A Synthetic Overview of New Molecules with 5-HT_{1A} Binding Affinities

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Abstract: The present review discusses the synthetic strategies of new ligands exhibiting mainly 5-HT_{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_{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 appearence 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-hydroxytriptamine, 5-HT) modulates the activity of central nervous system and peripheral tissues by interacting with multiple receptors.

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During the last 15 years, seven distinct families of 5-HT receptors have been identified (5-HT_1–5-HT_7), and at least 15 subpopulations have been described for several of these [4,5]. The 5-HT_{1A} receptors represent a major target for neurobiological research and drug developments. A study on distribution of 5-HT_{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_{1A} receptors located in the raphe nuclei are known as somatodendritic autoreceptors.

This receptors were originally defined as those 5-HT_1 sites labeled in rat brain homogenates by [^{3}H]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, [^{3}H]-8-OH -DPAT still remains a popular radioligand for labeling 5-HT_{1A} sites.

The serotonin 5-HT_{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_{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_1 adrenergic receptors subtype so a great number of ligands possess high affinity and poor 5-HT_{1A}/ α_1 selectivity. As a consequence many efforts have been directed to increase selectivity for the 5-HT_{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

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of extracellullar 5-HT, which reduces the firing of serotonergic neurones by activating somatodendritic 5-HT_{1A} autoreceptors [7].

After repeated antidepressant treatment, somatodendritic 5-HT_{1A} 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-HT_{1A} 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-HT_{1A} 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-HT_{1A} partial agonist. The isoindole-1,3-dione derivative NAN-190, displays high affinity for 5-HT_{1A} receptors (Ki= 0,6 nM) but also has a high potency for the α_1 receptor. In radioligand binding assays NAN-190 displays a partial agonist like activity [10].

WAY-100635 (N- (2- (4 - (2 – methoxyphenyl) -1-piperazineyl) ethyl)–N-(2- pyridyl)-cyclohexane carboxamide, is known to be one of the first potent, silent and selective antagonist for serotonin 5-HT_{1A} 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 $5HT_{1A}$ 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 $LiAlH_4$ 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-Ht_{1A} affinities were detected Fig.(**3**).

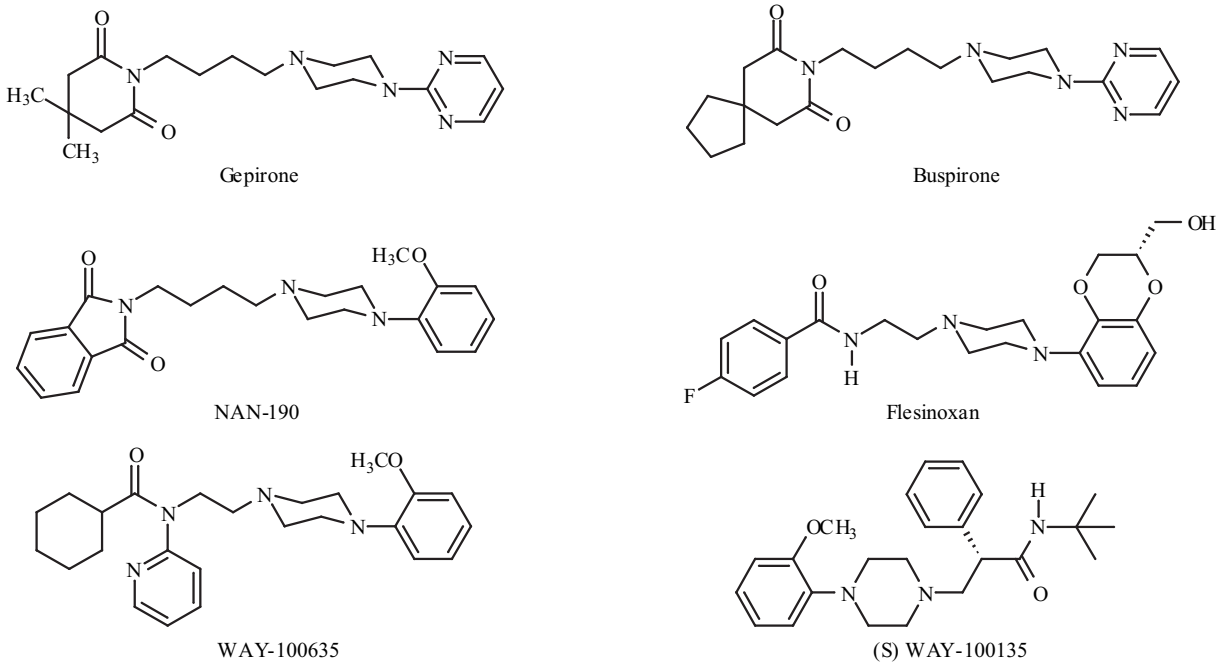


Fig. (1).

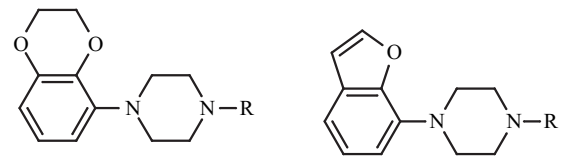


Fig. (2). R=Alkyl.

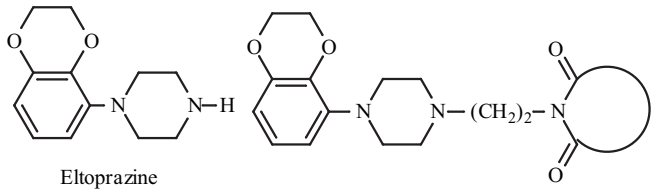


Fig. (3).

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 $LiAlH_4$ to reduce the cyano group The *p*-fluorobenzamide derivative was obtained by reaction of aminoalkylarylpiperazine with the corresponding benzoylchloride. 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-HT$_{1A}$ receptor antagonist was as potent as WAY- 100635. Orjales *et al.* [16] prepared a series of (*o*-methoxyphenyl)piperazine derivatives and evaluated their 5-HT$_{1A}$ 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.

Monge *et al.*, explored the synthesis of new antidepressants with a dual mode of action, [17] serotonin reuptake inhibition and 5-HT$_{1A}$ 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-HT$_{1A}$ 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-fluorotrifluoromethylbenzene in sodium hydride, to afford the phenolic ethers.

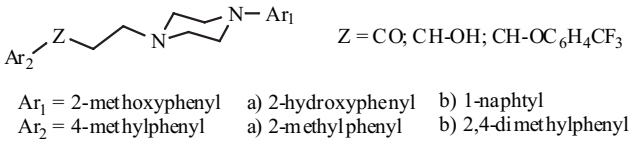
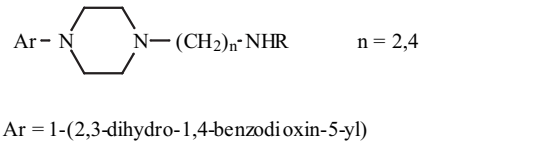


Fig. (6).

These results led the authors to the design and synthesis of a series of compounds able to inhibit 5HT reuptake and to block 5-HT$_{1A}$ 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 fluorobenzo[*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-HT$_{1A}$ receptors and 30 and 12 for SSRIs).



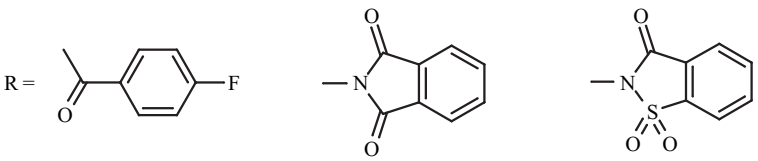


Fig. (4).

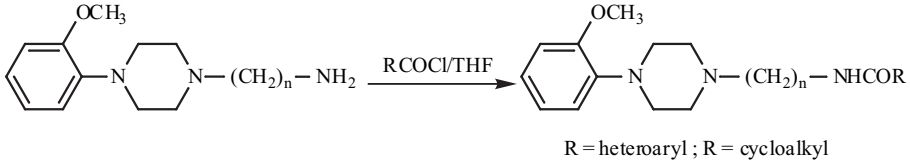
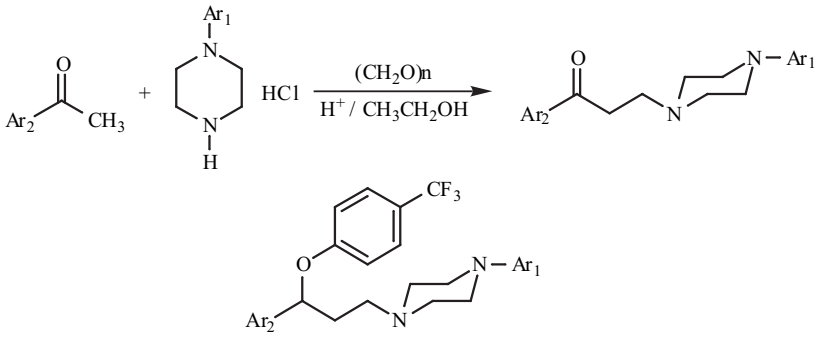


Fig. (5).



Ar^1= 2-methoxyphenyl, 2-hydroxyphenyl, 1-naphtyl

Ar^2= 4-methylphenyl, 2-methylphenyl, 2,4-dimethylphenyl

Scheme 1

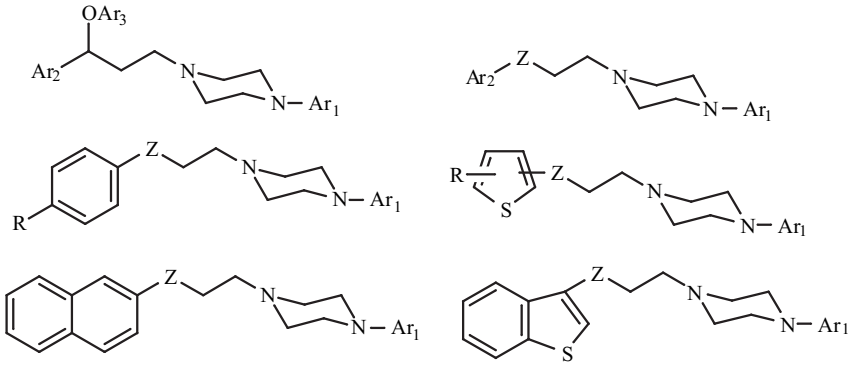
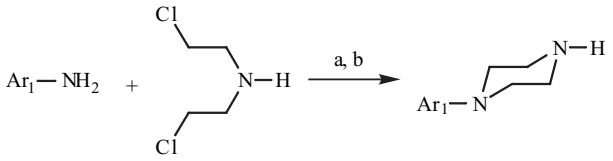
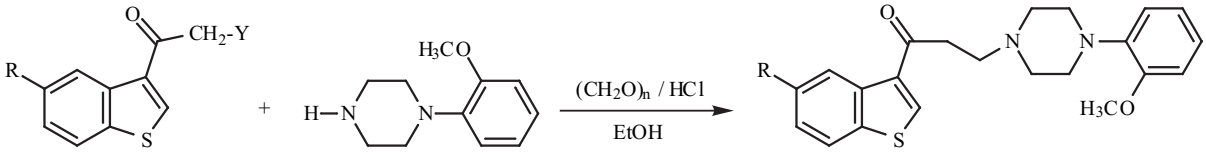


Fig. (7).



(a) K_2CO_3 / C_6H_5Cl ; (b) *p*-TosOH /C_6H_5Cl

Scheme 2



R = Cl ; Y = H
R = F ; Y = CH_2Cl

Fig. (8).

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 ethylpipecolinate 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 α_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$_{1A}$/α_1 affinity and selectivity Fig. (**10**).

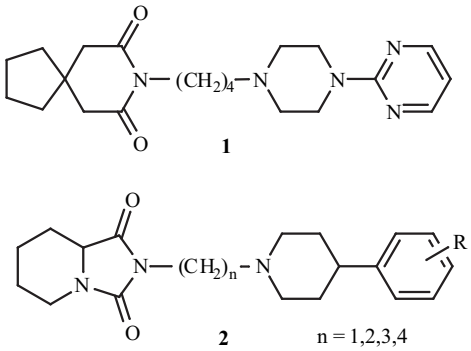


Fig. (9).

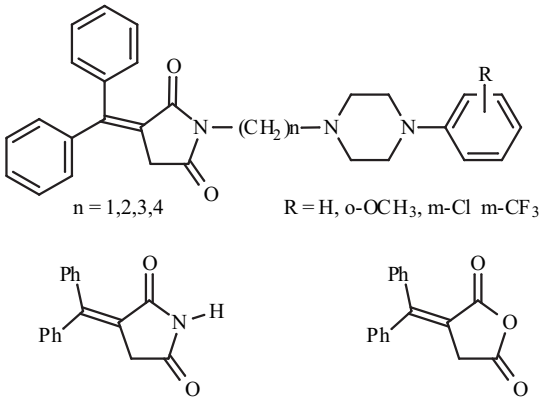


Fig. (10).

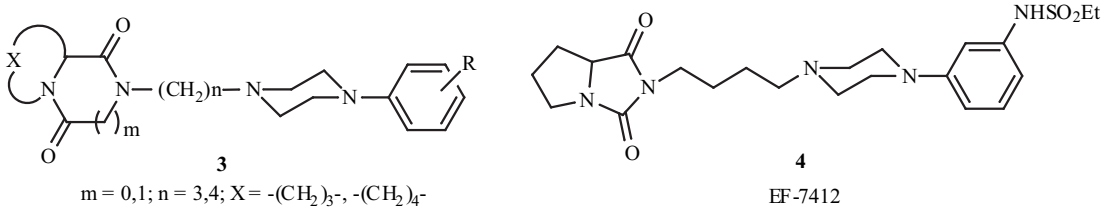
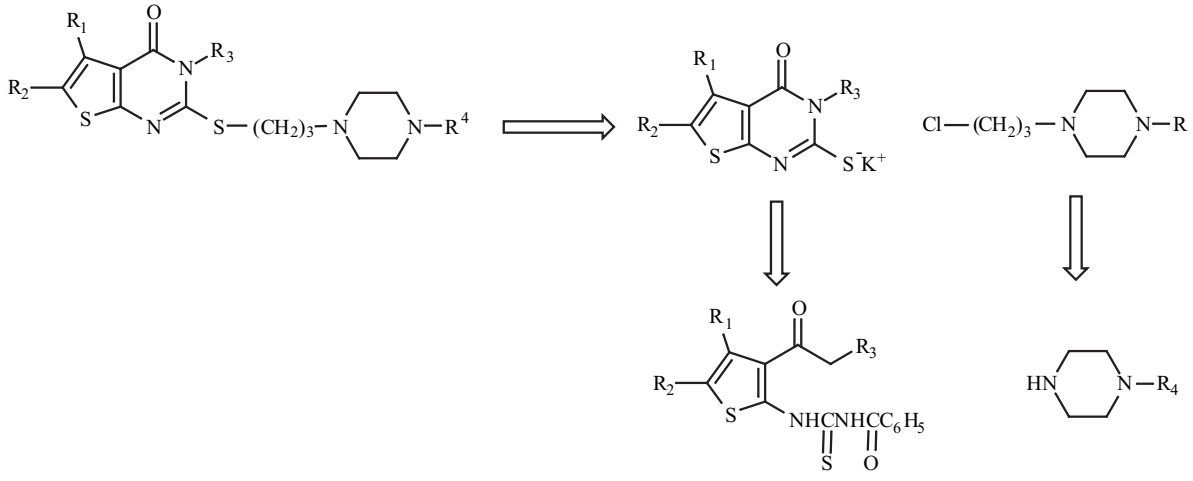


Fig. (11).

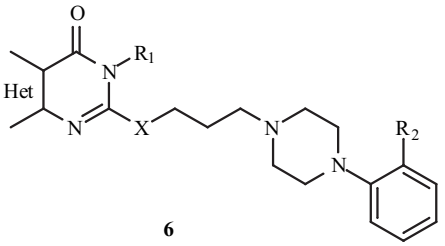


Scheme 3

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$_{1A}$-α_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 α_1 receptor and an appreciable affinity for D_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)alkyl]thio]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.

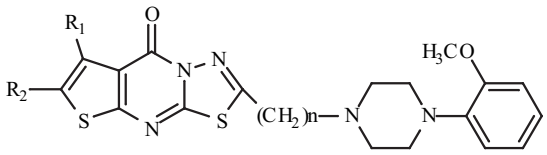
In the 2000 the author [28] described the synthesis of a series of thienopyrimidinones **6** and **7** with high affinities and selectivities for 5-HT$_{1A}$ versus α_{1A} receptors Fig. (**12**). Compounds belonging to the series **6** were obtained by reaction of the monopotassium salt **8** Fig. (**13**) 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_1= NH_2; X=S) displayed Ki values of 0.19nM and selectivity 115. In



6

$R^1 = C_2H_5, CH_2CH=CH_2, NHCOCH_3, NH_2$

$R^2=OCH_3, NO_2$; X=S, CH_2

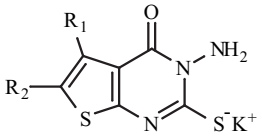


7

n = 1,3

Fig. (12).

the thiadiazolothienopyrimidinone series **7**, the best derivative (R^1, $R^2=CH_3$, 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 thioalkylarylpiperazines. One of the compounds of structure **9** showed affinities in the nanomolar range (0.26 nM) for the 5-HT_{1A} receptor affinity. Fig. (**14**)

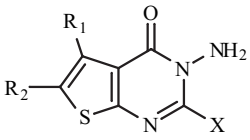


8

Fig. (13).

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-arylpiperazines to give the target compounds. The compounds showed high nanomolar affinity for 5-HT_{1A}, moderate affinity for D_2 and low affinity for 5-HT_2 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-HT_{1A} versus D_2, D_1, α_1 , σ an other 5-HT_1 receptors . Fig. (**15**). The exocyclically unsaturated compounds (kinetic compounds) were obtained by a similar approach : Grignards reaction of the corresponding methoxy-1-tetralone with magnesium cyclopropyl bromide, followed by a quick acid treatment (HCl-HOAc). The



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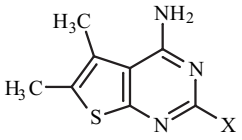

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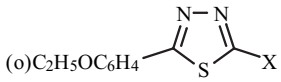

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X =

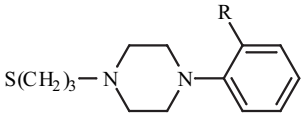
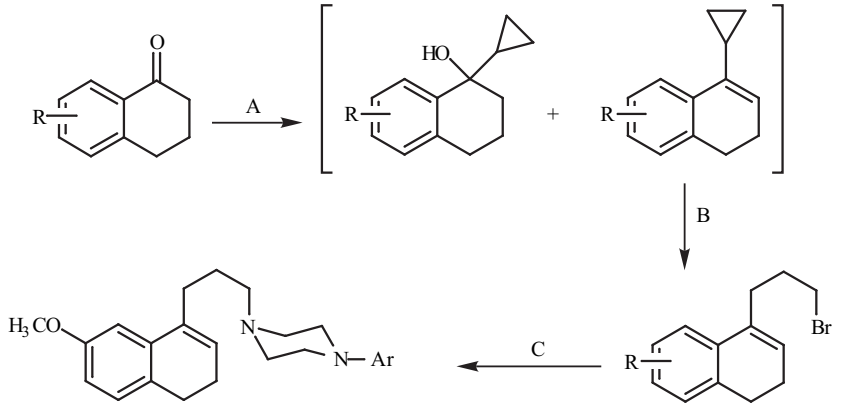


Fig. (14).



Scheme 4

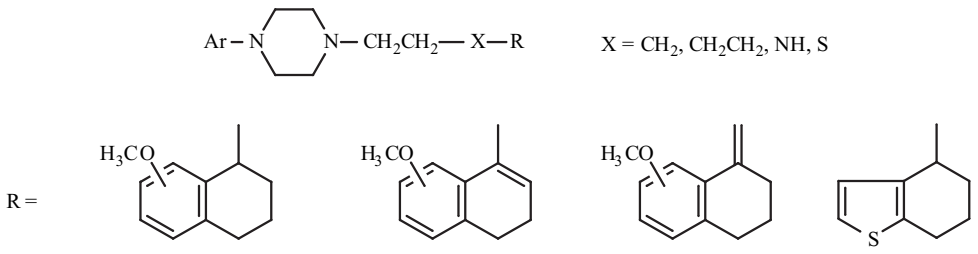


Fig. (15).

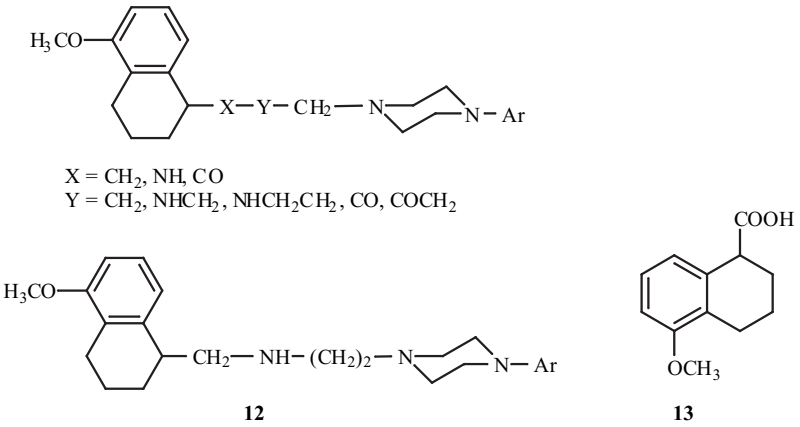
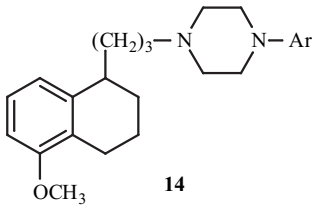


Fig. (16).

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 IC_{50} values (0.3nM) on $5HT_{1A}$ 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-HT_{1A} ligands, where CONHR,CH_2NR, NRCH_2, 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-HT_{1A} 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



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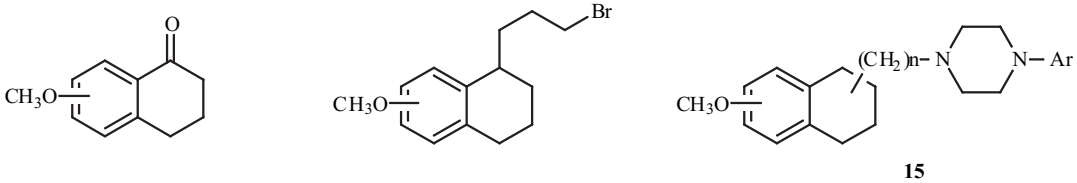

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Fig. (17).

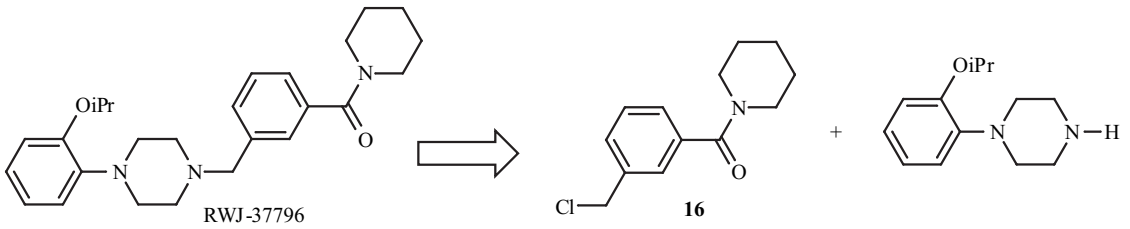


Fig. (18).

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 D_2, D_3, $5HT_{1A}$ and α_{1A} 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-HT_{1A} 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 $5HT_{1A}$ 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 $5HT_{1A}$ receptor agonist and antagonistic activity. Fig. (**20**). The synthetic sequence started by reaction of 3,4-dichloro- [1,2,5]- thiadiazole 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 : (R^1= OCH_3, R^2 =CH_3, R_3= 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-HT_{1A}, IC_{50} 0.059 and 0.54 nM respectivlely for (X= *o*-OCH_3, n =3 ; and X = *m*-CF_3 , n=3). Pawlowsky *et al.* [40] reported the synthesis of several N-phenylpiperazinylpropyl derivatives of tricyclic pyrimido and diazepino [2,1-*f*]theophylline, and evaluated its affinity for 5-HT_{1A} and 5-HT_{2A} receptors Fig. (**22**). Santana (1998) [41] and co-workers studied the importance of the N-arylpiperazine moiety on $5HT_{1A}$ and dopamine receptors, they synthetized a series of coumarins linked to the phenylpiperazine portion by a propoxy chain Fig. (**23**). The compound **20** (R^1=CH_3; R^2=H) showed the strongest affinity for 5-HT_{1A} receptors.

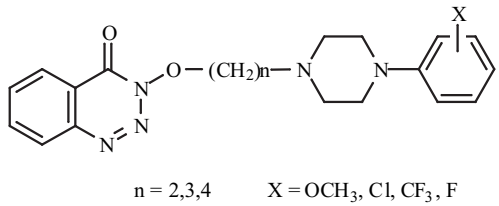


Fig. (21).

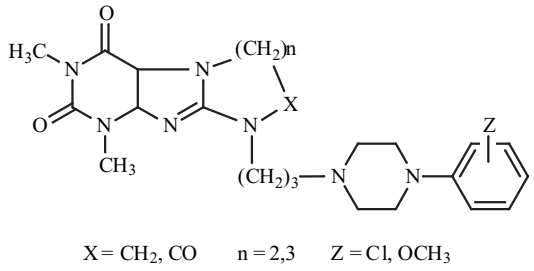
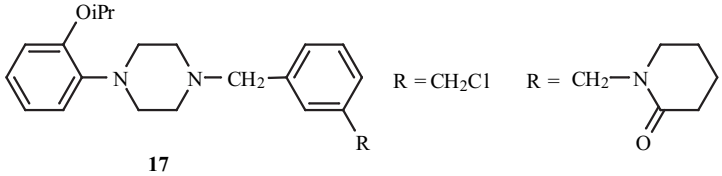
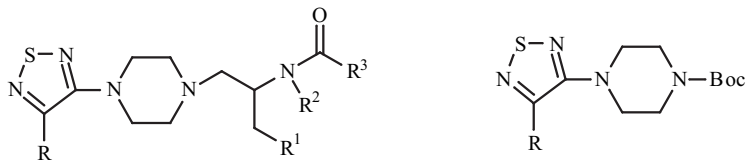


Fig. (22).



17

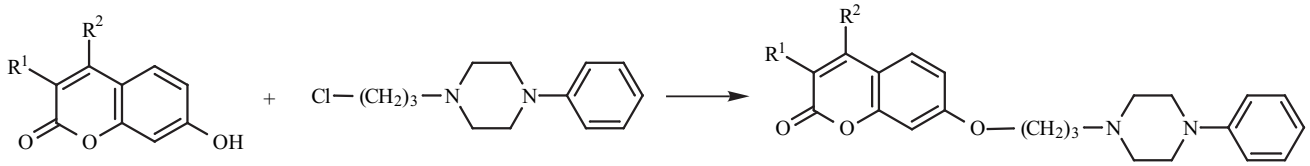
Fig. (19).



R = Cl, OCH_3 $R^1 = C_6H_5$ R^2 = H, CH_3 $R^3 = C_6H_5$, C_6H_{11}

18 **19**

Fig. (20).



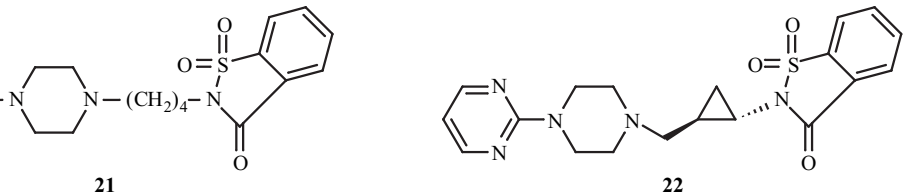
20

Fig. (23).

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 *vía* 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.

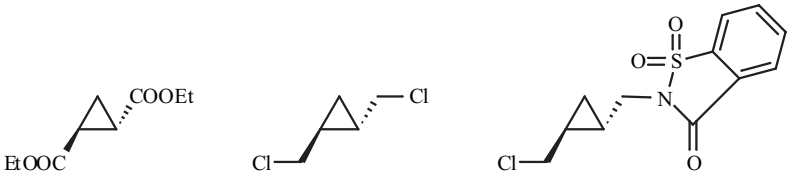
Strekowski *et-al*. [43] reported in 1996 the obtention of new N-methylpiperazino substituted quinazolines, phthalazines and quinoline derivatives, determining the receptor binding properties (α_1 , 5-HT$_{1A}$ and 5-HT$_{2A}$). The most active compound of the series was the 2-thienyl-quinazoline **26** (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-HT$_{1A}$ and antagonist properties for 5-HT$_3$ 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,



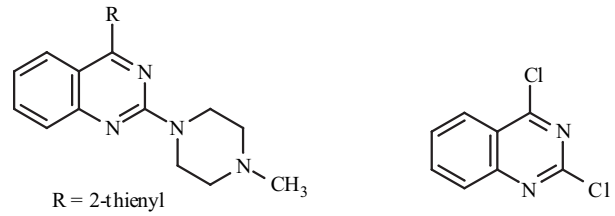
21 **22**

Fig. (24).



23 **24** **25**

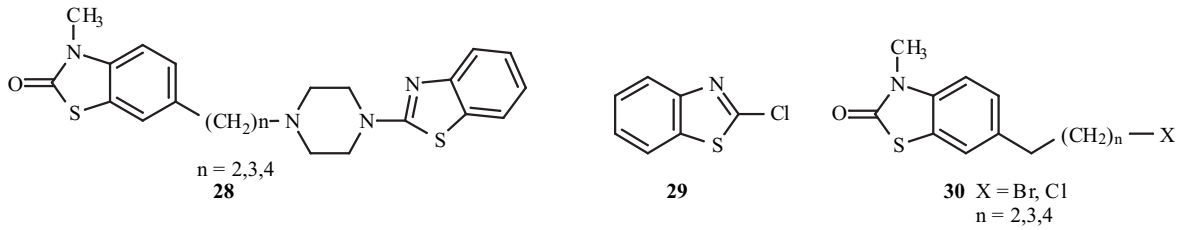
Fig. (25).



R = 2-thienyl

26 **27**

Fig. (26).



n = 2,3,4

28 **29** **30** X = Br, Cl n = 2,3,4

Fig. (27).

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-HT_{1A} 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**).

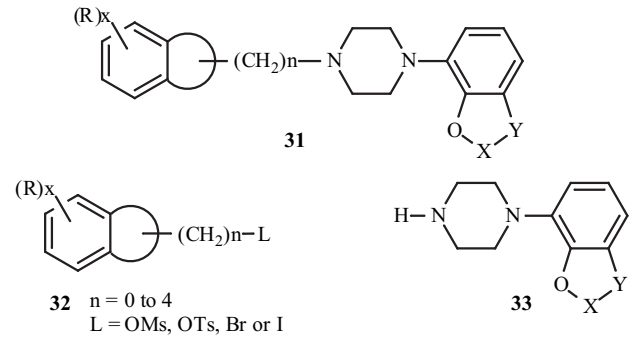


Fig. (28).

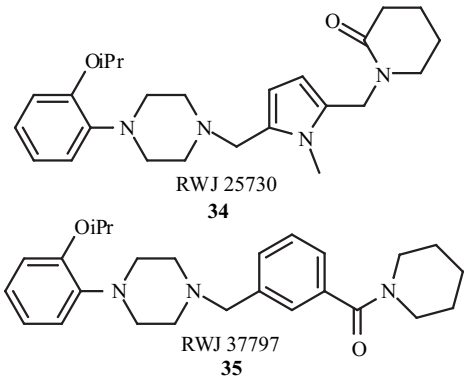


Fig. (29).

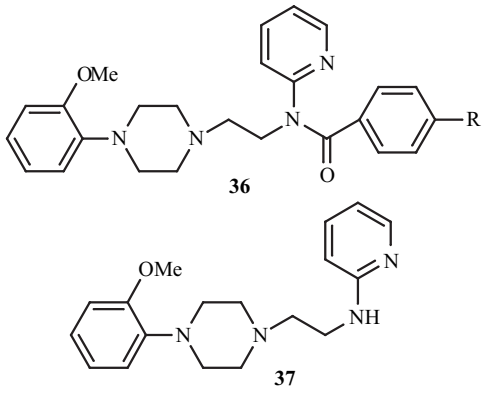


Fig. (30).

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.

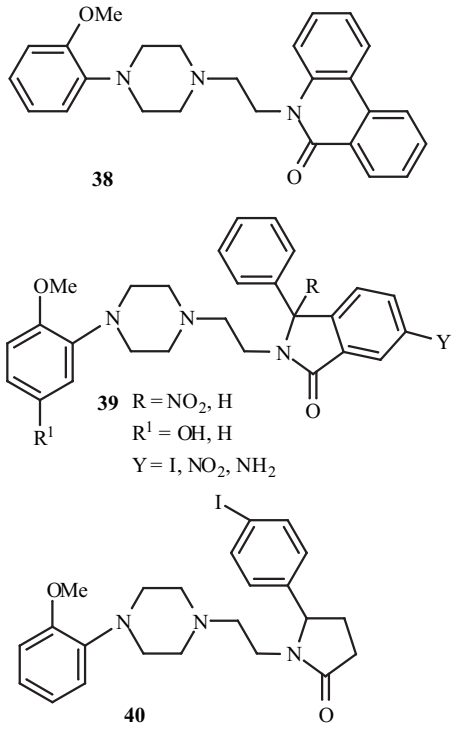


Fig. (31).

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.

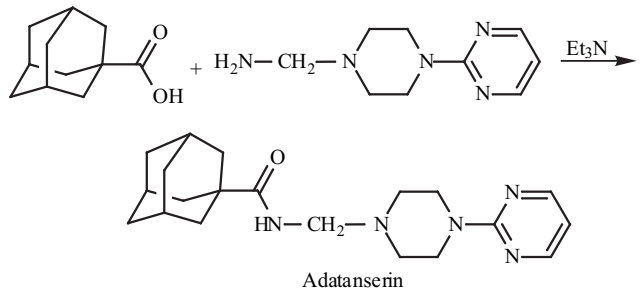
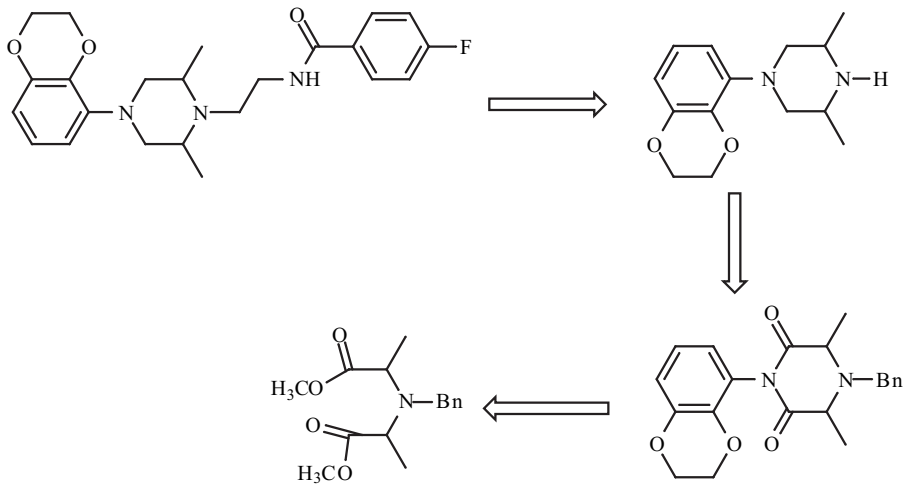


Fig. (32).

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.



Scheme 5

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**).

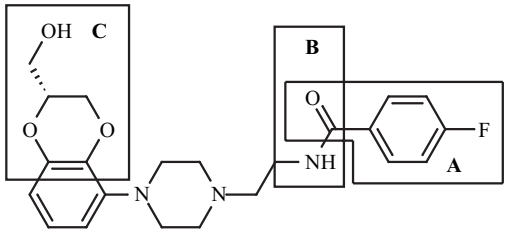


Fig. (33).

The *cis*-dimethyl-substituted arylpiperazine was synthesized according the retrosynthetic approach showed in the 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 α_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**.

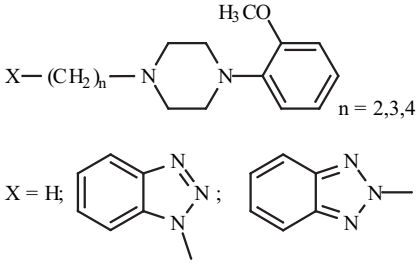
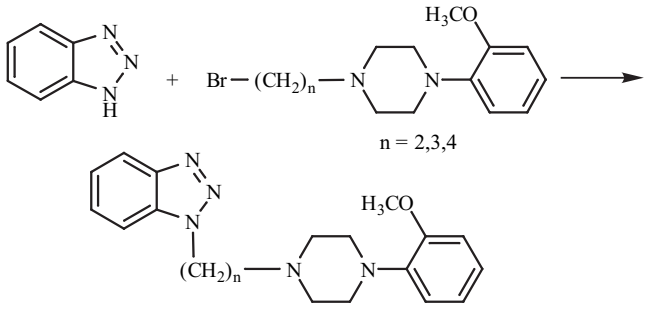
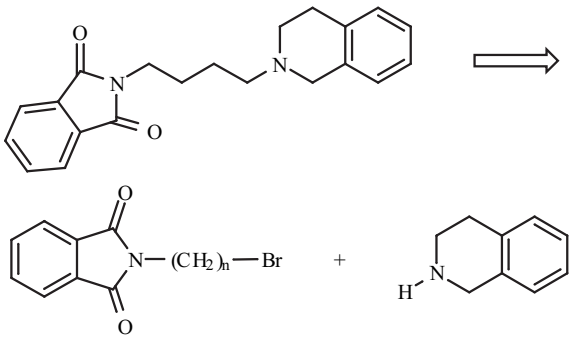


Fig. (34).



Scheme 6

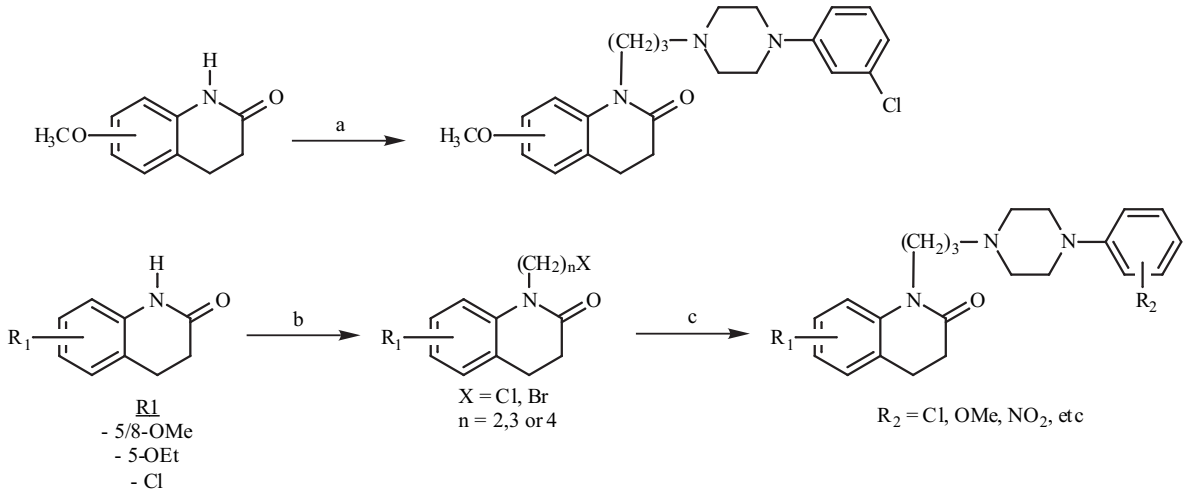


Scheme 7

An interesting synthetic approach that provides 3,4-dihydro-2-(1*H*)-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.

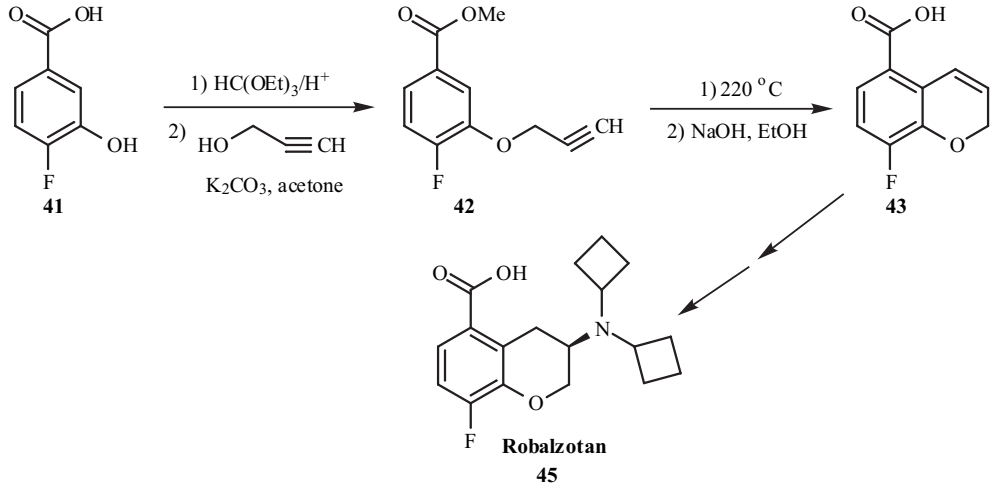
BENZOPYRAN DERIVATIVES

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, K_2CO_3, phenylpiperazinees in CH_3CN, n = 2,3 or 4

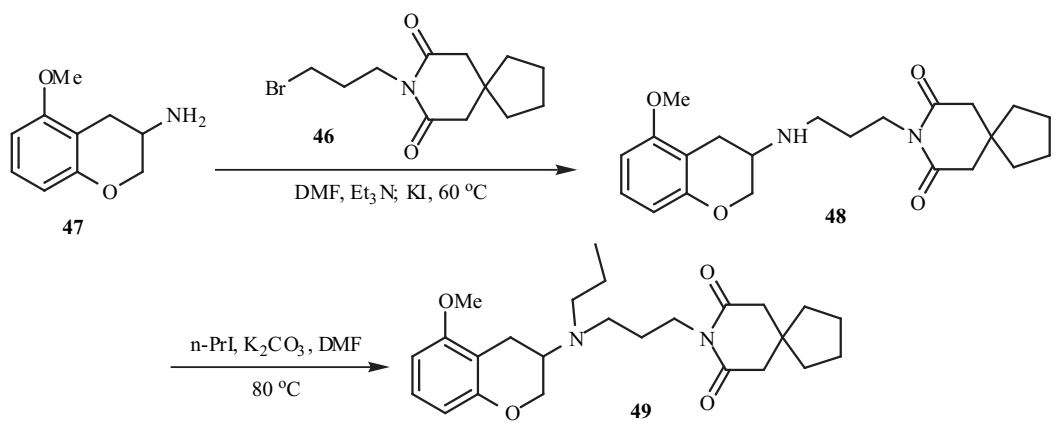
Scheme 8



Scheme 9

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-2*H*-1-benzopyran-5-carboxamide **44**.

Guillaumet *et al.* [55] prepared an evaluated a series of 3,4-dihydro-3-amino-2*H*-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-2*H*-1-benzopyran **47** to afford the amine



Scheme 10

48. 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**).

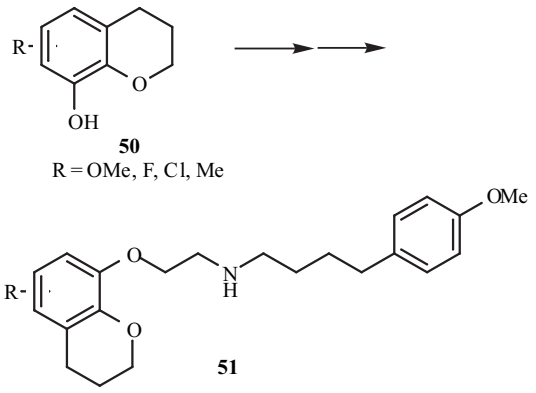


Fig. (35).

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-2*H*-1-benzopyran **53** (3-aminochromane) which involved the participation of intermediate **54**. Fig. (**36**)

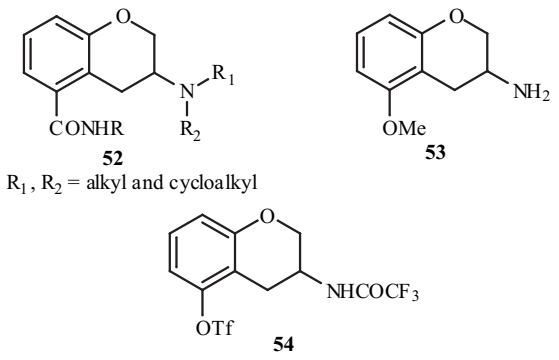


Fig. (36).

2-AMINOTETRALINS

The 8-hydroxy-2-(di-*n*-propylamino)tetralin (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**).

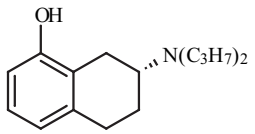
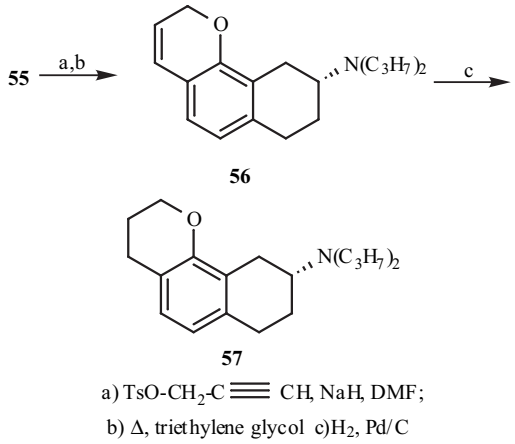


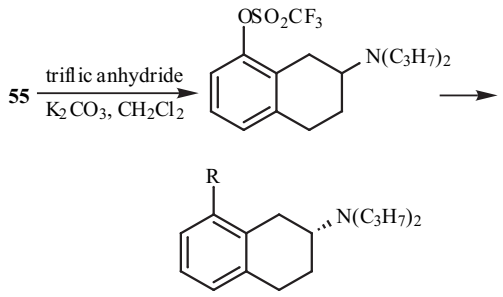
Fig. (37).

Hacksell [61] sinthesized 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)tetralin and 2-*N*-(propylamino)tetralin [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

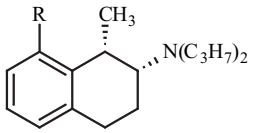
In a further work Hacksell [63,64] explored the importance of the C8 substituent in the interaction of 2-aminotetralin-based ligands with 5-HT$_{1A}$ receptors. Enantiopure derivatives were prepared by palladium-catalyzed reactions of the triflates of the enantiomers of **55**. With the exception of the carboxy-substituted derivative the compounds displayed moderate to high affinities (K_i 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 a affinity similar to **55**.



R = H, CH_3, Ph, -C≡CH, -$COCH_3$, -COBu, -COPh, -CO_2CH_3, Aryl (phenyl, furyl, 2-thienyl, etc)

Scheme 12

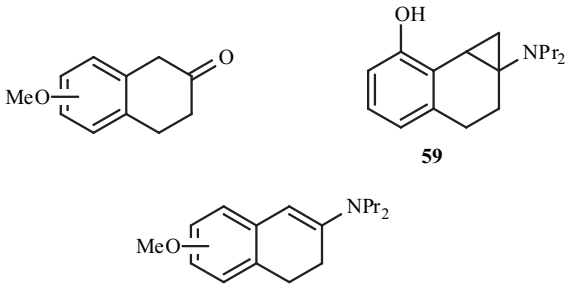
Using the same strategy [65], Hacksell *et al.* prepared new derivatives (1*S*,2*R*)- and (1*R*,2*S*) of 8-hydroxy-1-methyl-2-(dipropylamino) tetralin **58** previously characterized as a selective and potent 5-HT_{1A}-receptor agonist, in which various C8-substituents have been introduced Fig. (**38**).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



(1*S*,2*R*)
58
R = OH, $CONH_2$

Fig. (38).

Hacksell, working with a less explored structural hybrids of 8-OH-DPAT, obtained several phenolic derivatives of 1,2-methano-*N*,*N*-dipropyl-1,2,3,4-tetrahydronapht-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**).



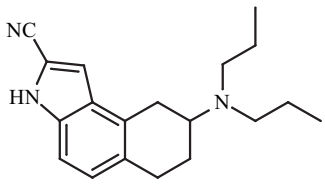
59

60

Fig. (39).

Stjernlöf [67] prepared and evaluated the enantiomers (*S*-(-) and *R*-(+)) of 6,7,8,9-tetrahydro-*N*,*N*-di-*n*-propyl-3*H*-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**).

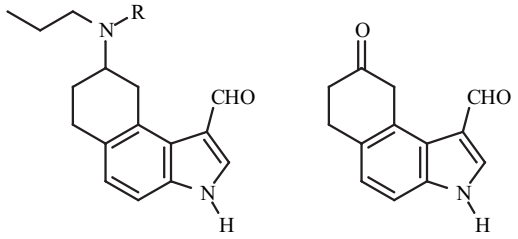
In a subsequent paper this group described another series of derivatives and isosteric derivatives of the aldehyde **62** [68]. Likewise Romero found that the 2-cyano **63** and related analogs [69] behaved as a potent 5-HT_{1A} agonist where the (*R*)-enantiomer of this series showed the highest potency Fig. (**41**).



(+)-R
(-)-S
63

Fig. (41).

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-HT_{1A} receptor, although most also displayed significant affinity for the dopamine D_2 receptor Fig. (**42**).

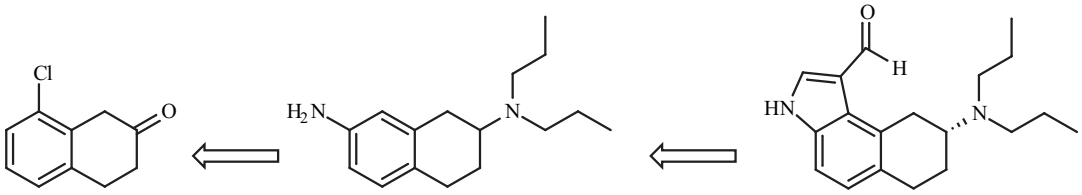


R = alkyl derivatives
64

65

Fig. (42).

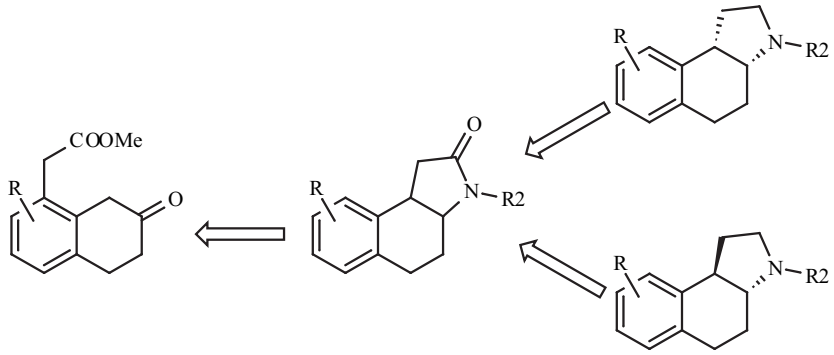
On the other hand Lin and co-workers [72] have described a series of 2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indole, these compounds are conformationally restricted, angular tricyclic analogs of 2-aminotetralin. The synthesis was achieved from the corresponding 2-tetralones, with two key steps: the regiospecific 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-HT_{1A} agonist and dopamine antagonist activity whereas the corresponding 9-hydroxy analogs displayed selective 5-HT_{1A} agonist activity. The *cis* derivatives were found to be more potent than the corresponding *trans* analogs and in the *cis* series, the (3a*R*)(-)-enantiomers displayed higher potency.



61

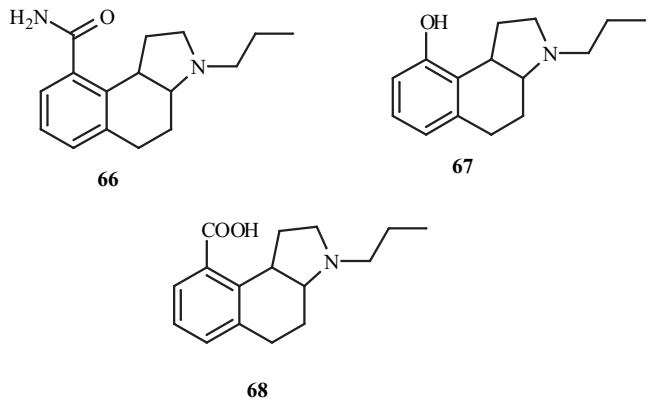
62

Fig. (40).



Scheme 13

Working with these frameworks [73] Lin reported the synthesis and pharmacological evaluation of *cis*-(3a*R*)-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*-(3a*R*)-(-); and the *cis*-(3a*S*)-(+). 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**).



66 **67**

68

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-HT$_{1A}$ and 5-HT$_{1B}$ 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-HT$_{1A}$ receptor. Methyl substitution in position 5 gave a compound with a good affinity for the 5-HT$_{1A}$ receptor. A further work [75] of the authors shown that the (-)-5-methyl-8-hydroxy-(di-n-propylamino)tetralin is a 5-HT$_{1A}$ receptor antagonist.

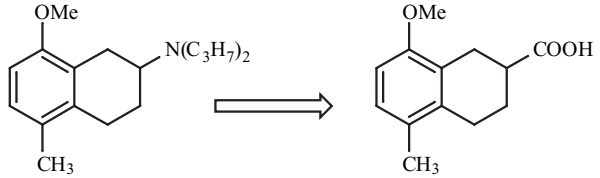


Fig. (44).

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