SYNTHESIS OF 2,3-DIHYDRO-1H-1,5-BENZODIAZEPINES CONTAINING THE 8- HYDROXYQUINOLINIC FRAGMENT

SÍNTESE DE 2,3-DI-HIDRO-1H-1,5-BENZODIAZEPINAS CONTENDO O FRAGMENTO DE 8- HIDROXIQUINOLINA

MARRUGO-GONZALEZ, A. Jose^{1,2}; ORLOV, V. D.³; FERNANDEZ-MAESTRE, Roberto^{1*}

¹ Programa de Química, Universidad de Cartagena, Campus de San Pablo, Cartagena, Colombia, tel-fax. 575-6469578.

³ Department of Organic Chemistry, V.N. Karazin Kharkov National University, 61077, Kharkov, Ukraine. Phone: +380 (57) 7075469. Fax: +380(57)7051249

* *Corresponding author*

e-mail: rfernandezm@unicartagena.edu.co

Received 31 March 2016; received in revised form 12 June 2016; accepted 14 December

RESUMO

Os benzodiazepínicos são utilizados como ansiolítico, hipnótico, sedativo e antidepressivos e para tratar a ansiedade, insônia e ataques epiléticos e mostrar outros tipos de atividades biológicas. Neste estudo, dez novos 4(2)-(8-hidroxiquinolinil-5)-2(-4)-aril-2,3-di-hidro-1H-1,5-benzodiazepinas e dos seus produtos de rearranjo, 2-benzimidazóis substituídos, foram sintetizados a partir de 1-aril-3- (8-hidroxiquinolinil-5) propenona-1 (-3) e o-fenilenodiamina em solução de metanol-trietilamina (1:1). A reação entre a diamina e calconas contendo o fragmento de 8-hidroxiquinolina foi efetuada sob condições suaves, por aminação de catalítica do fragmento β -enonic das calconas seguido de ciclocondensação. As estruturas destes compostos foram estudadas através de métodos espectroscópicos (IR e ¹H-RMN) e as suas propriedades quelantes foram demonstrados. Calculou-se e discuti-se a atividade biológica teórica e a influência de quelação de metais no fragmento hidroxiquinolina receptor de elétrons no espectro eletrônico.

Palavras-chave: 8-hidroxiquinolina, 2,3-di-hidro-1H-1,5-benzodiazepina, benzimidazol.

ABSTRACT

Benzodiazepines are used as anxiolytic, hypnotic, sedative and antidepressant drugs and to treat anxiety, insomnia, and epileptic seizures and show other types of biological activities. In this study, ten new 4(2)-(8-hydroxyquinolinil-5)-2(-4)-aryl-2,3-dihydro-1H-1,5-benzodiazepines and their rearrangement products, 2-substituted benzimidazoles, were synthesized from 1-aryl-3- (8-hydroxyquinolinil-5) propenone-1 (-3) and o-phenylenediamine in methanol-triethylamine (1:1) solution. The reaction between the diamine and chalcones containing the 8-hydroxyquinoline fragment was carried out under mild conditions by base-catalysis amination of the β -enonic fragment of the chalcones followed by cyclocondensation. The structures of these compounds were studied by spectroscopic methods (IR and ¹H-NMR) and their chelating properties were demonstrated. We calculated and discuss their theoretical biological activity, and the influence of metal quelation on the electron acceptor hydroxyquinolinic fragment on the electronic spectra.

Keywords: 8-hydroxyquinoline, 2,3-dihydro-1H-1,5-benzodiazepine, benzimidazole

INTRODUCTION

Benzodiazepines are biologically active compounds used as anxiolytic/hypnotic (Licata and Rowlett, 2008), sedative and antidepressant drugs (Riss *et al.*, 2008) and to treat anxiety, insomnia, and epileptic seizures (Tan *et al.*, 2011; Fisher and Blum, 1995). Benzodiazepines and their polycyclic derivatives exhibit a varied biological activity with applications in the drug industry as non-nucleoside inhibitors of HIV-1 reverse transcriptase, and antifungal, antiviral, antibacterial, anti-inflammatory, analgesic, antihypnotic, anticonvulsant, antidepressive and sedative drugs, and synthons for the preparation of fused rings. Some of their derivatives are used as dyes for acrylic fibers, exhibit activities as muscle relaxants, anticoagulants and antipsychotic, and are antiobesity, antiulcer, calcium channel blockers, thrombopoietin receptor agonist, and anti-HIV agents; and endothelin, cholecystokinin, and vasopressin receptor antagonists (Aastha, *et al.*, 2013).

The dihydrobenzodiazepine structure was first suggested as the product of the cyclocondensation of mesityl oxide with ortho-phenylenediamine (Mushkalo, 1958). The chemistry of aromatic derivatives of 2,3-dihydro-1H-1,5-benzodiazepine began to be studied especially after 1970 (Nawojski *et al.*, 1977; Yaremenko *et al.*, 1979; Orlov *et al.*, 1980). In 1983, it was found that the heptagonal cycle of benzodiazepines is decomposed into benzimidazole by heating in the presence of acids (Orlov *et al.*, 1983), which suggested the impossibility of the formation of the heptagonal dihydrodiazepinic heterocycle reaction product of chalcones with ortho-phenylenediamine (**1**) (Zheliakov *et al.*, 1972). Benzodiazepine 7-membered cycles are thermodynamically less stable than those of 5 and 6 members, especially if they are not aromatic. Only by 1997, it was demonstrated that the reaction of chalcones with ortho-phenylenediamine produces the benzodiazepine cycle (Nawojski and Nawrocka, 1977; Yaremenko *et al.*, 1979. Orlov *et al.*, 1980). Dihydrobenzodiazepines were also detected in the reaction of some aliphatic unsaturated ketones (Kalyanam and Manjunatha, 1991; Kaspzyk and Kolinski, 1984).

This cyclocondensation is carried out under mild conditions by base catalysis with a first

step of amination of the β -enonic fragment followed by cyclocondensation (Orlov *et al.*, 1980). Electrophilic substituents on the aromatic chalcone rings hinder the formation of the heptagonal heterocycle (Orlov *et al.*, 1981). The benzodiazepine cycle is formed by interaction of **1** with precursors of unsaturated ketones: Mannich base (Insuasty *et al.*, 2000) or acetophenones (Orlov *et al.*, 1984). The latter reaction has been performed in the absence of solvent and catalyzed by aluminododecamolibdatephosphate (AIP-Mo₁₂O₄₀) or aluminododecawolframophosphate (AIPW₁₂O₄₀) with 90% yields (Fazaeli *et al.*, 2007). The objective of this work was to obtain new 2,3-dihydro-1H-1,5-benzodiazepines (**4a-g** and **5a-g**) by reaction of diamine **1** and chalcones **2** and **3** containing the 8-hydroxyquinoline fragment (Figure 1) and demonstrate their chelating properties.

MATERIALS AND METHODS

Instrumentation

The monitoring of all reactions and the purity of products was performed by thin layer chromatography; the chromatograms were developed on Silufol UV-254 plates, using CHCl₃ as eluent; UV light or iodine were used to reveal the plates. All reagents were analytical grade (Merck, Darmstadt, Germany). Elemental analysis was performed to determine nitrogen (bromine indirectly) by the Dumas method. IR spectra were taken on an IR-75 Specord instrument. Melting temperatures of **4a-g**, **5a-g** and **6** (Figure 1) were determined in glass capillaries. The benzodiazepines and their precursors were identified by ¹H-NMR and IR spectroscopy. NMR

spectra were taken on a Varian Mercury VX-200 (200 MHz) in DMSO-d₆ solutions. The synthesis of chalcones **2a-g** and **3a-g** has been described (Marrugo-Gonzalez *et al.*, 2012).

Synthesis of 2-(8-hydroxyquinolinil-5)-4-aryl-2,3-dihydro-1,5-benzodiazepines 1H **4a-g** (general method)

1.0 mmol of the corresponding chalcone (**2a-g**) and 1.2 mmol of **1** were heated for 22 hours in a mixture of 10 ml of methanol and 10 ml of triethylamine (catalyst); then, the solvent and catalyst were evaporated and the residue was extracted for 6 hours with n-hexane in a Soxhlet ap-

paratus. The crystals of compound **4a-g** precipitated in cold hexane and were purified by recrystallization from aqueous methanol solution. When necessary, Soxhlet extraction with n-hexane was repeated to obtain a higher purity as determined by NMR analysis. Melting temperatures and yields are shown in Table 1. Likewise, compounds **5a-g** were obtained with different reagents. From the solid residue remaining in the Soxhlet, 2-(8-hydroxyquinolinil-5) (**6**) or 2-arilbenzimidazoles (**7a-g**) (Figure 1) were obtained after crystallization with dimethylformamide with identical features to those prepared before (Orlov *et al.*, 1983) with 20-30% yields. Figure S1 shows the 3D structures of **4a**, **5a**, **6** and **7**.

Biological activity

Theoretical biological activity was calculated with the computer software PASS (Prediction of Activity Spectra for Substances). PASS predicts hundreds of biological activity types for any drug-like compound. The prediction is based on the analysis of structure-activity relationships of the training set that includes more than 300.000 known biologically active compounds and nearly 4000 kinds of activities (Poroikov *et al.*, 2000).

RESULTS AND DISCUSSION

The reaction conditions were varied: solvents (alcohols, dimethylformamide, and acetic acid), catalysts (triethylamine, HCl), temperature (from ambient up to the boiling point of the solvent) and reaction time (from 0.5 hours up to several days). Control over the reaction mixture was performed by thin layer chromatography and IR spectroscopy of the resulting mixtures. In most cases, thin layer chromatography showed the disappearance of the starting chalcone and the corresponding disappearance of the IR peak of the carbonyl group, but a rather complex mixture of substances was obtained. Two benzimidazolic derivatives were separated by fractional crystallization of these mixtures; this means that during the reaction the benzodiazepine system described before (Orlov *et al.*, 1983) was partially obtained, with acetyl detachment of the initial chalcone. This was corroborated by the formation of the benzimidazole derivatives in the chalcones in which, in the second position, the aryl radical of

the aldehyde fragment was retained. Thus, from the reaction mixture obtained from chalcones **2a-g**, 2-(8-hydroxyquinolinil-5) benzimidazole (**6**) not reported before (Tables 1 and 2) and from the reaction product of isomeric chalcones **3a-g**, 2-arilbenzimidazoles **7a-g**, identical to those referenced in the literature (Orlov *et al.*, 1983), were obtained.

In the NMR spectra of the mixtures, the signals from the ABX system protons were observed, demonstrating the presence of dihydrobenzodiazepines. Only after many trials with column chromatography, it was possible to find the eluent (n-hexane) and stationary phase (SiO₂) necessary to purify benzodiazepines and separate in Soxhlet apparatus, the 2,3-dihydro-1H-1, 5-benzodiazepine 2,5-disubstituted, **4a-g** and **5a-g**, with very low yields.

The structure of **4a-g** and **5a-g** was demonstrated by quantitative elemental analysis of the nitrogen content, and by IR and ¹H NMR spectra (Tables 1 and 2, and Supporting Information). In most IR spectra, the peaks of the γ_{N-H} oscillations and a γ_{O-H} broad band were identified; in many cases, the overlapping of these peaks hindered their identification. In the ¹H-NMR spectra, the signals of the 8-hydroxyquinolinic protons are characteristic (Marrugo-Gonzalez *et al.*, 2012) (Table 2). Moreover, the chemical shifts, σ , of the hydroxyquinolinic cycle γ -proton (4-H) of compounds **4** (average of 8.6 ppm) and **5** (average of 9.2 ppm) are different, due to the different interaction of this proton with the pyridine nitrogens, and can be used to differentiate these series (Scheme 1). The formation of the dihydrobenzodiazepinic cycle is confirmed by the characteristic signals of the CH-CH₂ protons (the ABX system, Scheme 1) in the ¹H-NMR spectra of **4** and **5** which are found at low field with respect to protons of saturated systems (Table 2).

The low yield of **4a-g** and **5a-g** was due to its poor solubility in aprotic solvents and to the easy transformation of the heptagonal heterocycle at high temperatures in Protic and polar solvents. The poor solubility of **4a-g** and **5a-g** in aprotic solvents required extraction for many hours with n-hexane; the selection of n-hexane was due to its low boiling temperature.

The 8-hydroxyquinolinic fragment in **4** and

5, in which the hydroxyquinolinic fragment is part of the main chromophore system, gives these molecules chelating properties (Daneshfar *et al.*, 2012; Karatapanis *et al.*, 2011). The large π -conjugated system gives fragment **a** (Scheme 1) rigidity and planarity for an increased UV absorption (Marrugo-Gonzalez *et al.*, 2015). UV spectroscopy was used to test these properties of **5b** and **5e** in methanol with ZnCl_2 , AlCl_3 and BF_3 . The spectra of both molecules were similar in the near ultraviolet region, and showed overlapping absorption bands that decreased in intensity as the wavelength increased: λ_{max} . 310, 345 and 415 nm (Figure 2). The first two bands are typical of the 2,4-diaryl-2,3-dihydro-1H-1,5-benzodiazepines (Zheliakov *et al.*, 1972) (Figure 1). The third band of low intensity at 415 nm shifted depending on the metal used in the experiment, and could be associated with complexation products. By adding ZnCl_2 , the band with λ_{max} . 335 shifted to 399 nm, and with BF_3 two bands formed: one with λ_{max} at 365 nm and a weak one at 460 nm. These changes in the electronic absorption spectra of the diazepines **5**, containing the hydroxyquinolinic fragment, indicate chelation by the nitrogen and oxygen atoms of this fragment.

Figure 2. UV spectrum of **5e** (solid line) and **5e** after adding ZnCl_2 (dotted line). The wavelengths indicated are for **5e**. After Zn(II) is added, the bands at 310 and 345 nm shifted, and that at 415 nm disappeared due to chelation.

Biological activity. To calculate the potential biological activity, the PASS software was used (Poroiakov *et al.*, 2000). In general, all our compounds showed potential biological activity. Table 3 shows PASS results for compounds with more than 70% of probability for biological activity. For example, **4a** was found to be inhibitor of gluconate 2- dehydrogenase, amine dehydrogenase, glyceryl-ether

monooxygenase and dehydro-L-gulonate decarboxylase with a probability of more than 72%.

CONCLUSIONS

1. Benzodiazepines containing the hydroxyquinolinic fragment are very susceptible to chelation which is demonstrated by analyzing the shifts in the electronic absorption spectra after addition of metal solutions.

2. The formation of the dihydrobenzodiazepinic cycle is confirmed by the characteristic signals of the CH-CH_2 fragment protons of the ABX system in the $^1\text{H-NMR}$ spectra of **4** and **5**

3. The difference between the chemical shifts of the γ -proton signal (4-H) of the hydroxyquinolinic cycle in **4** and **5** is significant due to the electronic interaction of this proton with the pyridine nitrogen atoms.

By reaction between **1** and chalcones **2** and **3**, containing the 8-hydroxyquinolinic fragment, we have produced new 2,3-dihydro-1,5-benzodiazepines 1H-2,5-disubstituted (**4a-g** and **5a-g**).

ACKNOWLEDGMENTS

Part of this paper was formerly published in Russian and is only available as a hardcopy (not available online) in the Journal of Organic and Pharmaceutical Chemistry, 2008, 6, 2(22). It is published here in English, the potential biological activity was calculated and 3D structures included. The RMN, IR and UV spectra (not included before) were added (Appendix, Supporting Information).

Supporting information is available.

REFERENCES

1. Aastha, P.; Navneet, K.; Anshu, A.; Pratima, S.; Dharma, K. 1, 5 Benzodiazepines: overview of properties and synthetic aspects. *Res. J. Chem. Sci.* **2013**, 3, 90.
2. Daneshfar, A.; Ghaedi, M.; Vafafard, S.; Shiri, L.; Sahrai, R.; Soylak, M. *Biol. Trace Elem. Res.* **2012**, 145, 2, 240-247. doi: 10.1007/s12011-011-9171-1.
3. Fazaeli, R.; Aliyan, H.; Tangestaninejad,

- S. *Heterocycles* **2007**, 71, 4, 805. DOI: 10.3987/COM-06-10948
4. Fisher, R.; Blum, D. *Epilepsia*, **1995**, 36, S105. DOI: 10.1111/j.1528-1157.1995.tb05993.x
 5. Insuasty, B.; Abonia, R.; Quiroga, J.; Salcedo, A.; Kolshorn, H.; Meier, H. *Eur. J. Org. Chem.* **2000**, 10, 1973. DOI: 10.1002/(SICI)1099-0690(200005)2000:10<1973::AID-EJOC1973>3.0.CO;2-M
 6. Kalyanam, N.; Manjunatha, S.G. Stereoselective bridging of tetrahydro-1, 5-benzodiazepines. *Heterocycles*, **1991**, 32, 1131.
 7. Karatapanis, A.E.; Fiamegos, Y.; Stalikas, C.D. *Talanta*, **2011**, 84, 3, 834-839. doi:10.1016/j.talanta.2011.02.013
 8. Kaspzyk, S.P.; Kolinski, R.A. Synthesis and conformational analysis of C-alkyl derivatives of 2,3,6,7-tetrahydro-1H-1,4-diazepine. *Pol. J. Chem.* **1984**, 58, 721.
 9. Licata, S.C.; Rowlett, J.K. *Pharmacol. Biochem. Behav.* **2008**, 90, 74. doi: 10.1016/j.pbb.2008.01.001.
 10. Marrugo-Gonzalez, A.J.; Orlov, V.D.; Fernandez-Maestre, R. *J. Chil. Chem. Soc.* **2012**, 57, 3, 1-5. <http://dx.doi.org/10.4067/S0717-97072012000300019>
 11. Marrugo-Gonzalez, A.J.; Orlov, V.D.; Fernandez-Maestre, R. *J. Tche Quim.* **2015**, 24, 2, 51. <http://www.journal.tchequimica.com>
 12. Mushkalo, L.K. The condensation of ortho-aminothiophenol with unsaturated ketones and beta-halo ketones. 2. *Zhurnal Obshchei Khimii* **1958**, 28, 507.
 13. Nawojski, A.; Nawrocka, W.; *Rocz. Chem.* **1977**, 51, 11, 2117. Chem. Abstr. 1978, 88, 136578.
 14. Orlov, V.D.; Kolos, N.N.; Yaremenko, F.G.; Lavrushin, V.F. *Khim Geterotsikl+* **1980**, 5, 697. <http://link.springer.com/article/10.1007%2FBF00561358>. V.D. Orlov, N.N. Kolos, F. G. Yaremenko, V. F. Lavrushin, (1980) New aspects of the chemistry of 2, 3-dihydro-1H-1, 5-benzodiazepine. *Chem. Heterocycl. Comp.* 16(5), 547-550.
 15. Orlov, V.D.; Kolos, N.N.; Lavrushin, V.F. *Khim Geterotsikl+* **1981**, 6, 827. <http://link.springer.com/article/10.1007/BF00503491>
 16. Orlov, V.D.; Kolos, N.N.; Zolotarev, V.M. *Khim Geterotsikl+* **1983**, 3, 390. <http://link.springer.com/article/10.1007%2FBF00513270>
 17. Orlov, V.D.; Desenko, S.M.; Kolos, N.N. *Khim Geterotsikl+* **1984**, 1, 126. <http://link.springer.com/article/10.1007%2FBF00505862>
 18. Poroikov, V.V.; Filimonov, D.A.; Borodina, Y.V.; Lagunin, A.A.; Kos A. *J. Chem. Inf. Comput. Sci.* **2000**, 40, 6, 1349-55. DOI: 10.1021/ci000383k
 19. Riss, J.; Cloyd, J.; Gates, J.; Collins, S. *Acta Neurol. Scand.* **2008**, 118, 2, 69. doi: 10.1111/j.1600-0404.2008.01004.x.
 20. Tan, K.R.; Rudolph, U.; Lüscher, C. *Trends Neurosci.* **2011**, 34, 4, 188. doi: 10.1016/j.tins.2011.01.004.
 21. Yaremenko, F.G.; Orlov, V.D.; Kolos, N.N.; Lavrushin, V.F. *Khim. Geterotsikl. Soedin.* **1979**, 6, 848. Chem. Abstr. 1979, 91, 123717. Translated in: Yaremenko, F.G.; Orlov, V.D.; Kolos, N.N.; Lavrushin V.F. Synthesis of 2,4-diphenyl-2,3-dihydro-1H-1,5-benzodiazepine. *Chem. Heterocycl. Comp.* **1979**, 15, 697. DOI 10.1007/BF00539514
 22. Zheliakov, L.; Bizhev, A. *God. Khim. Tekhnol. Inst. Sofia* **1972**, 20, 851.

Table 1 Physicochemical properties of **4a-g**, **5a-g** and **6**

№	R	Formula	N% Yield/N% calculated	MT, °C	Yield, %	IR (KBr), cm ⁻¹	
						N-H	O-H
4a	H	C ₂₄ H ₁₉ N ₃ O	11.4\11.5	175-180	17/22	3370	2950
4b	CH ₃	C ₂₅ H ₂₁ N ₃ O	11.0\11.1	140	18/22	3383	2916
4c	OCH ₃	C ₂₅ H ₂₁ N ₃ O ₂	10.8\10.6	125-130	17/22	3409	2900
4d	N(CH ₃) ₂	C ₂₆ H ₂₄ N ₄ O	13.4\13.7	175-180	23/22	3323	2903
4e	Cl	C ₂₄ H ₁₈ N ₃ OCl	10.7\10.5	130-135	17/22	3363	2916
4f	Br	C ₂₄ H ₁₈ N ₃ OBr	9.5\9.5	150-160	7/22	3356	2923
4g	NO ₂	C ₂₄ H ₁₈ N ₄ O ₃	13.5\13.6	155	5/22		
5a	H	C ₂₄ H ₁₉ N ₃ O	11.4\11.5	120	16/22	3310	2923
5b	CH ₃	C ₂₅ H ₂₁ N ₃ O	11.2\11.1	110	19/22		
5c	OCH ₃	C ₂₅ H ₂₁ N ₃ O ₂	10.6\10.6	165-170	6/22		
5d	N(CH ₃) ₂	C ₂₆ H ₂₄ N ₄ O	13.8\13.7	150-155	6/22	3403	2883
5e	Cl	C ₂₄ H ₁₈ N ₃ OCl	10.6\10.5	130-145	7/22	3423	2916
5f	Br	C ₂₄ H ₁₈ N ₃ OBr	9.6\9.5	200-205	8/22	3310	2916
5g	NO ₂	C ₂₄ H ₁₈ N ₄ O ₃	13.6\13.6	150-152	10/22		
6		C ₆ H ₁₁ N ₃ O	16.0\16.1	203-205	40	3404	3003

MT: Melting temperature

Table 2. ¹H-NMR spectra of the quinolinic core of **4a-g** and **5a-g**. The signal of the 3H proton is located in the 7.5-7.8 region (Marrugo-Gonzalez *et al.*, 2012). Some signs of the 6H and 7H protons are shielded by the multiplet of the aromatic protons. The spin-spin constants, J, were, in Hz: 2H 1.2-1.5 and 3.0-4.6; 4H 0.9-1.6 and 7.3-9.5; 6H 7.9-8.6; 7H 7.9-8.6; Ha 0.6-1.0 and 3.6-8.5; Hb 0.6-1.2 and 4.2-8.5; Hx 0.9-6.7 and 2.5-13.4.

No	δ (ppm)									
	Quinolinic fragment				Benzodiazepinic fragment				Aryl	R
	2H	4H	6 H	7 H	Ha	Hb	Hx	N-H	C ₆ H ₄	CH ₃
4a	8.86	8.50	8.20	7.19	3.58	3.50	4.38	5.33	6.8-8.0	
4b	8.92	8.76	8.37	7.15	3.49	3.42	4.24	5.88	6.7-8.2	2.22
4c	8.86	8.7	8.39	7.07	3.48	3.41	4.56	5.83	6.9-8.1	3.85
4d	8.90	8.70	8.27	7.17	3.62	3.48	4.02	5.59	6.6-8.5	2.96
4e	8.80	8.24	7.98	7.29	3.56	3.52	4.36	5.88	6.8-8.1	
4f	8.85	8.64	8.36	7.22	3.54	3.48	4.11	5.85	6.7-8.4	
4g	8.65	8.47	8.22	7.22	3.48	3.40	4.69	5.88	6.3-8.7	
5a	8.91	9.24	8.33	7.14	3.67	3.62	5.00	6.27	7.0-8.0	
5b	8.92	9.23	8.33	7.00	3.48	3.41	5.16	5.95	7.0-8.0	2.33
5c	8.90	9.20	8.30	7.10	3.63	3.48	4.70	5.33	6.9-8.0	3.73
5d	8.90	9.14	8.25	7.13	3.62	3.57	4.56	5.58	6.7-8.1	2.63
5e	8.92	9.24	8.40	7.16	3.71	3.59	4.10	5.26	7.0-8.0	
5f	8.90	9.30	8.38	7.16	3.71	3.59	4.10	5.31	6.8-8.0	
5g	8.92	9.24	8.27	7.10	3.67	3.59	4.95	5.76	7.6-8.4	
6	8.87	8.64	7.62	6.93				5.96	7.8-7.0	
Average	8.9	8.9	8.2	7.1	3.6	3.5	4.5	5.7		3.0

Table 3 PASS results for compounds with more than 70% of probability for biological activity

Compound	Activity	Probability, %
4a	UGT2B12 substrate	74
4a	Dehydro-L-gulonate decarboxylase inhibitor	75
4a	Glycerol-ether monooxygenase inhibitor	74
4a	Amine dehydrogenase inhibitor	73
4a	Gluconate 2- dehydrogenase (acceptor) inhibitor	72
4b	Glycerol-ether monooxygenase inhibitor	71
4c	Gluconate 2- dehydrogenase (acceptor) inhibitor	77
4c	Amine dehydrogenase inhibitor	73
4c	UGT2B12 substrate	71
4d	Gluconate 2- dehydrogenase (acceptor) inhibitor	75
4g	UGT2B12 substrate	81
5a	UGT2B12 substrate	73
5a	Dehydro-L-gulonate decarboxylase inhibitor	73
5a	Glycerol-ether monooxygenase inhibitor	73
5a	Nicotinic $\alpha 6\beta 3\beta 4\alpha 5$ receptor antagonist	70
5b	Glycerol-ether monooxygenase inhibitor	70
5c	Gluconate 2- dehydrogenase (acceptor) inhibitor	76
5c	UGT2B12 substrate	70
5e	Gluconate 2- dehydrogenase (acceptor) inhibitor	73
5g	UGT2B12 substrate	81

Figure 1. Scheme of the synthesis of 2,3-dihydro-1H-1,5-benzodiazepines. ACD (Advanced Chemistry Development Inc.)/3D viewer version C10E41, Build 76694, **2015**, Toronto, Canada. R was, a: H, b: CH₃, c: OCH₃, d: N(CH₃)₂, e: Cl, f: Br, g: NO₂

Scheme 1. ABX system (left). The large π -conjugated system gives fragment **a** (right) an increased UV absorption and restricted rotation of the bond between the two polyaromatic rings in **5a-g**. This restriction increased the interaction between 4H and the benzodiazepinic nitrogen in **5a-g** that shifted the ^1H -NMR signal of 4H to low field in **5a-g** (Table 2). R was H, CH_3 , OCH_3 , $\text{N}(\text{CH}_3)_2$, Cl, Br, and NO_2

Supporting Information.

Figure S1 3D structures of **4a**, **5a**, **6** and **7**

Appendix ^1H -RMN spectra of **4a-g** and **5a-g**

IR spectrum of 4a

IR spectrum of 4b

IR spectrum of 4c

IR spectrum of 4d

IR spectrum of 4e

IR spectrum of 4f

IR spectrum of 5a

IR spectrum of 5d

HIT-NO=1552	SCORE= ()	SDBS-NO=1559	IR-NIDA-Q0925 : KBR DISC
5-[4-(4-Dimethyloranyl-phenyl)-4,5-dihydro-3H-benzo[<i>b</i>][1,4]diazepin-2-yl]-quinolin-8-ol

3179	41	1609	4	1244	72	1140	66	762	9
3067	42	1474	34	1229	29	1096	58	743	23	
3050	41	1434	45	1223	21	1060	68	711	16	
1909	74	1411	17	1208	23	976	77	638	49	
1902	77	1381	23	1202	38	898	66	587	72	
1896	77	1288	21	1176	46	819	31	581	72	
1680	63	1276	27	1167	43	807	57	576	70	

IR spectrum of 5e

HIT-NO=1552	SCORE= ()	SDBS-NO=1559	IR-NIDA-00925 : KBR DISC
S-[4-(4-Chloro-phenyl)-4,5-dihydro-3H-benzo[b][1,4]diazepin-2-yl]-quinolin-8-ol

3179	41	1608	4	1244	72	1140	66	782	9
3067	42	1474	34	1229	29	1096	58	743	23	
3050	41	1434	45	1223	21	1060	68	711	16	
1909	74	1411	17	1208	23	975	77	638	49	
1902	77	1381	23	1202	38	898	66	587	72	
1896	77	1288	21	1175	46	819	51	581	72	
1580	63	1276	27	1167	43	807	57	576	70	

IR spectrum of 5f

UV-vis spectrum of **5d** before (solid lines) and after adding BF_3 (dark dotted lines) or Zn(II) (gray dotted lines).

UV-vis spectrum of **5e** before (solid lines) after adding BF_3 (dark dotted lines) or Zn(II) (gray dotted lines).

UV-vis spectrum of **5b** before (solid lines) after adding BF_3 (dark dotted lines) or Zn(II) (gray dotted lines)

UV-vis spectrum of **4e** before (solid lines) after adding BF_3 (dark dotted lines) or Zn(II) (gray dotted lines).

UV-vis spectrum of **4d** before (solid lines) after adding BF_3 (dark dotted lines) or Zn(II) (gray dotted lines).

UV-vis spectrum of **4b** before (solid lines) after adding BF₃ (dark dotted lines) or Zn(II) (gray dotted lines).