A Synthetic Overview of New Molecules with 5-HT\textsubscript{1A} Binding Affinities

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Abstract: The present review discusses the synthetic strategies of new ligands exhibiting mainly 5-HT\textsubscript{1A} binding affinities. Specifically we focused our attention in the synthesis of compounds structurally related to arylpiperazine, 2-aminotetralin, and benzopyran derivatives.

Keywords: serotonin, 5-HT\textsubscript{1A} ligands, arylpiperazines, aminotetralins, benzopyrans.

INTRODUCTION

Depression is one of the most common illnesses, affecting up to one-third of all people at the same time. Depressive disorders encompass a variety of conditions including two major forms of unipolar depression (i.e. major depression and dysthymia), adjustment disorders, subsyndromal depression (minor depression), seasonal affective disorder (SAD), premenstrual dysphoric disorder (PMDD), postpartum depression, atypical depression and bipolar disorders [1]. The causes of depression are multifactorial, including hereditary aspects, childhood environment, or traumatic events which may predispose or trigger a depressive episode [2], although it is accepted that neurochemical disorders are ultimately responsible for the appearance of the depressive symptoms.

The monoaminergic hypothesis of depression [3] assumes that depressive disorders are a consequence of insufficient concentration of noradrenaline (NA), and serotonin in corticolimbic synaptic clefts. So that whatever molecule aimed to increase the concentration of these neurotransmitters available for release at the synapse, should be considered a potential antidepressive. The catecholamine theory first postulated began to be less accepted with the introduction of the first selective serotonin reuptake inhibitors in the early 1980s. Since that time, scientific discussion on the mechanisms and backgrounds of depression has been dominated by the serotonin hypothesis.

SEROTONIN THEORY

The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) modulates the activity of central nervous system and peripheral tissues by interacting with multiple receptors. During the last 15 years, seven distinct families of 5-HT receptors have been identified (5-HT\textsubscript{1}–5-HT\textsubscript{7}), and at least 15 subpopulations have been described for several of these [4,5]. The 5-HT\textsubscript{1A} receptors represent a major target for neurobiological research and drug developments. A study on distribution of 5-HT\textsubscript{1A} receptors in the brains of various animal species indicates that the highest densities are located in the hippocampus, septum, amygdale, and cortical limbic areas. The 5-HT\textsubscript{1A} receptors located in the raphe nuclei are known as somatodendritic autoreceptors.

This receptors were originally defined as those 5-HT\textsubscript{1} sites labeled in rat brain homogenates by \textsuperscript{[3H]}5-HT that displayed high affinity for spiperone. Almost simultaneously a novel serotonergic agent: 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) was incorporated. To date, this compound remains as one of the most selective serotonergic agents available. Although a number of other radioligands have been explored over the years, \textsuperscript{[3H]}-8-OH-DPAT still remains a popular radioligand for labeling 5-HT\textsubscript{1A} sites.

The serotonin 5-HT\textsubscript{1A} receptor subtype has been involved in the regulation of a variety of physiological and pathophysiological process like: psychosis, cognition, feeding/ satiety, temperature regulation, depression, sleep, pain perception and sexual activity [6]. The 5-HT\textsubscript{1A} receptor belong to the class of G-protein coupled receptors (GPCRs) and the receptors of this class have a number of aminoacid patterns in common; this conditions became noteworthy in the high degree of homology to α\textsubscript{1} adrenergic receptors subtype so a great number of ligands possess high affinity and poor 5-HT\textsubscript{1A}/α\textsubscript{1} selectivity. As a consequence many efforts have been directed to increase selectivity for the 5-HT\textsubscript{1A} receptors.

However one of the major disadvantage of used antidepressant agents independent of their mechanism of action, is the 4 - 6 week delayed requires to induce therapeutic effects. It has been hypothesized that this delay can be explained by the initial elevation in the raphe nuclei.
of extracellular 5-HT, which reduces the firing of serotonergic neurones by activating somatodendritic 5-HT1A autoreceptors [7].

After repeated antidepressant treatment, somatodendritic 5-HT1A receptors become desensitized, restoring the firing activity of serotonergic neurones and the increase in extracellular 5-HT in forebrain areas, coincides with the onset of antidepressant effect.

The first antidepressants available were classified either as tricyclic antidepressants or as monoamine oxidase inhibitors (MAOIs), a classification that mixes a structural criterion with a functional one. In an effort to avoid some of the many side effects such as hypertensive crisis (MAOIs) and anticholinergic effects (tricyclic derivatives), a broad range of new structures has been studied [8] and some of them incorporated for the treatment of depressive disorders. Important advances in the field of antidepressants led to the introduction of selective 5-HT reuptake inhibitor (SSRIs), joined to the development of new agonists and antagonists with pre-and post–synaptic adrenergic, serotonergic and dopaminergic activities. The present paper will review mainly the synthetic strategies focused to the obtention of new molecules with 5-HT1A subreceptor binding affinity, and will cover three main families: arylpiperazine, 2-aminotetralin, and benzopyran compounds.

ARYLPIPERAZINE DERIVATIVES

Long chain arylpiperazines with an amide or imide moiety represent one of the most important classes of the 5-HT1A receptor ligands. Among the commonly studied agents are buspirone, gepirone, NAN-190, flesinoxan, WAY-100135, and WAY-100635 Fig. (1). Buspirone, an azaspirodecanedione compound [9] introduced in the mid 1980s, is an arylpiperazine derivative used as a psychotropic drug with anxiolytic and antidepressant properties, classified as a 5-HT1A partial agonist. The isoindole-1,3-dione derivative NAN-190, displays high affinity for 5-HT1A receptors (K= 0.6 nM) but also has a high potency for the α1 receptor. In radioligand binding assays NAN-190 displays a partial agonist like activity [10].

WAY-100635 (N- (2- (4 - (2 – methoxyphenyl) -1-piperazinyl) ethyl)-N-(2-pyridyl)-cyclohexane carboxamide, is known to be one of the first potent, silent and selective antagonist for serotonin 5-HT1A receptors at both somatodendritic and postsynaptic receptor sites [11]. Considering that the synthesized compounds were not optimal in terms of selectivity, pharmacokinetics properties, and showed a slow set of action, more selective and potent 5HT1A chemical structures have been synthesized and tested pharmacologically for possible uses as antidepressive. We will give an overview of the new synthetic approaches generated in the last years.

van Steen et al. [12] [13] published a structure - affinity relationship study for two series of heterobicyclic phenylpiperazines with N-4 alkyl substituents (2,3-dihydro-1,4-benzodioxin-5-yl) piperazine and its benzofuranyl analogue Fig.(2). The compounds were obtained by direct alkylation of piperazine derivatives with alkyl halide or by reductive alkylation with the corresponding acid chloride followed by LiAlH4 reduction.

Following this search they synthesized [14] a series of succinimido, maleimido, and glutarimidoethyl derivatives of eltoprazine. The N-4-imidoethyl derivatives were obtained by reaction of the 1,4-benzodioxinylpiperazineethanamine with the corresponding anhydride in the presence of diisopropylethylamine. Moderate 5-HT1A affinities were detected Fig.(3).
Soudijn and van Steen reported in 1998 [15] the synthesis of a series of new N-4-substituted benzodioxinyl piperazines resumed in Fig. (4). The arylpiperazine moiety was done by reaction of 4-phenylpiperazine with 1-chloro-3-cyanopropane followed by treatment with LiAlH₄ to reduce the cyano group. The p-fluorobenzenamide derivative was obtained by reaction of aminoalkylarylziperazone with the corresponding benzoyle chloride. The reaction of N-(4-bromobutyl) phthalimide and N-(4-bromobutyl) saccharin with 1-(2,3-dihydro-1,4-benzodioxin-5-yl) piperazine afforded the corresponding derivatives. A novel potent full 5-HT₁₆ receptor antagonist was as potent as WAY-100635. Orjales et al. [16] prepared a series of (o-methoxyphenyl)piperazine derivatives and evaluated their 5-HT₁₆ affinities Fig. (5). They observed that the best affinities (Ki = 0.12-0.63 nM) were achieved increasing the lipophilicity of the cycloalkyl portion R = (cis-bicyclo[3.3.0]octan-2-yl and 5-norbornen-2-yl). The synthetic procedure involved alkylation of (o-methoxyphenyl)piperazine with bromoalkyl nitriles, followed by reduction of the cyano group, the resulting amine was reacted with the corresponding heteroaryl or cycloalkyl acid chloride.

Menge et al., explored the synthesis of new antidepressants with a dual mode of action, [17] serotonin reuptake inhibition and 5-HT₁₆ receptor antagonism, in a single chemical entity, this approach may facilitate the onset of the SSRIs antidepressant action. They linked a γ-phenoxypropylamine moiety (SSRI related) to an arylpiperazine ring (5-HT₁₆ ligand) Fig. (6). The 3-[(4-aryl)piperazine-1-yl]-1-arylpropane derivatives are represented in the Scheme 1. The synthesis of the ketone derivatives was carried out by using Mannich reaction of the corresponding acetophenones with different phenylpiperazine hydrochlorides and paraformaldehyde. The ketone-piperazines obtained were subsequently reduced and reacted with 4-fluorotrifuoromethylbenzene in sodium hydride, to afford the phenolic ethers.

These results led the authors to the design and synthesis of a series of compounds able to inhibit 5HT reuptake and to block 5-HT₁₆ receptors [18]. Utilizing the same strategy prepared a series of compounds of general structure Fig. (7). The phenylpiperazines not commercially availables were synthesized according to the procedure depicted in Scheme 2. They also [19] described new arylpiperazinyl benzo[b]thiophene derivatives with dual action Fig. (8). The chlorobenzothiophene derivative was synthetized analogously by reaction of 3-acetylbenzo[b]thiophene with 1-(2-methoxy-phenyl)piperazine under Mannich conditions. The fluoro benzo[b]thiophene was obtained by nucleophilic substitution of 3-chloro-1-(5-fluorobenzo[b]thiophene-3-yl)propan-1-one with 1-(2-methoxyphenyl)piperazine. Ki values were between (30 and 2.3 for 5-HT₁₆ receptors and 30 and 12 for SSRIs).
New arylpiperazine derivates of buspirone have been reported by Lopez et al. (1996) [20, 21] studying the synthesis and affinity for 5-HT$_{1A}$ receptors. In this series the imide moiety of buspirone 1 has been replaced by a bicyclohydantoin 2 Fig. (9) for (n=2) the bicyclohydantoin framework was constructed by reaction of ethylpipercolinate with 2-chloroethylisocyanate to afford the key intermediate 2-chloroethylbicyclohydantoin which was reacted with different arylpiperazines in N,N-DMF. The key intermediates (n=3,4) were obtained by reaction of bicyclohydantoin with appropriate dibromoalkanes in basic medium, which were finally reacted with arylpiperazines. The bicyclohydantoin derivative (n= 1), R=o-CH$_3$ binds at 5-HT$_{1A}$ sites with nanomolar affinity and devoid of affinity at $\alpha_1$-adrenergic, D$_2$ and 5-HT$_{2A}$ receptors. Continuing this work, [22-24] the author obtained new arylpiperazine derivatives considering steric modifications of the amide portions respect to the bicyclohydantoin moiety, and some derivatives devoid of
the terminal amide fragment were evaluated for 5HT\textsubscript{1A}/\alpha\textsubscript{1} affinity and selectivity Fig. (10).

Fig. (9).

In connection with the prior results, the same author [25,26] designed and synthesized new compounds of general structure 3 and 4 Fig. (11) focused on the study of physicochemical influence on the 5-HT\textsubscript{1A}/\alpha\textsubscript{1} receptor selectivities. In this series, the amide moiety is a diketopiperazine 3 or a bicyclohydantoin 4. The hydantoin derivative EF-7412 showed a high selectivity over the \alpha\textsubscript{1} receptor and an appreciable affinity for D\textsubscript{2} receptor subtype (Ki=22 nM). The synthesis was carried out from hydantoin with 1,4-dibromobutane in basic medium, followed by reaction with 1-(m-nitrophenyl) piperazine, nitro group reduction and treatment with ethylsulphonylchloride.

Santagati et al. reported in 1997 [27] the preparation of [(arylpiperazinyl)alkylthio]thieno[2,3-d]pyrimidinone derivatives 5. The synthetic strategy is showed in the Scheme 3. The potassium salts of the 2-thioxothieno[2,3-d]-pyrimidine derivatives reacted with the chloroalkylpiperazines to give the respective target compounds. The potassium salts were obtained from the corresponding 2-aminothiophene-3-carboxylates in the presence of ammonium thiocyanate and benzoyl chloride with subsequent heating of the N-(3-carbethoxythien-2-yl)-N'-benzoylthioureas.

In the 2000 the author [28] described the synthesis of a series of thienopyrimidinones 6 and 7 with high affinities and selectivities for 5-HT\textsubscript{1A} versus \alpha\textsubscript{1A} receptors Fig. (12). Compounds belonging to the series 6 were obtained by reaction of the monopotassium salt 8 Fig. (13) with 2-chloroacetylchloride, followed by nucleophilic attack of 1-(2-methoxyphenyl)piperazine. One of the derivatives belonging to the series 6 (Het.= 2-ethylthiophene; R\textsubscript{1}= NH\textsubscript{2}; X=S) displayed Ki values of 0.19nM and selectivity 115. In

Scheme 3
the thia diazolothienopyrimidinone series 7, the best
derivative (R1, R2=CH3, n=3), displayed Ki of 3.72 nM. In
an effort to improve this study [29] they reported new
ligands arylpiperazinylalkylthiothienopyrimidines 9, 10 and
thiazole derivatives 11 bonded to thioalkylarylpirperazines.
One of the compounds of structure 9 showed affinities in the
nanomolar range (0.26 nM) for the 5-HT1A receptor affinity.

Perrone et al. reported in 1994 [30] the synthesis and
evaluation of 4-alkyl-1-arylpiperazines. The series contains a
terminal dihydronaphtalene fragment on the alkyl chain,
Scheme 4. All compounds were synthesized starting from
the respective 1-tetralones, alkylated by Grignard reaction
using magnesium cyclopropyl bromide (A). The cyclopropyl
intermediates was cleavage and complete dehydration was
achieved by aqueous HBr in acetic acid (B). The bromo
derivatives were then reacted with 1-arylpirperazines to give
the target compounds. The compounds showed high
nanomolar affinity for 5-HT1A, moderate affinity for D2 and
low affinity for 5-HT2 receptors.

Using a similar strategy, they reported the synthesis [31],
of 4-alkyl-1-arylpiperazines bearing a tetralin moiety on the
terminal part of the side chain. The objective was to increase
selectivity on the 5-HT1A versus D2, D1, α1, σ and other 5-
HT1 receptors. Fig. (15). The exocyclically unsaturated
compounds (kinetic compounds) were obtained by a similar
approach : Grignard reaction of the corresponding methoxy-
1-tetralone with magnesium cyclopropyl bromide, followed
by a quick acid treatment (HCl-HOAc). The
thermodynamically favored endo compounds were obtained by reaction of exo compounds in cold acetic acid overnight. The 2-MeO-Ph, 2-pyridyl, and unsubstituted phenyl N-piperazine derivatives showed low IC₅₀ values (0.3nM) on 5HT₁A receptors and high selectivity. Searching for more potent derivatives, [32] they reported in 1996 the synthesis, and binding profile of a series of alkylamido and alkylamino derivatives of 1-aryl-4-[(1-tetralinyl)alkyl] piperazines [33] as 5-HT₁A ligands, where CONHR, CH₂NR, NRCH₂, or NHCO functions are linked to the α position of the tetralin nucleus (in place of the two methylene groups reported in the others arylpiperazines). The amine derivative 12 was prepared by reaction of 5-methoxy-1-tetralone with trimethylsilyl cyanide, providing a trimethylsilyl cyanohydrin which was hydrolyzed, dehydrated and reduced to obtain the corresponding carboxylic acid derivative 13. The reaction of 13 with phenylpiperazine derivatives in the presence of 1,3-dicyclohexylcarbodiimide, D.C.C., afforded an amide that was finally reduced to the amine. Fig. (16).

In a further work and taking the prior derivative 14 (Ar=Ph) as reference, Perrone Fig. (17) [34] obtained new compounds of structure 15 with high affinity and selectivity for the 5-HT₁A receptor. He reported the synthesis of new 1-phenylpiperazines linked to the α or β position of tetralin moiety, bearing a methoxy group in the aromatic ring, and attached to a different length of the methylene spacer between the basic nitrogen and the tetralin nucleus. The compounds were prepared by reaction of 1-tetralone as starting material, and converted in the 3-bromoalkyltetralone by a Grignard reaction, followed by acidic treatment and
catalytic hydrogenation on Pd/C. The bromoalkyl derivatives were then reacted with 1-arylpiperazine, to afford the expected products. Reitz et al. described in 1994 [35] the synthesis and activity of RWJ-37796, an arylpiperazine derivative later known as mazapertine, which binds with high affinity (Ki < 4 nM) to D2, D3, 5HT1A and α1A adrenergic receptors (Fig. 18). Compound RWJ-37796 was synthesized by reaction of 3-(chloromethyl)benzoyl chloride with piperidine to obtain 16 followed by nucleophilic displacement with 2-(isopropoxy)phenylpiperazine.

Keeping this findings, they synthesized in (1995) [36] a series of N-(2-alkoxyphenyl) piperazines containing an N-benzyl group bearing a variety of functions (R = aldehyde, alcohol, amide, imide etc). The interest of the authors was to reverse the catalepsy induced by antipsychotic agents, through the use of 5-HT1A agonists. Fig. (19)

The framework and related structures were constructed by reaction of N-(2-isopropoxyphenyl) piperazine with 1,3-bis-(chloromethyl)benzene. Compound 17 (R= δ-valerolactam), generated by displacement of the anion of δ-valerolactam with the chloromethyl derivative, proved to be the most active. Baxter and Reitz in 1997 described [37] the synthesis of a series of hindered rotation analogs of mazapertine, showing high affinity for the 5HT1A receptor but not for other serotonin or dopamine receptors. Sabb et al., (2001) [38] reported the synthesis of a series of phenylalanine and 3-pyridylalanine derivatives of 4-substituted [1,2,5]-thiadiazolepiperazines 18 with 5HT1A receptor agonist and antagonistic activity. Fig. (20). The synthetic sequence started by reaction of 3,4-dichloro- [1,2,5] thia diazole with N-Boc-piperazine, to afford the protected piperazine 19 which was then deprotected and treated with the N-Boc protected aminoacids, using D.C.C. (as coupling agent). The antagonist with the best profile was : (R1= OCH3, R2 =CH3, R3= Cyclohexyl ). Caliendo et al. [39] prepared a series of novel 1,2,3-benzotriazin-4-one arylpiperazines, and were evaluated for 5-HT receptors. The molecules exhibited Fig. (21) a good affinity, and two of them showed subnanomolar affinity on 5-HT1A, IC50 0.059 and 0.54 nM respectively for (X= OCH3, n =3 ; and X = m-CF3 , n=3). Pawlowsky et al. [40] reported the synthesis of several N-phenylpiperazinylpropyl derivatives of tricyclic pyrimido diazepino [ 2,1-f]theophylline, and evaluated its affinity for 5-HT1A and 5-HT2A receptors Fig. (22). Santana (1998) [41] and co-workers studied the importance of the N-aryl piperazine moiety on 5HT1A and dopamine receptors, they synthetized a series of coumarins linked to the phenylpiperazine portion by a propoxy chain Fig. (23). The compound 20 (R1=CH3; R2=H) showed the strongest affinity for 5-HT1A receptors.
Romero et al. [42] showed interest for increase the bioavailability of the antidepressant ipsapirone 21. They found that cyclopropanating the n-butyl chain of ipsapirone Fig. (24), the trans analog was more resistant to metabolism. The trans-cyclopropanated analog 22 was obtained via reduction of ester 23 Fig. (25) to afford chloroderivative 24 and reacted with sodium saccharin to provide 25, which was nucleophilically substituted by addition of 4-pyrimidopiperazine.

Strekowski et al. [43] reported in 1996 the obtention of new N-methylpiperazino substituted quinazolines, phthalazines and quinoline derivatives, determining the receptor binding properties (α1, 5-HT1A and 5-HT2A). The most active compound of the series was the 2-thienyl-quinazoline 26 (Ki=43nM), obtained by a regioselective substitution of 2,4-dichloroquinazoline 27 with 2-thienyllithium, followed by addition of N-methylpiperazine. Fig. (26).

Poupaert et al. [44] synthesized a series of mixed ligands of 2-piperazinylbenzothiazole 28 with agonist properties for 5-HT1A and antagonist properties for 5-HT3 receptor subsites, this profile could be useful in the treatment of psychotropic diseases. Fig. (27) The 1-(benzothiazol-2-yl)piperazine moiety was synthesized using 2-chlorobenzothiazole 29 and piperazine, in the presence of potassium carbonate. The 3-methyl-6-(ω-haloalkyl)benzothiazolinones 30 were obtained by a Friedel-Crafts acylation reaction on the 3-methylbenzothiazolinone,
followed by carbonyl reduction, and finally a condensation reaction between the arylpiperazine and the benzothiazolinone moiety 30.

Peglion et al. reported in 1995 the synthesis for novel compounds of structure 31 having selective antagonists at postsynaptic 5-HT1A receptors Fig. (28) [45]. The compounds were obtained by two ways: nucleophilic displacement between compound 32 and the appropriate piperazine, or by coupling of 33 with the acid derivative and subsequent amide reduction. Scott et al. [46] reported in 1995 the 1-[2-(methylethoxy)phenyl] pyrrole piperazine 34 (RWJ 25730), and the compound RWJ-37796 35, a promising candidate for further development. However in aqueous media at pH: 2, 34 probably underwent a retro-Mannich reaction or pyrrole hydrolysis to a 1,4-diketone. In this way new analogues were prepared where the pyrrole ring has been replaced by thiophene, furan, isoxazoline and pyridine (Fig. 29).

Kung et al. [47, 48] reported the preparation of p-alkylbenzamido derivatives of 4-(2’-methoxyphenyl)-1-[2’-(N-2”-pyridinyl)-p-iodobenzamido)ethyl]piperazines 36, by reaction of arylpiperazine 37 with the corresponding benzoylhalide derivatives. Figs. (30, 31). In order to improve the in vivo stability of 36, a series of cyclized amide analogues [48] such as 38, 39 and 40 were synthesized.

Abou-Gharbia et al. [49] reported in 1999 the synthesis of adamantylaryl and heteroarylpiperazine derivatives. Hydroxyalkyl arylpiperazines were obtained by treating arylpiperazines with 2-bromoethanol or 3-bromopropanol under basic catalysis. The aminoalkyl arylpiperazines were obtained by reaction of arylpiperazines with bromoacetonitrile or bromopropionitrile and subsequent reduction to the primary amine.

Three methods were proposed to synthesize the adamantyl esters and amides. One of these methods is showed in the Fig. (32). This study led to the discovery of adatanserin, a compound with mixed anxiolytic and antidepressant activities.
In order to study the structural requirements for a high 5-HT$_{1A}$ affinity of the agonist flesinoxan Fig. (1) and its selectivity versus D$_2$ receptors, a series of arylpiperazine congeners of flesinoxan were synthesized and evaluated by Kuipers et al. (1997) [50] Fig. (33).

The cis-dimethyl-substituted arylpiperazine was synthesized according to the retrosynthetic approach shown in Scheme 5.

Mokrosz et al. [51,52] obtained 4-alkyl-1-(o-methoxyphenyl) piperazines bearing a terminal benzotriazole fragment, determining their 5-HT$_{1A}$-5HT$_2$ affinity as is shown in Fig.(34). The series were obtained by a simple alkylation, as is shown in the Scheme 6. The compound 4-[3-(benzotriazol-1-yl)propyl]-1-(2-methoxy-phenyl)piperazine (n=3) is a potent presynaptic and postsynaptic 5-HT$_{1A}$ receptor antagonist (non selective for 5-HT$_{1A}$ versus $\alpha_1$ receptors). They also described in 1996 the synthesis of new analogs of buspirone [52]. The obtention of 2-(4-N-phthalimidobutyl)-1,2,3,4-tetrahydroisoquinoline is showed in Scheme 7.

An interesting synthetic approach that provides 3,4-dihydro-2-(1H)-quinolinones linked to an arylpiperazine moiety was reported by Oshiro in the 2000. [53] The Scheme 8 represent two methods utilized for the preparation of these compounds.

**BENZOPYRAN DERIVATIVES**

Robalzotan is a potent substituted chroman with selective 5-HT$_{1A}$ receptor antagonism and potential antidepressant properties [54]. This compound can be obtained starting from 4-fluoro-3-hydroxybenzoic acid 41 according Scheme 9. The esterification with trimethylorthoformate and sulfuric acid, provided the resulting ester 42 that was condensed with propargyl bromide. Subsequent cyclization and ester hydrolysis of 42
a = (1) 60%NaH, DMF, (2) 1-chloro-3-[4-(3-chlorophenyl)-1-piperazineyl]propane hydrochloride in DMF;

b = (1) 60%NaH, DMF, (2) 1, ω-dihaloalkane in DMF;

c = NaI, K₂CO₃, phenylpiperazinees in CH₃CN, n = 2, 3 or 4

Scheme 8

afforded the intermediate acid 43, finally converted in the expected robalzotan 45 through a two steps sequence involving the racemic intermediate: 3-amino-8-fluoro-3,4-dihydro-2H-1-benzopyran-5-carboxamide 44.

Guillaumet et al. [55] prepared an evaluated a series of 3,4-dihydro-3-amino-2H-benzopyran derivatives exploring modifications, such as extracyclic amino substituents and the length of the alkyl side chains. The best compounds possessed imido or sulfonamido functional groups with a preferential length of four methylenes for the side chain. The general synthetic approach considered the reaction between bromoazaspiro 46 and compound and 5-methoxy-3,4-dihydro-3-amino-2H-1-benzopyran 47 to afford the amine

Scheme 10
This amine was subsequently reacted with 1-iodopropane to give the desired substituted amine 49 in acceptable yields (Scheme 10). Further studies of the author included the obtention of rigid spirobenzopyran analogues [56].

Yasunaga et al. [57] reported the obtention of a series of novel 8-hydroxychroman derivatives as intermediates, evaluating their 5-HT$_{1A}$ antagonist activity. The 8-hydroxychromans 50 were converted to the desired products 51 via O-bromoethylation followed by coupling with $p$-methoxyphenylbutylamine Fig. (35).

Fig. (35).

Compounds possessed a potent affinity for the 5-HT$_{1A}$ receptor, where the C6-fluoro analog showed a Ki of 0.22 nM. Further studies have been carried out directed to the preparation and evaluation of new 6-fluorochroman [58]. Likewise Hammarberg in the 2000, [59] designed a series of 3-aminochromans derivatives 52 starting from the enantiomerically pure 3-amino-3,4-dihydro-2H-1-benzopyran 53 (3-aminochromane) which involved the participation of intermediate 54. Fig. (36)

Fig. (36).

2-AMINOTETRALINS

The 8-hydroxy-2-(di-n-propylamino)tetrinal (8-OH-DPAT) 55, which was reported by Arvidsson et al. [60] to be a potent centrally active 5-HT receptor agonist, is a selective 5-HT$_{1A}$-receptor ligand. It has been utilized as a lead compound in the search for compounds with improved pharmacological and pharmacokinetic profiles Fig. (37).

Fig. (37).

Hacksell [61] synthesized naphto[1,2-b]pyrans 56 and 57 using pure enantiomers of 55 as starting material. These compounds were considerably less potent as serotonergic agents but presented pharmacological stereoselectivities greater than 55 Scheme 11. On the other hand 8-methoxy-2-(di-n-propylamino)tetrinal and 2-N-(propylamino)tetrinal [62], which lacks an aromatic substituent also present affinity for 5-HT$_{1A}$. Thus, the presence of a free hydroxyl group does not appear to be essential for binding, although it may increase affinity and agonist potency.

Scheme 11

In a further work Hacksell [63,64] explored the importance of the C8 substituent in the interaction of 2-aminotetralin-based ligands with 5-HT$_{1A}$ receptors. Enantiopure derivatives were prepared by palladium-catalyzed reactions of the triflates of the enantiomers of 55. With the exception of the carboxy-substituted derivative the compounds displayed moderate to high affinities (Ki values range from 0.7 to 130 nM) for 5-HT$_{1A}$ receptors (Scheme 12). The (S)-2-furyl derivative was the most potent, with an affinity similar to 55.

Scheme 12
Using the same strategy [65], Hacksell et al. prepared new derivatives (1S,2R)- and (1R,2S)- of 8-hydroxy-1-methyl-2-(dipropylamino) tetralin 58 previously characterized as a selective and potent 5-HT1A receptor agonist, in which various C8-substituents have been introduced Fig. (38). Only one derivative (the C8 carboxamide derivative (1S,2R)) behaved like a selective 5-HT1A receptor agonist.

Hacksell, working with a less explored structural hybrids of 8-OH-DPAT, obtained several phenolic derivatives of 1,2-methano-NN,N-dipropyl-1,2,3,4-tetrahydronaph-2-ylamine 59. Compounds were synthesized through a three steps sequence, which involved the enamine intermediate 60, using the modified Simmons-Smith reaction [66] on the corresponding tetralone Fig. (39).

Stjernlöf [67] prepared and evaluated the enantiomers (S-(-) and R- (+)) of 6,7,8,9-tetrahydro-NN,N-di-n-propyl-3H-benz[e]indol-8-amino and their corresponding (R,S) 1-formyl analogs 62. The enantiomers obtained from tetralone 61 were agonists with full intrinsic activity exhibiting an affinity comparable to 8-OH-DPAT Fig. (40).

In a subsequent paper this group described another series of derivatives and isosteric derivatives of the aldehyde 62 [68]. Likewise Romero found that the 2-cyano 63 and related analogs [69] behaved as a potent 5-HT1A agonist where the (R)-enantiomer of this series showed the highest potency Fig. (41).

On the other hand Lin and co-workers [72] have described a series of 2,3,3a,4,5,9b-hexahydro-1H-benz[e]indole, these compounds are conformationally restricted, angular tricyclic analogs of 2-aminotetralin. The synthesis was achieved from the corresponding 2-tetralones, with two key steps: the regiospecific introduction of the alkyl side chain at the C-1 position, and the subsequent ring closure with the C-2 nitrogen to form lactam derivatives Scheme 13. Analogs with 9-methoxy substitution showed mixed 5-HT1A agonist and dopamine antagonist activity whereas the corresponding 9-hydroxy analogs displayed selective 5-HT1A agonist activity. The cis derivatives were found to be more potent than the corresponding trans analogs and in the cis series, the (3aR)(-) -enantiomers displayed higher potency.

A complementary study of these systems was performed by Stjernlöf [70] who studied the effect of the substituents in the aromatic system on serotonin and dopamine receptor subtypes. Ennis et al. [71] carried out structure-activity relationships studies in these systems, and obtained the indole ring derivative 64 by reaction of ketone 65 with propylamine followed by sodium cyanoborohydride reduction of the resulting enamine. Nearly all the studied compounds were exceedingly potent at the 5-HT1A receptor, although most also displayed significant affinity for the dopamine D2 receptor Fig. (42).
Scheme 13

Working with these frameworks [73] Lin reported the synthesis and pharmacological evaluation of cis-(3aR)-3-propyl-1H-benz[e]indole-9-carboxamide (-) (66). The cis racemate and its enantiomer as well as the corresponding trans enantiomers were also synthesized and evaluated. The synthesis take place from the hydroxy compound 67 (cis (+); the cis-(3aR)-(-); and the cis-(3aS)-(+). The compounds were converted in the corresponding triflates, carbonylated and hydrolyzed to the acid 68, to give the amide 66 by treatment with gaseous ammonia in the presence of diethylcyanophosphonate Fig. (43).

Fig. (43).

Several new derivatives of 8-OH-DPAT were prepared by Langlois et al. using Curtius degradation of 2-tetralin carboxylic acid derivatives [74] Fig. (44), and their affinity for 5-HT1A and 5-HT1B receptors was evaluated. The results emphasized the favorable effect of the substitution on the phenyl ring of a homocyclic ring fused in positions [6,7] or [6,5] to obtain specific ligands for the 5-HT1A receptor. Methyl substitution in position 5 gave a compound with a good affinity for the 5-HT1A receptor. A further work [75] of the authors shown that the (-)-5-methyl-8-hydroxy-(di-n-propylamino)tetralin is a 5-HT1A receptor antagonist.

Fig. (44).

REFERENCES


