to the location in periodic table of the elements. Those categories are also visible in the scattegram from Fig. 4. Keeping in mind that the number of Y-elements is too small for generalization, we intend to expand our stud-

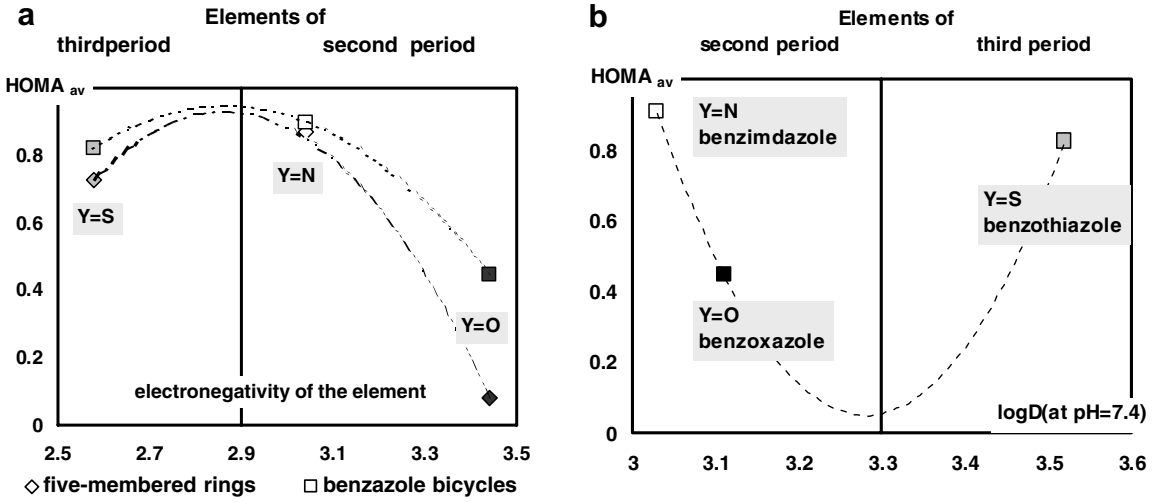


Fig. 5. Relation between $HOMA_{av}$ and (a) Y-heteroatom electronegativity (Pauling's scale); (b) lipophilicity of respective phenoxymethyl–benzazoles.

ies to include phosphorus as additional element from third period. The paper, discussing this subject, will be published in special edition of Polish. J. Chem., addressed to Prof. M. Krygowski's 70-th birthday jubilee [35].

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