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SYNTHESIS OF HALOGENATED/NITRATED FLAVONE DERIVATIVES AND EVALUATION OF THEIR AFFINITY FOR THE CENTRAL BENZODIAZEPINE RECEPTOR

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Abstract: A series of halogenated/nitrated flavone compounds were synthesized. Some of the products were found to be potent central benzodiazepine receptor (BDZ-R) ligands. The structure-activity relationships (SAR) analysis of the new synthetic compounds, together with that of others already described, indicates that substitutions at position 6 or 6 and 3' in the flavone nucleus are the only ones that give rise to high affinity BDZ-R ligands. © 1997 Elsevier Science Ltd.

Introduction

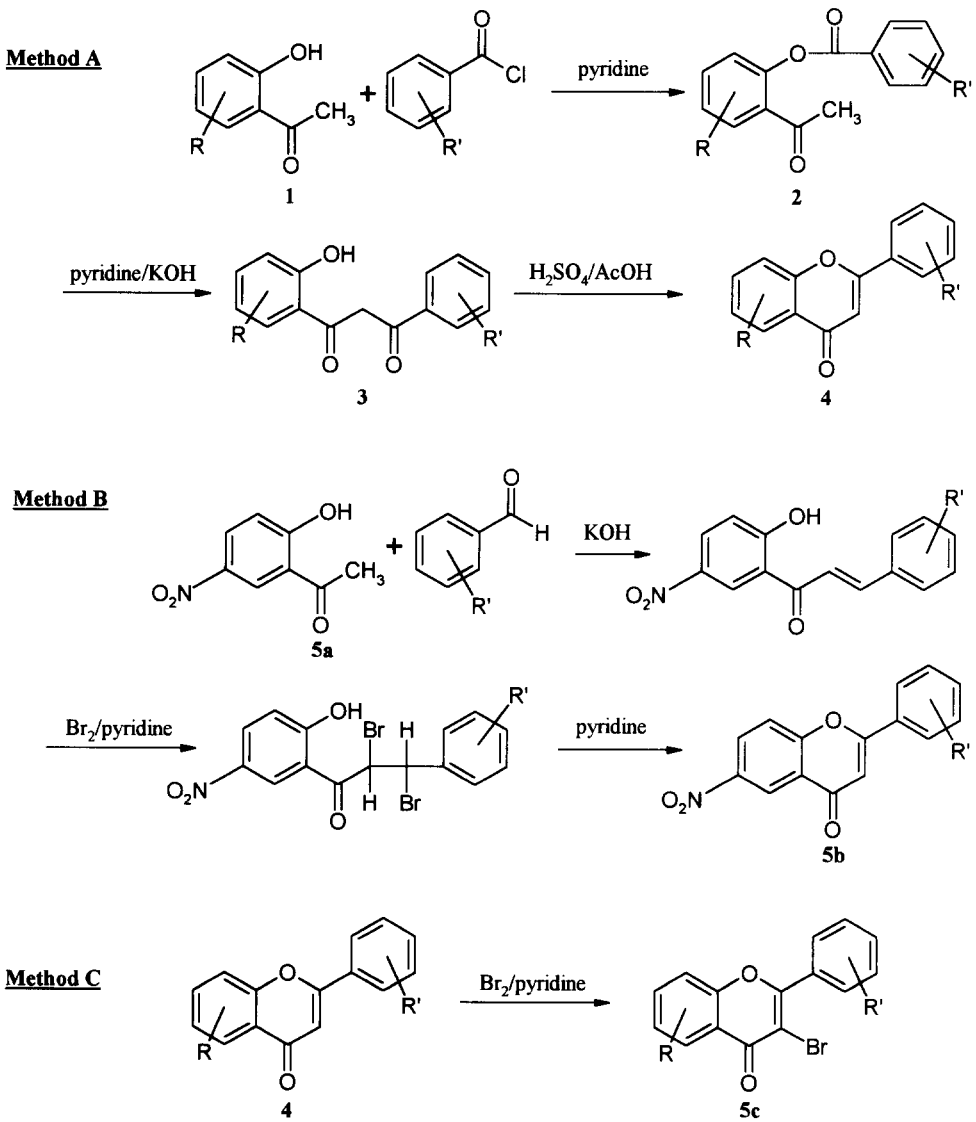
Previous work from our laboratories disclosed that some naturally occurring flavonoids, as well as the flavone nucleus itself, were ligands for the BDZ-Rs that exhibited low-medium affinity in vitro and anxiolytic activity in vivo, with minor sedative or myorelaxant effects.[1-3]

The introduction of electronegative substituents in the flavone nucleus led to the discovery of novel high affinity ligands for the BDZ-Rs endowed with potent anxiolytic effects.[4-7] Although it has yet to be established whether any of these compounds may originate a useful therapeutic drug, it was deemed important to synthesize a wider series of analogous compounds. In this Letter we describe the synthesis of 15 new halo/nitro derivatives of flavone and the measurement of their affinities for the BDZ-Rs. A series of SARs could be established that proved useful to define the minimum requirements for the generation of a high affinity ligand.

Chemistry

Three methods (A, B, and C), indicated in Scheme 1, were employed to prepare the analogs of interest in this study.

Scheme 1



We used the Baker-Venkataraman transformation, the most common method of synthesizing flavones.

In this process (Method A, Scheme 1) a hydroxyacetophenone (**1**) is first converted into a benzoyl ester (**2**) and this species is then treated with base, forming a 1,3-diketone (**3**). Treatment of this diketone with acid leads to generation of the desired flavone (**4**).[8]

In method B (Scheme 1), 2-hydroxy-5-nitro-acetophenone (**5a**) prepared according to Cushman et al.,[9] was transformed into the corresponding B-ring substituted flavone(s) (**5b**) following the procedure described in reference 10.

In method C (Scheme 1), 3-bromine substituted flavones (**5c**) were obtained by treatment of the corresponding flavone (**4**) with bromine in pyridine.

Results and Discussion

Application of the chemical methods A, B, and C led to the synthesis of the majority of the flavone derivatives listed in Table 1, which also includes several similar compounds prepared and studied previously by us.[4,5,7]

Binding affinities to BDZ-Rs were determined by the ability of the compounds to inhibit ^{3}H-flunitrazepam binding to extensively washed rat cerebral cortical membranes. The methodology for the preparation of the membranes and the performance of the binding assays has already been described.[11]

The following SARs were obtained by analysis of the information collected in Table 1 and are expressed as flavone substitutions that produce the following changes in the binding affinity of the mother compound (flavone, **6**).

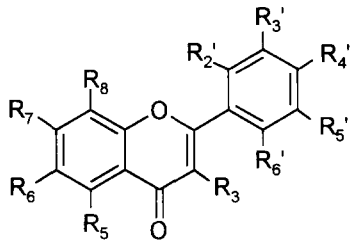
(A) Great increases (40 to 1000 times):

- A bromine or chlorine atom, or a nitro group in carbon 6 plus a halogen or nitro group in carbon 3' (**22**, **25**, **27**, **29**, **30**).

(B) Moderate increases (3.6 to 13 times):

- A bromine, or a chlorine atom, or a nitro group in carbon 6 (**8**, **9**, **10**).
- A bromine atom in carbon 6 plus a nitro group in carbon 2' (**26**), or in carbon 4' (**28**).
- A nitro group, or a bromine, or a chlorine atom in carbon 3' (**12**, **13**, **14**).
- A fluorine atom in carbon 6 plus a nitro group in carbon 3' (**24**).

Table 1: Binding affinity of flavone derivatives for the BDZ-Rs



Compoud[a]	R_3	R_6	$R_{2'}$	$R_{3'}$	$R_{4'}$	$R_{5'}$	K_i[b] (μM)
6	H	H	H	H	H	H	1[c]
7	H	F	H	H	H	H	4.5
8	H	Cl	H	H	H	H	0.164
9	H	Br	H	H	H	H	0.075[c]
10	H	NO_2	H	H	H	H	0.275
11	H	H	NO_2	H	H	H	>20
12	H	H	H	NO_2	H	H	0.285
13	H	H	H	Cl	H	H	0.614
14	H	H	H	Br	H	H	0.413
15	H	H	H	H	NO_2	H	>20
16	H	H	H	H	Br	H	>20
17	H	H	H	NO_2	H	NO_2	>20
18	Br	H	H	H	H	H	>75[c]
19	Br	Br	H	H	H	H	>75[c]
20	Br	H	H	NO_2	H	H	>20
21	H	NO_2	NO_2	H	H	H	>10
22	H	NO_2	H	NO_2	H	H	0.026[d]
23	H	NO_2	H	H	NO_2	H	>10[d]
24	H	F	H	NO_2	H	H	0.180
25	H	Cl	H	NO_2	H	H	0.008
26	H	Br	NO_2	H	H	H	0.208[e]
27	H	Br	H	NO_2	H	H	0.001 and 0.016[e]
28	H	Br	H	H	NO_2	H	0.200[e]
29	H	Br	H	Br	H	H	0.019
30	H	NO_2	H	Br	H	H	0.025

[a] All described compounds were fully characterized including spectroscopic and elemental analysis.
[b] $K_i \pm$ SEM values are means of 3 to 5 independent determinations. For values ranging from 0.001 to 4.5, the SEM varied between 6 to 13% of the absolute values listed. The low affinity values are the result of duplicate measurements.
[c] Ref. 5.
[d] Ref. 4.
[e] Ref. 7.

(C) Great decreases:

- A fluorine atom in carbon 6 (**7**).
- A nitro group in carbon 2' (**11**); a nitro group, or a bromine atom in carbon 4' (**15**, **16**).
- Nitro groups in carbons 3' and 5' (**17**); in carbons 6 and 2' (**21**); or in carbons 6 and 4' (**23**).
- A bromine atom in carbon 3 (**18**) or in carbons 6 and 3 (**19**), a bromine atom in carbon 3 plus a nitro group in carbon 3' (**20**).

The effectiveness of the different substituents in carbon 6 is as follows: Br > Cl > NO_2 > F.

The influence of halogen atoms or nitro groups in carbons 5, 7, or 8 has not been established. However, some information on the relevance of these positions on the affinity for the BDZ-Rs of this kind of compounds can be obtained from the properties of several natural or synthetic flavonoids as reported by us.[5] For instance, the presence of hydroxy groups in carbon 5 and 7 or 5, 7 and 4' is compatible with the occurrence of low to medium affinity properties. Further, the addition of halogen atoms in carbons 6 and 8, in one of those molecules (see compounds **23** and **24** in reference 5) does not appreciably modify the affinity of the mother molecule.

In conclusion, substitution with halogen atoms, or nitro groups, in carbon 6 or carbon 6 and 3' of flavone gives rise to fairly active compounds, both in vitro and in vivo.[4-7] Similar substitutions in other carbons, with the limitations indicated before, are less effective or, alternatively, originate inactive compounds. Compound **9** behaves as a full BDZ-R agonist[4], while compounds **22** and **27** have a partial agonist profile at the BDZ-R[6,7] with potent anxiolytic properties, without evidencing myorelaxant or sedative actions. Biochemical and pharmacological experiments are now in progress to characterize the properties of compounds **25**, **29**, and **30**.

Acknowledgements

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