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CONCISE ARTICLE

Potential atypical antipsychotics: synthesis, binding affinity and SAR of new heterocyclic bioisosteric butyrophenone analogues as multitarget ligands†

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A series of 15 heterocyclic butyrophenone analogues was synthesized as potential multi-target ligands. The compounds were assayed for their *in vitro* human D_2 and $5\text{-}HT_{2A}$ receptor affinity, and those compounds exhibiting the highest affinities were evaluated for binding affinity on D_1, D_3, $5\text{-}HT_{1A}$, $5\text{-}HT_{2C}$ and $5\text{-}HT_6$ receptors.

Introduction

Schizophrenia is a complex neuropsychiatric disorder characterized by the development of three distinct kinds of symptoms: positive (hallucinations, hyperactivity, delusions, disorganized speech), negative (anhedonia, avolition, social isolation), and cognitive (attentional impairment, memory deficits). For the treatment of this disorder, the first generation of antipsychotic drugs was discovered about fifty years ago (*e.g.* chlorpromazine, haloperidol); described as selective D_2 dopamine antagonists, today they are known as "typical antipsychotics".[1] These drugs produce however a host of adverse side effects including induction of acute extrapyramidal symptoms (EPS), without having any effect on the negative or cognitive symptoms of schizophrenia.[2] Later, the introduction of clozapine for treatment-resistant schizophrenia gave rise to a new group of "atypical" or "nonclassical" antipsychotics that have no EPS at the doses frequently used in therapy, and are effective also against the negative symptoms.[3–5] A new generation of atypical antipsychotics (also known as "dopamine stabilizers") such as aripiprazole, with a concrete efficacy spectrum in different receptors (inverse agonist at $5\text{-}HT_{2B}$ receptors, partial agonist at D_2, D_3, $5\text{-}HT_{2A}$ and $5\text{-}HT_{2C}$ receptors),[6] offered further advantage due to an improved efficacy in treating negative symptoms of schizophrenia and a decreased incidence and severity of central and peripheral side effects.[7] Now, while the treatment and maintenance of the positive symptoms of schizophrenia are largely addressed with current medications, the major challenge is to identify compounds showing clinically significant improvements in the treatment of negative symptoms and cognitive dysfunction. In addition, a major issue with many of the currently prescribed atypical antipsychotic drugs remains the side-effect liabilities of weight gain, metabolic abnormalities, diabetes liabilities and potential cardiovascular safety concerns and so significant improvements can still be made. Consequently, much of the current focus in the design of new antipsychotic drugs has been centered on trying to improve upon these liabilities.

At the molecular level, while traditional antipsychotics bind principally and most avidly to D_2 receptors, atypical antipsychotics exhibit high affinities for other receptors equal to or exceeding that for the D_2 receptor; clozapine and the closely related compound olanzapine are good examples of drugs with a complex multi-receptor profile; they have affinities toward serotonin, dopamine, α-adrenergic, muscarinic, and histamine receptors, among others.[8] Moreover, the second-generation atypical antipsychotics are partial agonists of D_2 and $5\text{-}HT_{1A}$ receptors, and antagonists of $5\text{-}HT_{2A}$ receptors and also a number of other targets. In general, experimental evidence suggests that a complex binding profile is linked to the clinical efficacy of antipsychotic drugs, and indeed, the importance of multivalent ligands targeting G-protein-coupled receptors design to deal with schizophrenia has been pointed by many authors.[9,10] In fact, some of the latest efforts in the development of novel antipsychotic drugs are aimed at obtaining compounds with binding affinities for a certain number of receptors.[11–14] To validate this multireceptor affinity profile approach to antipsychotics and to achieve an optimum interaction with dopamine and serotonin receptors, we exploited our knowledge acquired in the development of aminobutyrophenone potential antipsychotics. Herein we report on the design, synthesis, and pharmacological evaluation of new aminobutyrophenone heterocyclic derivatives as multi-target compounds potentially useful as antipsychotics.

Over the last years, we have been working on the modulation of the butyrophenone system, with the aim of combining the antagonism at the $5\text{-}HT_2$ family and the D_2 receptors in a single molecule.[15–18] We have described a series of

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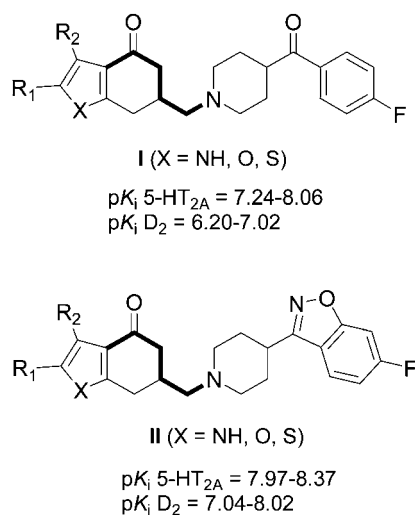
Fig. 1 Structures of some heterocyclic aminobutyrophenone analogues.

aminobutyrophenones type **I** and **II** (Fig. 1, substructure marked bold) which showed high affinity for the 5-HT$_{2A}$ receptor subtype, with pK_i values between 7.24 and 8.37.[19,20] We explored now the possibility of synthesizing analogues of the above mentioned aminobutyrophenones, in which the furan or pyrrole ring of these compounds was replaced by five-membered heterocycles containing two heteroatoms: pyrazole, isoxazole, oxazole, and thiazole, to form a tetrahydro-indazolone, -benzi-soxazolone, -benzoxazolone, or -benzothiazolone system, respectively, considering that the substitution of –CH= by –N= in aromatic rings has been one of the most-successful applica-tions of classical isosterism.[21–23] These modifications should deliver insight into the dependency of the receptor binding effi-cacies on the number of heteroatoms in the ring system and their position there. The isosteric replacement of the benzene ring at the butyrophenone motif resulted in 15 analogues with different substitutions. Some preliminary results of this work have been published in a previous communication.[24]
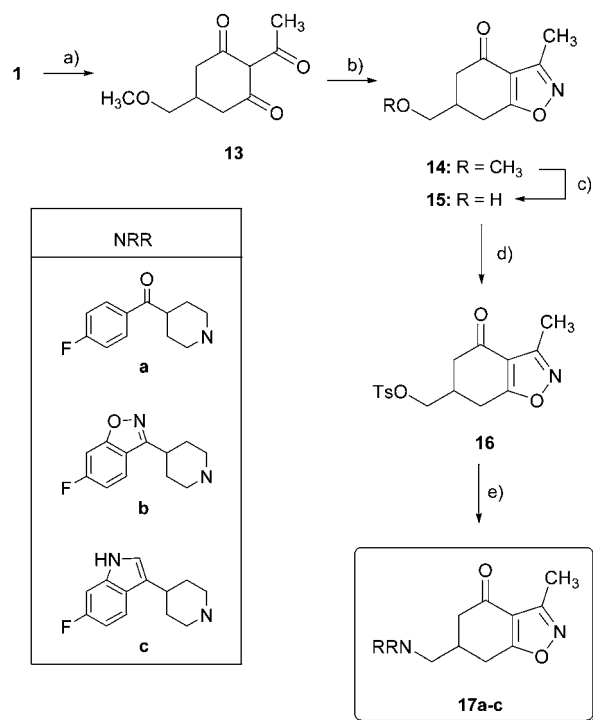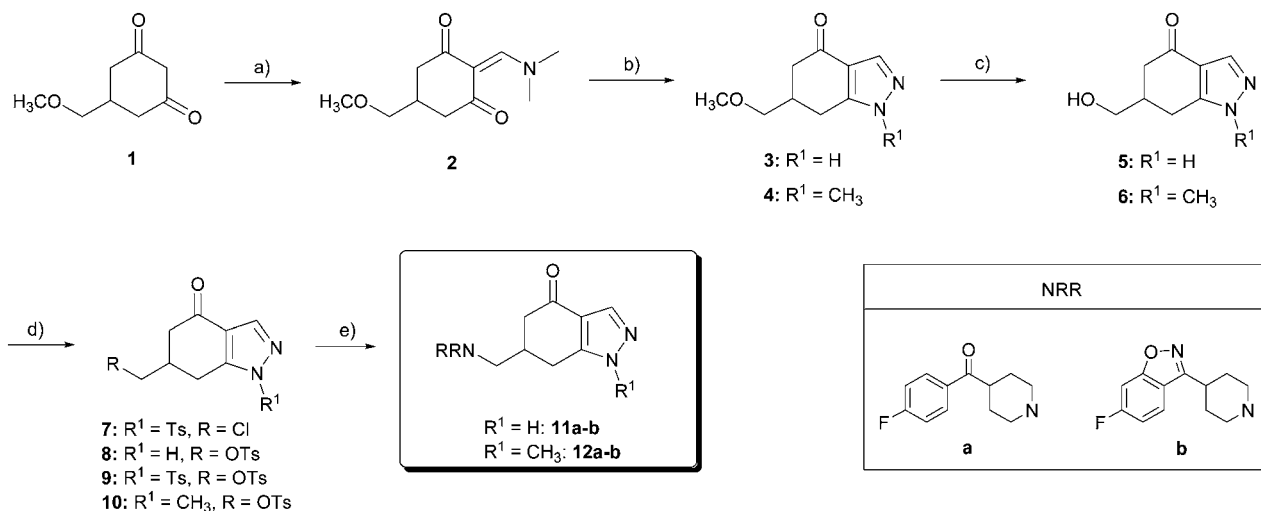

Scheme 2 *Reagents and conditions*: (a) Ac$_2$O, Et$_3$N, DMAP, CHCl$_3$, r.t., 24 h, 69%; (b) NH$_2$OH·HCl, KOH, MeOH, C$_6$H$_6$, r.t., 48 h, 71%; (c) BBr$_3$, 15-crown-5, CH$_2$Cl$_2$, −30 °C, 4 h, 56%; (d) *p*-TsCl, pyridine, 0 °C, 12 h, 61%; and (e) HNRR, CH$_3$CN, reflux.

Chemistry

The starting product for the synthesis of the target compounds **11–17**, **22**, and **27** (Schemes 1–3) was 5-(methoxymethyl)-cyclo-hexane-1,3-dione **1**, which was prepared from the commercial 3,5-dimethoxy- (or 3,4,5-trimethoxy-) benzoic acid in a four step procedure, as previously described by our research laboratory.[25]

For the synthesis of indazolones **11** and **12** (Scheme 1), dike-tone **1** was condensed with *N,N*-dimethylformamide

Scheme 1 *Reagents and conditions*: (a) DMFDMA, THF, 80 °C, 3 h, 95%; (b) Ac$_2$O, Et$_3$N, DMAP, CHCl$_3$, r.t., 24 h, 69%; (c) NH$_2$NH$_2$·2HCl, NaOH, MeOH, 80 °C, 4 h, 70%; (d) NH$_2$NHCH$_3$, MeOH, 80 °C, 2.5 h, 70%; (e) NH$_2$OH·HCl, KOH, MeOH, C$_6$H$_6$, r.t., 48 h, 71%; (f) BBr$_3$, CH$_2$Cl$_2$, −40 °C → r.t., 24 h, 40–81%; (g) BBr$_3$, 15-crown-5, CH$_2$Cl$_2$, −30 °C, 4 h, 56%; (h) TsCl, Py, r.t., 24 h, 50–71%; and (i) HNRR, solvent, reflux.
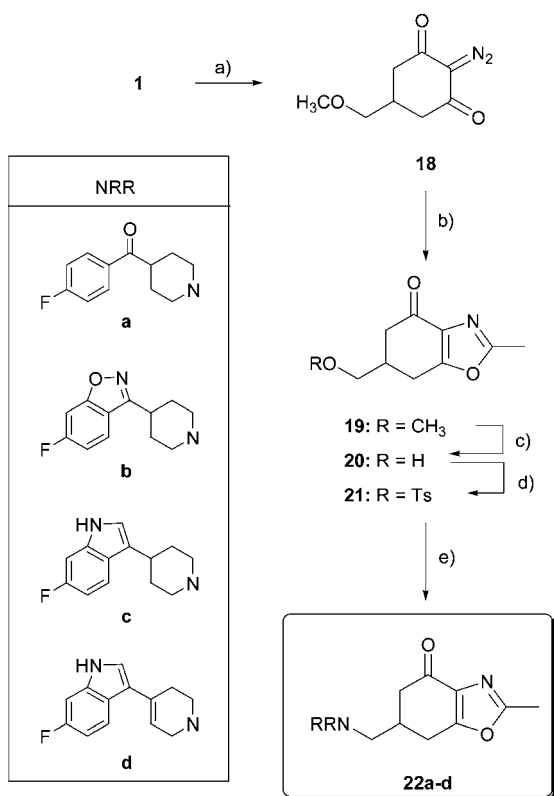
Scheme 3 *Reagents and conditions*: (a) *p*-tosyl azide, Et₃N, CH₂Cl₂, r.t., 15 h, 80%; (b) Rh₂(OAc)₄, CH₃CN, 60 °C, 7 h, 60%; (c) BBr₃, CH₂Cl₂, −40 °C, 12 h, 0 °C, 12 h, 65%; (d) *p*-TsCl, pyridine, 0 °C, 12 h, 66%; and (e) HNRR, CH₃CN, reflux.

Scheme 4 *Reagents and conditions*: (a) thiourea, NBS, benzoyl peroxide, benzene, reflux, 48 h, 70%; (b) 1,4-dibromobutane, NaOH, reflux, 7 h, 70%; (c) BBr₃, CH₂Cl₂, −40 °C, 12 h, then 0 °C, 12 h, 91%; (d) *p*-TsCl, pyridine, 0 °C, 12 h, 57%; and (e) HNRR, CH₃CN, reflux.

dimethylacetal (DMFDMA) to give amino ketone **2** in 95% yield. By a *Michael* addition–elimination/cyclodehydration process, using hydrazine dihydrochloride and NaOH at reflux, **2** was transformed into pyrazole **3** in 70% yield, and methylhydrazine at reflux afforded **4** as a single regioisomer, also in 70% yield. Methyl ethers of **3** and **4** were cleaved with BBr₃ in CH₂Cl₂ at −40 °C → r.t., affording the corresponding alcohols **5** and **6** in 81% and 40% yield, respectively. Forcing these conditions (2 mol equiv. BBr₃, higher temperatures, or longer reaction times) or using other reagents, such as trimethylsilane iodide, gave complex mixtures of products.

Tosylation of **5** was complicated due to the reaction between the unprotected nitrogen of the pyrazole ring and the tosyl chloride: first attempts for tosylation of the hydroxyl group led to a mixture of chloride **7**, monotosylate **8** and ditosylate **9**. Then, we decided to increase the number of equivalents of tosyl chloride to force the formation of the ditosyl derivative **9**, to further deprotect the pyrazole ring. Under these conditions, ditosylate **9** was obtained in 50% yield as the major product. Tosylation of alcohol **6** under standard conditions furnished the corresponding sulfonate **10** in 71% yield. Tosylates **9** and **10** were converted into the required amines **11–12** by nucleophilic displacement of the tosyl group by the corresponding substituted piperidines **a** or **b** (Scheme 1). Nucleophilic substitution reaction on ditosylate **9** proceeded with simultaneous attack at the electron-deficient sulfur atom of the *N*-tosylpyrazole, which resulted in deprotection of the pyrazole ring, affording the desired amines **11a** and **11b** in a single step.[24]

On the other hand, **1** was converted into a 2-acetyl derivative **13** (Scheme 2) by treatment with acetic anhydride and triethylamine in the presence of 4-(dimethylamino)pyridine (DMAP) in 69% yield. Condensation of **13** with hydroxylamine hydrochloride in the presence of KOH yielded **14** in 71%. Methylether cleavage in benzisoxazolone **14** with BBr₃ led to alcohol **15** in a modest 30% yield. The addition of 15-crown-5 to BBr₃ allowed us to improve the yield up to 56%. Tosylation of alcohol **15** gave the corresponding sulfonate **16** in 61% yield, and nucleophilic displacement of the tosyl group by the corresponding substituted piperidines **a**, **b** or **c** furnished amines **17a–c**.

For the synthesis of oxazolones **22** (Scheme 3), the construction of the oxazole ring was tackled by rhodium-catalyzed cyclocondensation of a diazocarbonyl derivative with a nitrile, following the method reported by Lee and Suk.[26] Thus, reaction of compound **1** with tosylazide in the presence of Et₃N afforded the diazodicarbonyl derivative **18** (IR peak at 2142 cm⁻¹) in 80% yield. Dipolar cycloaddition of **18** with acetonitrile (as the solvent and reagent) in the presence of 2 mol% of Rh₂(OAc)₄ at reflux gave 6,7-dihydro-2-methyl-6-(methoxymethyl)-benzoxazol-4(5H)-one (**19**) in 60% yield. As described above, methylether cleavage of tetrahydrobenzoxazolone **19** with 1 M solution of BBr₃ led to alcohol **20** in 65% yield. Tosylation of **20** (66% yield) and subsequent reaction with amines **a–d** furnished final tetrahydrobenzoxazolones **22a–d** in 20–50% yield.

Benzothiazolones **27** (Scheme 4) were prepared using thiourea as a source of heteroatoms for the construction of the thiazole ring. Accordingly, one pot reaction of diketone **1** with thiourea, NBS and benzoyl peroxide (catalytic) in benzene gave the

Table 1 Results of binding assays (pK_i or % of displacement at 10 μM)[a]

Compound	Structure	D$_2$	5-HT$_{2A}$	pK_i 5-HT$_{2A}$/pK_i D$_2$
11a (QF4104B)		6.40 ± 0.15	7.37 ± 0.22	1.15
11b (QF4108B)		6.95 ± 0.06	8.67 ± 0.19	1.25
12a (QF4124B)		1.4%	7.52 ± 0.16	—
12b (QF4128B)		10.9%	7.76 ± 0.44	—
17a (QF4214B)		<5	7.39 ± 0.12	—
17b (QF4218B)		6.92 ± 0.3	7.76 ± 0.32	1.12
17c (QF4216B)		7.20 ± 0.10	8.00 ± 0.09	1.11
22a (QF4414B)		35%	6.90 ± 0.10	—
22b (QF4418B)		7.49 ± 0.06	7.70 ± 0.05	1.03
22c (QF4416B)		6.70 ± 0.20	8.30 ± 0.05	1.24
22d (QF4417B)		6.76 ± 0.12	7.10 ± 0.10	1.05
27a (QF4514B)		30%	6.55 ± 0.20	—
27b (QF4518B)		6.70 ± 0.08	7.70 ± 0.20	1.15
27c (QF4516B)		6.80 ± 0.10	8.10 ± 0.09	1.19
27d (QF4517B)		7.26 ± 0.13	7.40 ± 0.09	1.02
Haloperidol		9.22 ± 0.12	6.78 ± 0.25	0.73
Clozapine		6.65 ± 0.17	8.04 ± 0.31	1.21
Risperidone		8.21[b]	9.30 ± 0.25	1.13

[a] Values are means of two separate experiments. [b] Value taken from ref. 43.

benzothiazolone **23** in 70% yield. The amino group was alkylated with 1,4-dibromobutane in acetone in the presence of NaOH to afford 5,6-dihydro-5-(methoxymethyl)-2-(pyrrolidin-1-yl)benzo-thiazol-7(4H)-one (**24**) in 70% yield. From methyl ether **24**, the same three-step procedure described above yielded the final aminomethylbenzothiazolones **27a–d**.

Receptor binding studies

One way to distinguish the atypical antipsychotics from the conventional agents is that they block 5-HT$_{2A}$ receptors as well as D$_2$ receptors and have fewer motor side effects such as EPS than the conventional antipsychotics have at standard doses. On this basis, the affinity of the compounds **11**, **12**, **17**, **22** and **27** for cloned human D$_2$ and 5-HT$_{2A}$ receptors was first evaluated in *in vitro* binding assays using the radioligands [^{3}H]spiperone and [^{3}H]ketanserin, respectively, according to our previously described procedures.[27] Affinity values (expressed as pK_i) were calculated according to the Cheng–Prusoff equation,[28] and the *in vitro* receptor binding data are summarized in Table 1.

In general, the synthesized compounds showed greater affinity for the serotonin 5-HT$_{2A}$ receptor (pK_i range of values between 6.55, for **27a**, and 8.67, for **11b**) than dopamine D$_2$ receptors. Furthermore, in those series in which it has been incorporated, the fragment fluoroindolylpiperidine led to compounds with higher affinity for the two receptors tested. We can establish a decreasing order of affinities for the four amines used in the receptors tested that, with a few exceptions, is fulfilled in the synthesized compounds: **c > b > d > a**.

Compounds bearing the **4-(4-fluorobenzoyl)piperidine** fragment (Table 1) have low or no affinity for dopamine D$_2$ receptors, except the pyrazole derivative **11a**, with a pK_i D$_2$ = 6.40, which is the only one of the five compounds tested containing a hydrogen donor group in its heterocyclic system. This fact points to the existence of an interaction with the D$_2$ receptor binding site that would not occur in the rest of the compounds. Judging from the dopaminergic hypothesis of schizophrenia, those compounds without affinity for the D$_2$ receptor could not be considered as potential antipsychotics. As regards the 5-HT$_{2A}$ receptors, some derivatives have moderate affinity for this receptor, with pK_i values ranging from 6.55 to 7.52, the *N*-methylpyrazole derivative **12a** being the compound with higher affinity in this series.

Compounds bearing a **4-(benzoisoxazolyl)piperidine** system generally have a higher affinity for the two receptors studied than their counterparts that contain a benzoylpiperidine (Table 1). Therefore, the interaction between the benzoisoxazole system and the receptor binding site must be stronger than that of the benzoyl system, such that those compounds with no affinity now have affinity for D$_2$ (**17a** *vs.* **17b**; **22a** *vs.* **22b**; **27a** *vs.* **27b**) receptors. Among the five benzoisoxazolylpiperidine derivatives synthesized, compound **11b**, from the point of view of the potential antipsychotic activity would show, based on the *Meltzer index*,[29] an atypical profile (pK_i 5-HT$_{2A}$/pK_i D$_2$ = 1.25). Furthermore, its profile is similar to that shown for clozapine.

Compounds bearing a **4-(6-fluoroindol-3-yl)piperidine** (**17c**, **22c** and **27c**) were those that showed higher affinity at the 5-HT$_{2A}$ receptors, while unsaturated analogues **22d** and **27d**, containing a tetrahydropyridine moiety, have lower affinity at 5-HT$_{2A}$ receptors, but higher affinity at D$_2$ receptors, probably due to the different spatial arrangement that takes the indole ring when it is attached to a piperidine or to a tetrahydropyridine ring, and thus different interactions in the binding site of the receptors studied.

The indolylpiperidine derivatives **22c** and **27c** (together with the above mentioned benzoisoxazolylpiperidine **11b**) also showed a *Meltzer index* predictive of an atypical profile, making

Table 2 Results of binding assays (pK_i) for selected compounds

Compound	D$_1$	D$_3$	5-HT$_{1A}$	5-HT$_{2C}$	5-HT$_6$
11b (QF4108B)	7.41	6.73	5.82	6.91	6.20
22c (QF4416B)	7.47	5.87	6.31	7.00	6.67
27c (QF4516B)	7.44	5.96	6.99	6.90	6.45

them candidate compounds for further pharmacological study to determine the affinity profile on other receptors involved in the antipsychotic effect.

Apart from D$_2$ and 5-HT$_{2A}$ receptors, other GPCRs have been proposed to be involved in the antipsychotic effect. The dopamine D$_1$ receptor plays an important role in mediating dopaminergic transmission in the prefrontal cortex, which is decreased in schizophrenia patients. Controversy about this topic still exists despite ample evidence suggesting that the D$_1$ receptor gene is associated with performance on neuropsychological tests probing the function of the prefrontal cortex in schizophrenia, as well as positive and negative symptoms and therapeutic response to antipsychotics. As an important dopaminergic gene, the D$_1$ receptor may contribute to schizophrenia by interacting with other genes.[30]

Dopamine, through D$_3$ receptors, modulates the cholinergic system at the prefrontal cortex level. Although the D$_3$ receptor involvement in antipsychotic therapy is not already clear, D$_3$ antagonists (devoid of muscarinic effects) may enhance acetylcholine release in the frontal cortex,[31] thus improving cognitive deficits poorly treated by currently available agents.[32]

5-HT$_{1A}$ affinity contributes to the clinical efficacy of most of the atypical antipsychotics (aripiprazole, clozapine, olanzapine) and their low liability for EPS.[33,34] Moreover, there are several clinical studies which indicate that 5-HT$_{1A}$ agonism may be beneficial to improve cognition in some patients with schizophrenia.[35] Indeed, it has been proposed that 5-HT$_{1A}$ receptor stimulation, as well 5-HT$_6$ and 5-HT$_7$ antagonism, may contribute to the beneficial effects in cognition of atypical antipsychotic drugs.[36]

Evidence suggests that 5-HT$_{2C}$ receptors play a role in schizophrenia.[37,38] 5-HT$_{2C}$ receptor antagonists have been shown to reduce neuroleptic-induced catalepsy and thus it has been suggested that antagonism of 5-HT$_{2C}$ receptors may be responsible for the reduced risk of extrapyramidal side effects associated with the atypical antipsychotic medications,[39] and also affects cognition and psychosis by modulating the cortical and limbic dopaminergic activity.[36]

On the other hand, neurobiology and *in vivo* pharmacology studies in rodents have shown that 5-HT$_6$ antagonists improve memory and cognition through involvement in multiple neurotransmission systems including both cholinergic and glutamatergic systems and, therefore, can potentially provide an effective treatment for cognitive dysfunction in schizophrenia.[36,40,41]

Based on this evidence as well as their internal experience, Payne proposed five key receptors for antagonism for the treatment of schizophrenia, proposing that a compound should have p$K_i \geq 8$ at D$_3$, 5-HT$_{2A}$, 5-HT$_{2C}$ and 5-HT$_6$ receptors, and p$K_i \geq 7$ at D$_2$ receptors for showing atypical antipsychotic behaviour.[11,42]

Taking all these into account, the binding profile of the three selected compounds was tested over these receptors (Table 2).

The three selected compounds have an equivalent selectivity profile, with similar affinities on the seven receptors tested: $5\text{-HT}_{2A} > D_1 > D_2 \approx D_3 \approx 5\text{-HT}_{2C} \approx 5\text{-HT}_6 \approx 5\text{-HT}_{1A}$. The binding profile was close to that proposed for the five key receptors, with the only exception of D_3 receptors where compounds **22c** and **27c** showed pK_i values of 5.87 and 5.96, respectively, *vs.* a proposed $pK_i \geq 8$, while compound **11b** showed a pK_i value of 6.73 at D_3 receptors, closer to the proposed one for an atypical antipsychotic profile. In addition to their interest as leads for antipsychotics, the subtle differences observed in their profile make these compounds very interesting as pharmacological tools because they could allow to ascertain the involvement of 5-HT_6 and, overall, D_3 receptors in the antipsychotic pharmacology.

Conclusions

In this work we describe the synthesis, binding affinity and SAR of new heterocyclic bioisosteric butyrophenone analogues as multi-target ligands. For the 15 compounds synthesized, binding affinity assays on D_2 receptors showed that compounds with higher affinity were those bearing an indolylpiperidine system followed by those containing a benzisoxazolylpiperidine fragment. With respect to the heterocycle fused to the cyclohexanone, the isoxazole ring afforded the highest affinity compounds. For the 5-HT_{2A} receptor, the trend observed in the piperidine moiety seems the same to that for the dopamine D_2 receptor: indolyl > benzisoxazolyl > benzoyl. In relation to the fused heterocyclic ring, available data showed a higher affinity for the pyrazole derivatives. Moreover, in the thiazole series, the presence of a bulky amine such as pyrrolidine did not seem to have a great influence on the affinity for this receptor. In particular, among the compounds prepared, **11b**, **22c** and **27c** exhibited the highest affinity for binding to the D_2 and 5-HT_{2A} receptors, and consequently the affinities on D_1, D_3, 5-HT_{1A}, 5-HT_{2C} and 5-HT_6 receptors were determined for these three compounds. The affinities of the selected compounds on the receptors assayed could allow to ascertain the involvement of 5-HT_6 and D_3 receptors in the antipsychotic effect.

Acknowledgements

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