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SYNTHESIS, BIOLOGICAL ACTIVITY AND QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIPS OF *N*-SUBSTITUTED-3,4-DIHYDRO-2*H*-1-BENZOPYRAN DERIVATIVES

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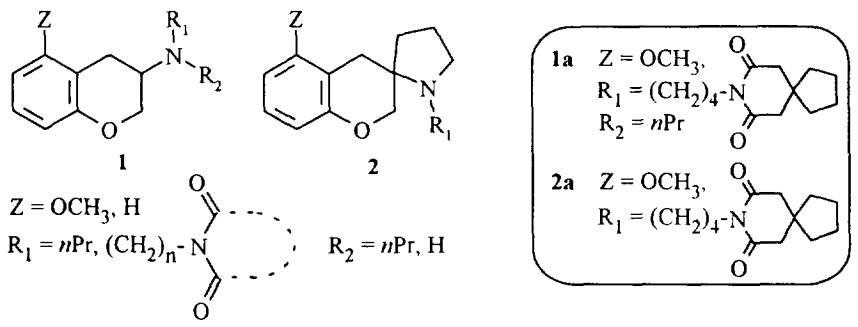
Abstract : Synthesis of *N*-substituted-3,4-dihydro-2*H*-1-benzopyran derivatives which have a potential affinity for the 5-HT_{1A} receptor is reported. The comparison between the experimental values of binding and the prediction of Q.S.A.R. studies is described. Copyright © 1996 Elsevier Science Ltd

Introduction

Since its discovery forty years ago, serotonin (5-hydroxytryptamine, 5-HT) has been involved in many physiological or pathological processes.[1-4] In 1981, the 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) was discovered to be a potent centrally active 5-HT receptor agonist,[5] and subsequently a 5-HT_{1A} receptor agonist.[6] The existence of this ligand has led to an understanding of the 5-HT_{1A} receptor agonists which play an important role both in the control of anxiety and depression without hallucinogenic activity[7] and in the regulation of sympathetic nerve activity which may regulate blood pressure.[8]

In recent papers, we have reported the synthesis and the biological activity of 3-amino-3,4-dihydro-2*H*-1-benzopyran and 3,4-dihydro-1'-substitutedspiro[1-benzopyran-3(2*H*),2'-pyrrolidine] derivatives **1** and **2** (Figure 1).[9-11] Among these compounds, several have shown a high affinity and a good selectivity for the 5-HT_{1A} receptor.

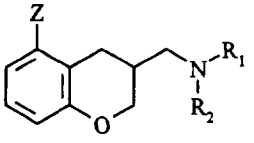
Figure 1



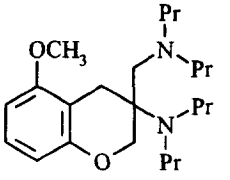
With a view to obtain the compounds showing a higher affinity and selectivity for receptors 5-HT_{1A}, the synthesis of new series has been studied. The first family concerns derivatives **3**, aminomethyl analogues of **1**.

The other series **4** and **5** result from the structural combination of amino- and aminomethyl-3,4-dihydro-2*H*-1-benzopyran derivatives **1**, **2** and **3** (Figure 2).

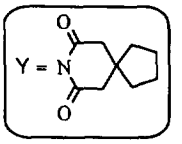
Figure 2

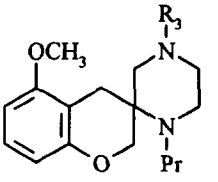


	Z	R_1	R_2
3a	OCH_3	H	$(CH_2)_4$-Y
3b	H	H	$(CH_2)_4$-Y
3c	OCH_3	*n*Pr	*n*Pr
3d	OCH_3	*n*Pr	$(CH_2)_4$-Y



4



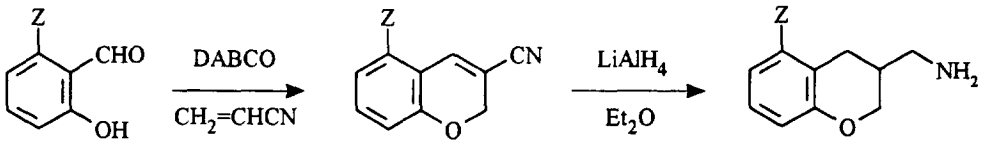


	R_3
5a	*n*Pr
5b	CH_2Ph
5c	$(CH_2)_4$-Y

Chemistry

The first series studied was the *N*-alkylated-3-aminomethyl-3,4-dihydro-2*H*-1-benzopyrans **3a-d**. The precursors of these derivatives were prepared as shown in Scheme 1. *O*-Cyanoethylation of the appropriate substituted salicylaldehydes followed by cyclization afforded the expected 3-cyano-3,4-dihydro-2*H*-1-benzopyrans **6a** and **6b** according to the method described by Wise *et al*, in 70 % and 73 % yield respectively.[12] Reduction of nitriles **6a** and **6b** using lithium aluminium hydride in dry diethyl ether gave the amines **7a** and **7b** in 63 % and 97 % yield, respectively.

Scheme 1

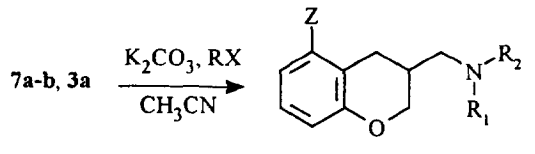


6a Z = OCH_3 70%
6b Z = H 73%

7a Z = OCH_3 63%
7b Z = H 97%

The expected products **3a-d**[13,14] were prepared by *N*-alkylation of amines **7a-b** with the required halogeno derivatives. This reaction was performed in the presence of potassium carbonate and in acetonitrile as solvent with low or moderate yields (37-54 %) (Scheme 2).

Scheme 2



3a-d

Entry	RX	Cpd	Yield (%)
7a[a]	Y-$(CH_2)_4$-Br	**3a**	41
7b[a]	Y-$(CH_2)_4$-Br	**3b**	42
7a	*n*Pr-I	**3c**	54
3a	*n*Pr-I	**3d**	37

[a] A catalytic amount of potassium iodide was used.

The elaboration of compounds **4** and **5a-c** has been reported in a recent paper.[10] These derivatives were prepared from the substituted salicylaldehydes as starting material *via* 3,4-dihydro-2*H*-benzopyran-3-one derivatives as intermediates.[12]

Pharmacology characterisation

The pharmacological characterisation of the ligands was carried out by measuring the ability of the compounds **3a-d**, **4**, **5a-c** to displace different radioligands. These data are reported in Table 1. The data for the receptors 5-HT_{1D} and 5-HT_3 are not reported in Table 1 due the low affinity.[15]

Table 1. Binding values of compounds **1a**, **2a**, **3**, **4** and **5**

	$pIC_{50} \pm SE^a$					
Cpd	**5-HT_{1A}**	**5-HT_{1B}**	**5-HT_{2A}**	**5-HT_{2C}**	**D_1**	**D_2**
3a[b]	9.89±0.04	5.52±0.23	7.31± 0.07	6.77±0.05	6.08±0.08	7.53±0.03
3b[b]	8.20±0.03	5.16±0.03	7.25±0.03	5.91±0.09	5.48±0.01	7.17±0.04
3c[b]	6.63±0.06	4.64±0.06	4.80±0.18	4.47±0.03	4.46±0.03	5.59±0.04
3d[b]	6.29±0.03	5.13±0.08	5.11±0.06	5.50±0.15	4.86±0.01	5.75±0.09
4[c]	5.38±0.02	3.86±0.21	3.67±0.07	3.33±1.86	ND	ND
5a[b]	5.52±0.15	< 4	5.00±0.12	4.52±0.02	ND	ND
5b[b]	4.80±0.03	4.45±0.20	4.61± 0.07	4.11±0.10	ND	ND
5c[b]	4.80±0.09	5.80±0.14	4.95±0.07	4.51±0.02	ND	ND
1a[d]	9.70	5.30	6.00	-	4.40	8.00
2a[e]	7.97	5.42	5.18	4.98	<5	5.96

[a]The radioligands used were : [^{3}H]-8-OH-DPAT for 5-HT_{1A}; [^{3}H]-5-OH-Tryptamine for 5-HT_{1B} and 5-HT_{1D}; [^{3}H]-*N*-Methylmesulergine for 5-HT_{2C}; [^{3}H]-Ketanserin for 5-HT_{2A}; [^{3}H]-BRL43694 for 5-HT_3; [^{3}H]-SCH 23390 for D_1; [^{3}H]-Raclopride for D_2. [b,c]All compounds tested were racemic forms and used respectively as oxalate or chlorhydrate forms. [d]See reference 9. [e]See reference 11. [f]ND : Not determined.

Following the results mentioned in Table 1, compounds belonging to families **4** and **5** show low pIC_{50} values (4.80-5.52) *versus* derivatives **3** (6.29-9.89). The simultaneous presence of the amino- and aminomethyl chain on 3-position decreases the activity. On the other hand, for compounds **3** which possess only one aminomethyl chain, a higher activity has been noted. Concerning this same family **3**, it seems that the replacement of secondary amine by tertiary amine decreases the activity for the receptor 5-HT_{1A} (pIC_{50} **(3a)** = 9.89 *versus* pIC_{50} **(3d)** = 6.29) and the methoxy group in 5-position of benzopyran derivatives is necessary to obtain the higher activity (pIC_{50} **(3a)** = 9.89 *versus* pIC_{50} **(3b)** = 8.20). Compound **3a** shows a slightly higher affinity for 5-HT_{1A} receptors than the reference compound **1a** (pIC_{50} **(3a)** = 9.89 *versus* pIC_{50} **(1a)** = 9.70). Moreover the activity of **3a** towards 5-HT_{1A} receptors is higher *versus* the activity of **2a** (pIC_{50} **(3a)** = 9.89

versus pIC_{50} (**2a**) = 7.97). Concerning the D_2-dopaminergic activity, the lead derivative **3a** exhibited a 10 fold selectivity compared to compound **1a**.

Molecular modeling and results of Q.S.A.R. analysis

It has recently been shown that good quantitative structure-activity relationships can be obtained through statistical analysis of molecular similarity matrices.[16] We have previously used this approach on a series of fifty-two benzopyran compounds (forty-eight compounds in training set which include compounds **1a** and **2a** and four in the test set) with good predictive power.[11] Results of this analysis and also the classical pharmacophores approach[17,18] are used for the prediction of the binding of the eight new products (**3a-d**, **4**, **5a-c**) presented in this paper (Table 1).

The eight products present an excellent fit with the proposed pharmacophores for the 5-HT_{1A} ligands and it is not possible to make a correlation with their binding values using this approach. The relationship between affinity and descriptors of similarity was analysed using partial least squares[19] (PLS) module of the TSAR V2.2[20] program. From the complete study of the forty-eight compounds,[11] we deduced that the best methods in terms of statistical results are the electrostatic potential and field (r^2 = 0.82 and 0.89, $r(CV)^2$ = 0.46 and 0.45). The average difference between predicted and experimental binding values was 0.32 in the training set and 0.22 for the test set. We have used these two evaluation methods for the eight compounds presented in this paper. In Table 2 the results of the predictions of binding values using these two methods and their mean value for each compound are compared with the experimental ones. The regression coefficient between the mean of the predictions and the experiment is 0.9 and the average difference for the eight products is 0.68. However, these differences are not homogeneous; for five compounds the difference is lower than 0.5, for two compounds between 1 and 1.5 and for one (compound **4**) its value is 2.2. The explanation for these differences can be found in the composition of the training set. Compounds **3a-3d** are close to this set, the mean difference between prediction and experiment is 0.08 unit of pIC_{50}, a very good result. Compounds **5a-5c** are close to the spiro compounds with one nitrogen of the training set but they have two nitrogens in the spiro ring. The predictive value is on average, superior by 1 unit to the experimental one. This is a proof of a repulsive phenomenon due to this second nitrogen of the spiro ring and this effect is not represented in the model. Compound **4** is the most different from the training set; it has two nitrogens on the chains of the C-3 of the benzopyran ring and a great conformational freedom of these chains. Then the predicted value is 2.2 units of pIC_{50} superior to the experimental one. These results are a direct example of the power of QSAR approach for compounds close to the training set but also of the limits of this technique for the activity prediction of new structures.

Conclusion

In conclusion, compound **3a** presents an excellent affinity for the receptor 5-HT_{1A} and a high selectivity. Furthermore this compound **3a** exhibited a 100-10000 fold selectivity for 5-HT_{1A} compared to the receptors 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, D_1 and D_2. According to these results, the derivative **3a** could be a promising compound for future development.

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Table 2. Experimental and Q.S.A.R. prediction values of binding of compounds **3-5** for 5-HT_{1A} receptor

Cpd	pIC_{50}			
	Electrostatic Potential[a] Predicted Values	Electrostatic Field[a] Predicted Values	Mean Values	Experimental Values[b]
3a	9.57	9.92	9.74	9.89
3b	7.65	8.95	8.30	8.20
3c	6.82	6.68	6.75	6.63
3d	6.89	6.24	6.56	6.29
4	7.85	7.27	7.56	5.38
5a	7.10	6.03	6.57	5.52
5b	5.21	5.27	5.24	4.80
5c	6.80	5.77	6.28	4.80

[a] For calculation method of similarity indices see reference 21. [b] For SE values see Table 1.

References and notes :

1. Johnston, A.; File, S. E. *Pharmacol. Biochem. Behav.* **1986**, *24*, 1457.
2. Eison, M. S. *Psychopathology* **1984**, *17*, 37.
3. Peroutka, S. J.; Snyder, S. H. *J. Pharmacol. Exp. Ther.* **1981**, *216*, 142.
4. Norman, A. B.; Battaglia, G.; Morrow, A. L.; Creese, I. *Eur. J. Pharmacol.* **1984**, *106*, 461.
5. Arvidsson, L. E.; Hacksell, U.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Lindberg, P.; Sanchez, D.; Wikström, H. *J. Med. Chem.* **1981**, *24*, 921.
6. Middlemiss, D.; Fozard, J. R. *Eur. J. Pharm.* **1983**, *90*, 151.
7. Traber, J.; Glaser, T. *Trends Pharmacol. Sci.* **1987**, *8*, 422.
8. a) Fozard, J. R.; Mir, K. A.; Middlemiss, D. N. *J. Cardiovasc. Pharmacol.* **1987**, *9*, 328. b) Mc Call, R. B.; Pattel, B. N.; Harris, L. T. *J. Pharmacol. Exp. Ther.* **1987**, *242*, 1152. c) Clement, M. E.; Mc Call, R. B. *Brain Res.* **1990**, *525*, 232.
9. Podona, T.; Guardiola-Lemaître, B.; Caignard, D. H.; Adam, G.; Pfeiffer, B.; Renard, P.; Guillaumet, G. *J. Med. Chem.* **1994**, *37*, 1779.
10. Comoy, C.; Guillaumet, G. *Heterocyclic Commun.*, in press.
11. Comoy, C.; Marot, C.; Podona, T.; Baudin, M. L.; Morin-Allory, L.; Guillaumet, G.; Pfeiffer, B.; Caignard, D. H.; Renard, P.; Rettori, M. C.; Adam, G.; Guardiola-Lemaître, B. *J. Med. Chem.* submitted for publication.
12. Wise, L. D.; DeWald, H. A.; Hawkins, E. S.; Reynolds, D. M.; Heffner, T. G.; Meltzer, L. T.; Pugsley, T. A; *J. Med. Chem.* **1988**, *31*, 688.
13. All compounds reported gave satisfactory ^{1}H-NMR, IR, mass spectra and elemental analysis data, in full agreement with their assigned structures.
14. Representative physical data of derivatives **3a-d** are as follows :
8-[N-(5-Methoxy-3,4-dihydro-2H-1-benzopyran-3-ylmethyl)-4-aminobutyl]-8-azaspiro[4.5]decane-7,9-dione (3a) : Oil; IR (film) ν (cm^{-1}) : 1715 and 1660 (C=O); ^{1}H NMR ($CDCl_3$) δ : 1.45-1.85 (m, 13H, **NH**, $\mathbf{CH_2}$); 2.12-2.21 (m, 1H, $\mathbf{CHCH_2}$); 2.30 (dd, 1H, $\mathbf{CH_2}$Ar, J = 7.0, J = 17.0); 2.59 (s, 4H, $\mathbf{NCOCH_2}$);

2.65-2.70 (m, 4H, CH_2N); 2.84 (dd, 1H, CH_2Ar, J = 17.0, J = 6.0); 3.70-3.85 (m, 6H, CH_3O, CH_2NCO, CH_2O); 4.22-4.29 (m, 1H, CH_2O); 6.41 (d, 1H, H_{ar}, J = 8.1); 6.48 (d, 1H, H_{ar}, J = 8.1); 7.05 (t, 1H, H_{ar}, J = 8.1); MS (CI/NH_3) m/z = 415 (M+1); Anal. for ($C_{24}H_{34}N_2O_4$, $C_2H_2O_4$) C, H, N.

8-[4-[N-(3,4-Dihydro-2H-1-benzopyran-3-ylmethyl)amino]butyl]-8-azaspiro[4.5]decane-7,9-dione (3b) : Oil; IR (film) ν (cm^{-1}) : 3700-3200 (NH); 1720 and 1660 (NCO); ^1H NMR ($CDCl_3$) δ : 1.46-1.60 (m, 8H, CH_2); 1.66-1.75 (m, 4H, CH_2); 1.81-2.01 (br s, 1H, NH); 2.24-2.37 (m, 1H, CH); 2.52-2.75 (m, 5H, CH_2Ar, NCH_2); 2.59 (s, 4H, $NCOCH_2$); 2.92 (dd, 1H, CH_2Ar, J = 5.6, J = 16.2); 3.74-3.81 (m, 2H, CH_2NCO); 3.92 (dd, 1H, CH_2O, J = 2.7, J = 10.8); 4.25-4.31 (m, 1H, CH_2O); 6.77-6.86 (m, 2H, H_{ar}); 7.02-7.12 (m, 2H, H_{ar}); MS (CI/NH_3) m/z = 385 (M+1); Anal. for ($C_{23}H_{32}N_2O_3$, $C_2H_2O_4$) C, H, N.

5-Methoxy-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (3c) : Oil; IR (film) ν (cm^{-1}) : 1230 (COC); ^1H-NMR ($CDCl_3$) δ : 0.87 (t, 6H, CH_3, J = 7.9) ; 1.40-1.51 (m, 4H, CH_2CH_3); 2.15-2.47 (m, 8H, CH_2, CH_2N, $CHCH_2$, CH_2Ar); 2.83 (dd, 1H, CH_2Ar, J = 6.1, J = 17.0); 3.75 (t, 1H, CH_2O, J = 10.4); 3.80 (s, 3H, CH_3O); 4.25-4.32 (m, 1H, CH_2O); 6.43 (d, 1H, H_{ar}, J = 8.3); 6.46 (d, 1H, H_{ar}, J = 8.3); 7.05 (t, 1H, H_{ar}, J = 8.3); MS (CI/NH_3) m/z = 277 (M+1); Anal. for ($C_{17}H_{27}NO_2$, $C_2H_2O_4$) C, H, N.

8-[4-[N-(5-Methoxy-3,4-dihydro-2H-1-benzopyran-3-ylmethyl)-N-propyl]aminobutyl]-8-azaspiro [4.5] decane-7,9-dione (3d) : Oil; IR (film) ν (cm^{-1}) : 1715 and 1660 (C=O); ^1H-NMR ($CDCl_3$) δ : 0.87 (t, 6H, CH_3, J = 7.0); 1.45-1.75 (m, 1H, CH_2); 2.10-2.48 (m, 6H, $CHCH_2$, CH_2Ar, CH_2N); 2.60 (s, 4H, CH_2CO); 2.80 (dd, 1H, CH_2Ar, J = 6.0, J = 17.0); 3.70-3.81 (m, 6H, CH_2NCO, CH_2O, OCH_3); 4.20-4.27 (m, 1H, CH_2O); 6.39 (d, 1H, H_{ar}, J = 8.3); 6.46 (d, 1H, H_{ar}, J = 8.3); 7.02 (t, 1H, H_{ar}, J = 8.3); MS (CI/NH_3) m/z = 457 (M+1); Anal. for ($C_{27}H_{40}N_2O_4$, $C_2H_2O_4$) C, H, N.

15. pIC_{50} values of compounds **3-5** for 5-HT_{1D} and 5-HT_3 are respectively between 3.4-5.8 and 3.5-4.8.
16. Good, A. C.; Peterson, S. J.; Richards, W. G. *J. Med. Chem.* **1993**, *36*, 2929.
17. Mellin, C.; Vallgarda, J.; Nelson, D. L.; Björk, L.; Yu, H.; Anden, N. E.; Csöregh, I.; Arvidsson, L. E.; Hacksell, U. *J. Med. Chem.* **1991**, *34*, 497.
18. Hibert, M. F.; McDermott, I.; Middlemiss, D. N.; Mir, A. K.; Fozard, J. R. *J. Med. Chem.* **1988**, *31*, 1087.
19. Wold, S.; Ruhe, A.; Dunn, W. *SIAM J. Sci. Statist. Comput.* **1984**, *5*, 735.
20. Oxford Molecular Ltd, The Magdalen Center, Oxford Science Park, Sandford on Thames, Oxford OX4 4GA, United Kingdom.
21. Kubinyi, H. *QSAR : Hansch Analysis and Related Approaches*, Vol. 1, pp. 149-177, Mannhold, R.; Krogsgaard-Larsen, P.; Timmerman, H., Ed.; VCH; New York, 1993.

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