*Chemistry Research Journal*, 2018, 3(4):169-175

*Available online www.chemrj.org*

**Research Article**

**ISSN: 2455-8990**
**CODEN(USA): CRJHA5**

# A Note on the Binding of N-2-Methoxybenzyl-phenethylamines (NBOMe Drugs) to the 5-$HT_{2C}$ Receptors

**Juan S. Gómez-Jeria*, Camila Moreno-Rojas, Pablo Castro-Latorre**

Quantum Pharmacology Unit, Department of Chemistry, Faculty of Sciences, University of Chile, Las Palmeras 3425, Santiago 7800003, Chile

**Abstract** A study of the relationships between electronic structure and $5HT_{2C}$ receptor binding affinity was carried out for a group of N-2-methoxybenzyl-phenethylamines with the Klopman-Peradejordi-Gómez method. A statistically significant equation was obtained. The analysis strongly suggests that the variation of affinity with modifications of the ethylamine side chain is a task that must be continued to be explored with new substituents.

**Keywords** KPG method, NBOMe, 25-NB, serotonin, 5-$HT_{2C}$ receptor, receptor affinity, hallucinogens, QSAR, molecular interactions.

## Introduction

The 25-NB or NBOMe (abbreviation for N-methoxybenzyl) series is a family of serotonergic psychedelics. Most of them are extremely potent and highly selective for the 5-$HT_{2A}$ receptor. Let us remember that it is generally accepted that the activation of the 5-$HT_{2A}$ receptor is the mediator of the subjective and behavioral effects of hallucinogens.

In previous works we have obtained interesting results concerning the relationships between electronic structure and receptor affinities for various molecular systems and serotonin receptors [1-12]. Recently we obtained good relationships for the interaction of 2,5-dimethoxyphenethylamines and their N-2-methoxybenzyl-substituted analogs with 5-$HT_{2A}$ and 5-$HT_A$ serotonin receptors [1, 13]. In this note we present the results of a study of the interaction of N-2-methoxybenzyl-phenethylamines with 5-$HT_{2C}$ receptors.

## Methods, Models and Calculations

### Molecules Selected

The molecules and their 5-$HT_{2C}$ receptor binding results were taken from a recent publication, and are presented in Fig. 1 and Table 1 [8].

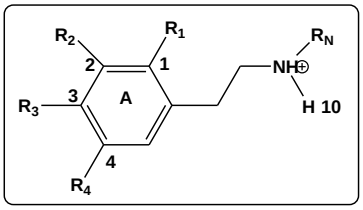


*Figure 1: General formula of the molecules used in this study ($R_N$= 2-methoxybenzyl)*

**Table 1:** N-2-methoxybenzyl-substituted analogs of 2,5-dimethoxyphenethylamines and their 5-$HT_{2C}$ receptor binding affinity.

| Mol. | Name | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $\log(K_i)$ 5-$HT_{2C}$ |
|---|---|---|---|---|---|---|
| 1 | 25B-NBOMe | OMe | H | Br | OMe | -2.21 |
| 2 | 25C-NBOMe | OMe | H | Cl | OMe | -2.28 |
| 3 | 25D-NBOMe | OMe | H | Me | OMe | -1.89 |
| 4 | 25E-NBOMe | OMe | H | Et | OMe | -2.14 |
| 5 | 25H-NBOMe | OMe | H | H | OMe | -0.89 |
| 6 | 25I-NBOMe | OMe | H | I | OMe | -2.34 |
| 7 | 25N-NBOMe | OMe | H | $NO_2$ | OMe | -1.68 |
| 8 | 25P-NBOMe | OMe | H | *n*-Pr | OMe | -2.22 |
| 9 | 25T2-NBOMe | OMe | H | SEt | OMe | -2.19 |
| 10 | 25T4-NBOMe | OMe | H | S-*i*-Pr | OMe | -1.80 |
| 11 | 25T7-NBOMe | OMe | H | S-*i*-Pr | OMe | -2.19 |
| 12 | Mescaline-NBOMe | H | OMe | OMe | OMe | -0.19 |

**Calculations [**14]

The electronic structure of all molecules was calculated within the Density Functional Theory (DFT) at the B3LYP/6-31g(d,p) level with full geometry optimization of the protonated form. The Gaussian suite of programs was used [15]. All the information needed to calculate numerical values for the local atomic reactivity indices needed in the Klopman-Peradejordi-Gómez model [16, 17] was obtained from the Gaussian results with the D-Cent-QSAR software [18]. All the electron populations smaller than or equal to 0.01 e were considered as zero [19]. Negative electron populations coming from Mulliken Population Analysis were corrected as usual [20]. Since the resolution of the system of linear equations is not possible because we have not enough molecules, we made use of Linear Multiple Regression Analysis (LMRA) techniques to find the best solution. For each case, a matrix containing the dependent variable (the receptor affinity) and the local atomic reactivity indices of all atoms of the common skeleton as independent variables was built (see Refs. [21] for details about the building of data matrix). The Statistica software was used for LMRA [22].

We employed the *common skeleton hypothesis* stating that there is a group of atoms, common to all molecules analyzed, accounting for nearly all the binding affinity. The action of the substituents consists in modifying the electronic structure of this common skeleton and influencing the right alignment of the drug throughout the orientational parameters. The common skeleton for this case is shown in Fig. 2.

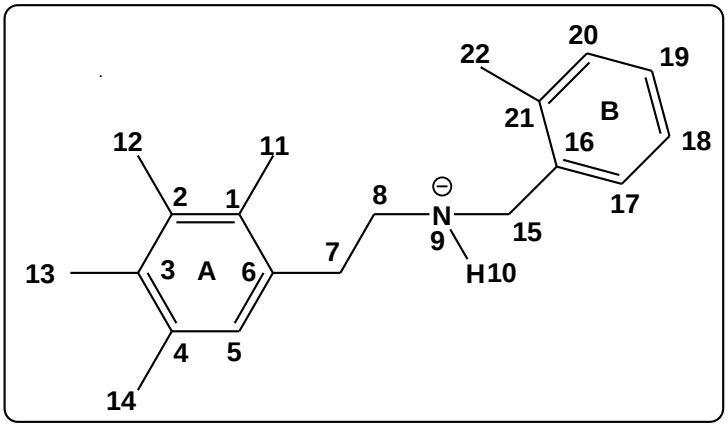


*Figure 2: Common skeleton numbering*

**Results**

The best statistically significant equation obtained is the following:

$$\log(K_i) = -12.59 + 0.003S_{15}^{N} + 1.34\eta_9 + 0.25\eta_8 \quad (1)$$

with n=12, R= 0.97, $R^2$=0.93, adj-$R^2$=0.91, F(3,8)=37.70 (p<0.00005) and a standard error of the estimate of 0.20. No outliers were detected and no residuals fall outside the ±2σ limits. Here, $S_{15}^{N}$ is the total atomic nucleophilic superdelocalizability, $\eta_9$ is the local atomic hardness of atom 9 and $\eta_8$ is the total atomic hardness of atom 9. Tables 2 and 3 show the beta coefficients, the results of the t-test for significance of variable and the matrix of squared correlation coefficients for the variables of Eq. 1. There are no significant internal correlations between independent variables (Table 3). Figure 3 displays the plot of observed *vs.* calculated log($K_i$).

**Table 2:** Beta coefficients and t-test for significance of coefficients in Eq. 1

| | **Beta** | **t(8)** | **p-level** |
|---|---|---|---|
| $S_{15}^{N}$ | 0.96 | 9.86 | 0.000009 |
| $\eta_9$ | 0.37 | 4.00 | 0.004 |
| $\eta_8$ | 0.32 | 3.25 | 0.01 |

**Table 3:** Matrix of squared correlation coefficients for the variables in Eq. 1

| | **$S_{15}^{N}$** | **$\eta_9$** | **$\eta_8$** |
|---|---|---|---|
| $S_{15}^{N}$ | 1.00 | | |
| $\eta_9$ | 0.00 | 1.00 | |
| $\eta_8$ | 0.12 | 0.03 | 1.00 |

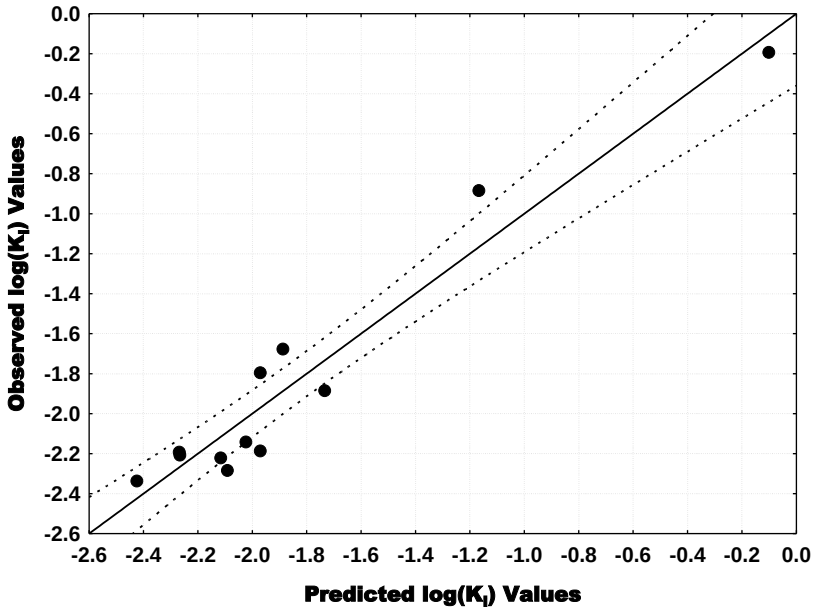


*Figure 3: Plot of predicted vs. observed log($K_i$) values (Eq. 1). Dashed lines denote the 95% confidence interval*

The associated statistical parameters of Eq. 1 indicate that this equation is statistically significant and that the variation of the numerical values of a group of three local atomic reactivity indices of atoms of the common skeleton explains about 91% of the variation of log($K_i$). Figure 3, spanning about 2.4 orders of magnitude, shows that there is a good correlation of observed *versus* calculated values.

**Local Molecular Orbitals**

Table 4 shows the local MO structure of atoms 8, 9 and 15 (see Fig. 2). Nomenclature: Molecule number (HOMO) / (HOMO)* - (LUMO)*.

**Table 4:** Local molecular orbitals of atoms 8, 9 and 15

| Mol. | Atom 8 (C) | Atom 9 (N) | Atom 15 (C) |
|---|---|---|---|
| 1 (98) | 98σ-100σ | 94σ- 99σ | 94σ- 99σ |
| 2 (89) | 89σ- 91σ | 85σ- 90σ | 85σ- 90σ |
| 3 (85) | 84σ- 88σ | 82σ- 86σ | 82σ- 86σ |
| 4 (89) | 89σ- 92σ | 86σ- 90σ | 86σ- 90σ |
| 5 (81) | 80σ- 82σ | 78σ- 82σ | 78σ- 82σ |
| 6 (107) | 107σ-108σ | 104σ-108σ | 102σ-108σ |
| 7 (92) | 89σ- 93σ | 86σ- 94σ | 86σ- 94σ |
| 8 (93) | 93σ- 94σ | 90σ - 94σ | 90σ- 94σ |
| 9 (97) | 95σ- 98σ | 93σ- 98σ | 93σ- 98σ |
| 10 (97) | 95σ- 98σ | 93σ- 98σ | 93σ- 98σ |
| 11 (101) | 101σ-102σ | 97σ-102σ | 97σ-102σ |
| 12 (89) | 89σ - 90σ | 85σ- 90σ | 85σ- 90σ |

**Discussion**

Table 2 shows that the importance of variables in Eq. 1 is $S_{15}^{N} >> \eta_9 > \eta_8$.An analysis of Eq. 1 suggests that a high receptor affinity is associated with small positive values of $S_{15}^{N}$, $\eta_9$ and $\eta_8$.The first important and interesting fact to note is that only atoms of the chain linking rings A and B of Fig. 2 appear in Eq. 1. Moreover, these three atoms possess only σ molecular orbitals. This is in agreement with the results of our previous works. Atom 15 is the carbon atom linking ring B with the N atom of the chain (Fig. 2). From previous considerations, the dominant term in the total atomic nucleophilic superdelocalizability is the lowest empty local molecular orbital, ($LUMO_{15}$*) [16]. A small value for $S_{15}^{N}$ can be obtained by lowering the numerical value of the Fukui index corresponding to $LUMO_{15}$*, $F_{15}$(LUMO)*. This means that this atom will behave as a bad electron acceptor. In the limit situation we may find an appropriate substitution to remove the actual $LUMO_{15}^{*}$, replacing it by the following upper empty local MO: $(LUMO+1)_{15}^{*}$ becomes now $LUMO_{15}^{*}$. The other possibility is to increase $LUMO_{15}^{*}$ energy. This requirement could correspond to the interaction between empty orbitals (zero-electron), which are usually repulsive but become attractive after charge transfer to or from the receptor macromolecule [23]. In this case charge transfer is difficult by the nature of the MOs involved (σ-σ and/or σ-π and/or σ-π bonds) and we may think only in weak interactions. It is possible to suggest that the linking chain is facing a region with sigma molecular orbitals, region that could be formed by amino acids' alkyl side chains (i.e. $CH_2$ groups). Table 4 shows that in all cases but one the local LUMO* coincides with the molecules' LUMO. We must note that the positively charged amine region was probably attracted toward a negatively charged region during the earlier stages of the drug-receptor interaction [17]. At the end of the process, when the molecule is momentarily docked to the receptor, the amine hydrogen undergo through specific interactions, such as the ones showed in our study of the docking of some hallucinogens to the $5\text{-}HT_{2A}$ receptor [11]. Atom 9 is the nitrogen atom in the chain linking rings A and B (Fig. 2). A low positive numerical value of $\eta_9$ is associated with high affinity. By definition, the local atomic hardness $\eta_9$ corresponds to the $HOMO_9^{*}$-$LUMO_9^{*}$energy gap. There are three ways to obtain lower values for this index: lowering the $LUMO_9^{*}$ energy, lowering the $HOMO_9^{*}$ energy or by both procedures simultaneously. Table 4 shows that in almost all cases the local $LUMO_9$* coincides with the molecules' LUMO and that the local $HOMO_9^{*}$ is energetically far from the molecules' HOMO. Therefore, the fastest way to proceed is to localize the molecular HOMO on atom 9. This means that this nitrogen atom will increase its electron donor capacity and, if N-H is facing an oxygen atom for example, the possibility of a hydrogen bond arises [11, 24]. Atom 8 is one of the carbon atom of the linker of ring A and the nitrogen atom (Fig. 2). Given that the condition of a low value for $\eta_8$ is similar to the case just discussed, the reasoning to obtain lower values is analogous. But now Table 2 shows now that in almost two thirds of the cases the local $LUMO_8$* coincides with the molecules' LUMO and that almost in half of the cases the local $HOMO_8^{*}$ coincides with the molecules' HOMO. Therefore, we are in presence of four different cases. In the first one, the local atomic frontier molecular orbitals coincide with the molecules' frontier molecular orbitals. Here, one way to

proceed to diminish the $HOMO_8^*$- $LUMO_8$* energy gap is by substituting in such a way that the $HOMO_8^*$ and/or $LUMO_8$* energies decrease (i.e., their energies approach zero). Another way is to substitute the molecule to introduce new molecular orbitals having a lower energy than the original frontier MOs. In the second case neither $HOMO_8^*$ nor $LUMO_8$* coincide with the molecules' frontier MOs. Here the technique consists in lowering the $HOMO_8^*$ and/or $LUMO_8$* energies. In the third case only $HOMO_8^*$ do coincide with the molecular HOMO. Therefore, we need to lower the $LUMO_8$* energy, making this MO more reactive. In the last case only $LUMO_8$* coincides with the molecular LUMO. Here we need to lower the $HOMO_8^*$ energy, making this MO more reactive. Note the interesting fact that at this level of the discussion we are not able to determine who, $HOMO_8^*$ or $LUMO_8$*, is the most important factor. If we consider that $C_8$ is in fact a $CH_2$ group we may think in weak CH-O, CH-N and/or CH-π bonds [24, 25]. Another possibility is that $C_8$ be involved in two simultaneous interactions involving its two frontier local MOs. We think that the only way to solve definitively this problem is by synthesizing and testing new molecules.All the suggestions are displayed in the partial 2D pharmacophore of Fig. 4.

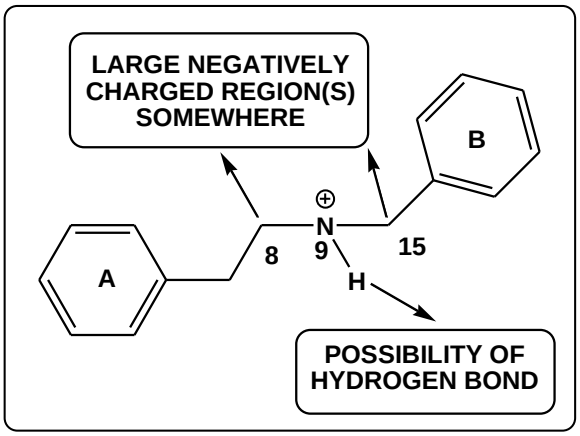


*Figure 4: Partial 2D pharmacophore for the interaction of N-2-methoxybenzyl-phenethylamines with 5-$HT_{2C}$ receptors*

The main conclusion of this work is that the electronic properties of the chain linking rings A and B seems to be extremely important in regulating receptor affinity. This is important because the class of substituted phenethylamines includes, among others, the substituted amphetamines and substituted methylenedioxyphenethylamines. Also this class contains mescaline and its derivatives. Some derivatives with methyl groups at positions 8 and 9 are known. The question that remains to be analyzed is the exact role of ring B in the high receptor affinity. Is this ring interacting with an extra site of the 5-$HT_{2C}$ receptor? Is this aromatic system modifying the σ MO structure of the whole molecule and especially of the original ethylamine chain?

**References**

1. Gómez-Jeria, J. S.; Moreno-Rojas, C. Dissecting the drug-receptor interaction with the Klopman-Peradejordi-Gómez (KPG) method. I. The interaction of 2,5-dimethoxyphenethylamines and their N-2-methoxybenzyl-substituted analogs with 5-$HT_{1A}$ serotonine receptors. *Chemistry Research Journal* 2017, 2, 27-41.
2. Gómez-Jeria, J. S.; Becerra-Ruiz, M. B. Electronic structure and rat fundus serotonin receptor binding affinity of phenetylamines and indolealkylamines. *International Journal of Advances in Pharmacy, Biology and Chemistry* 2017, 6, 72-86.
3. Gómez-Jeria, J. S.; Cassels, B. K.; Saavedra-Aguilar, J. C. A quantum-chemical and experimental study of the hallucinogen (±)-1-(2,5-dimethoxy-4-nitrophenyl)-2-aminopropane (DON). *European Journal of Medicinal Chemistry* 1987, 22, 433-437.

4. Gómez-Jeria, J. S.; Morales-Lagos, D.; Cassels, B. K.; Saavedra-Aguilar, J. C. Electronic structure and serotonin receptor binding affinity of 7-substituted tryptamines. *Quantitative Structure-Activity Relationships* 1986, 5, 153-157.
5. Gómez-Jeria, J. S.; Morales-Lagos, D.; Rodriguez-Gatica, J. I.; Saavedra-Aguilar, J. C. Quantum-chemical study of the relation between electronic structure and pA2 in a series of 5-substituted tryptamines. *International Journal of Quantum Chemistry* 1985, 28, 421-428.
6. Gómez-Jeria, J. S.; Morales-Lagos, D. R. Quantum chemical approach to the relationship between molecular structure and serotonin receptor binding affinity. *Journal of Pharmaceutical Sciences* 1984, 73, 1725-1728.
7. Gómez-Jeria, J. S.; Abuter-Márquez, J. A Theoretical Study of the Relationships between Electronic Structure and 5-$HT_{1A}$ and 5- $HT_{2A}$ Receptor Binding Affinity of a group of ligands containing an isonicotinic nucleus. *Chemistry Research Journal* 2017, 2, 198-213.
8. Rickli, A.; Luethi, D.; Reinisch, J.; Buchy, D.; Hoener, M. C.; Liechti, M. E. Receptor interaction profiles of novel N-2-methoxybenzyl (NBOMe) derivatives of 2,5-dimethoxy-substituted phenethylamines (2C drugs). *Neuropharmacology* 2015, 99, 546-553.
9. Gómez-Jeria, J. S.; Robles-Navarro, A. A Quantum Chemical Study of the Relationships between Electronic Structure and cloned rat 5-$HT_{2C}$ Receptor Binding Affinity in N-Benzylphenethylamines. *Research Journal of Pharmaceutical, Biological and Chemical Sciences* 2015, 6, 1358-1373.
10. Gómez-Jeria, J. S.; Robles-Navarro, A. DFT and Docking Studies of the Relationships between Electronic Structure and 5-$HT_{2A}$ Receptor Binding Affinity in N-Benzylphenethylamines. *Research Journal of Pharmaceutical, Biological and Chemical Sciences* 2015, 6, 1811-1841.
11. Gómez-Jeria, J. S.; Robles-Navarro, A. A Note on the Docking of some Hallucinogens to the 5-$HT_{2A}$ Receptor. *Journal of Computational Methods in Molecular Design* 2015, 5, 45-57.
12. Gómez-Jeria, J. S.; Robles-Navarro, A. A Density Functional Theory and Docking study of the Relationships between Electronic Structure and 5-$HT_{2B}$ Receptor Binding Affinity in N-Benzyl Phenethylamines. *Der Pharma Chemica* 2015, 7, 243-269.
13. Gómez-Jeria, J. S.; Moreno-Rojas, C.; Castro-Latorre, P. Dissecting the drug-receptor interaction with the Klopman-Peradejordi-Gómez (KPG) method. II. The interaction of 2,5-dimethoxyphenethylamines and their N-2-methoxybenzyl-substituted analogs with 5-HT2A serotonin receptors. *Chemistry Research Journal* 2018.
14. Note. The results presented here are obtained from what is now a routinary procedure. For this reason, we built a general model for the paper's structure. This model contains *standard*phrases for the presentation of the methods, calculations and results because they do not need to be rewritten repeatedly. In 2018.
15. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J., J.A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N. *G03 Rev. E.01*, Gaussian: Pittsburgh, PA, USA, 2007.
16. Gómez-Jeria, J. S.; Kpotin, G. Some Remarks on The Interpretation of The Local Atomic Reactivity Indices Within the Klopman-Peradejordi-Gómez (KPG) Method. I. Theoretical Analysis. *Research Journal of Pharmaceutical, Biological and Chemical Sciences* 2018, 9, 550-561.
17. Gómez-Jeria, J. S. 45 Years of the KPG Method: A Tribute to Federico Peradejordi. *Journal of Computational Methods in Molecular Design* 2017, 7, 17-37.
18. Gómez-Jeria, J. S. *D-Cent-QSAR: A program to generate Local Atomic Reactivity Indices from Gaussian 03 log files. v. 1.0*, v. 1.0; Santiago, Chile, 2014.
19. Gómez-Jeria, J. S. A New Set of Local Reactivity Indices within the Hartree-Fock-Roothaan and Density Functional Theory Frameworks. *Canadian Chemical Transactions* 2013, 1, 25-55.

20. Gómez-Jeria, J. S. An empirical way to correct some drawbacks of Mulliken Population Analysis (Erratum in: J. Chil. Chem. Soc., 55, 4, IX, 2010). *Journal of the Chilean Chemical Society* 2009, 54, 482-485.
21. Gómez-Jeria, J. S. *Elements of Molecular Electronic Pharmacology (in Spanish)*. 1st ed.; Ediciones Sokar: Santiago de Chile, 2013; p 104.
22. Statsoft. *Statistica v. 8.0*, 2300 East 14 th St. Tulsa, OK 74104, USA, 1984-2007.
23. Joselevich, E. Electronic Structure and Chemical Reactivity of Carbon Nanotubes: A Chemist's View. *ChemPhysChem* 2004, 5, 619-624.
24. Gilli, G.; Gilli, P. *The nature of the hydrogen bond: outline of a comprehensive hydrogen bond theory*. Oxford University Press: 2009; Vol. 23.
25. Alonso, M.; Woller, T.; Martín-Martínez, F. J.; Contreras-García, J.; Geerlings, P.; De Proft, F. Understanding the Fundamental Role of π/π, σ/σ, and σ/π Dispersion Interactions in Shaping Carbon-Based Materials. *Chemistry – A European Journal* 2014, 20, 4931-4941.