Synthesis of Compounds as Melatonin Agonists and Antagonists

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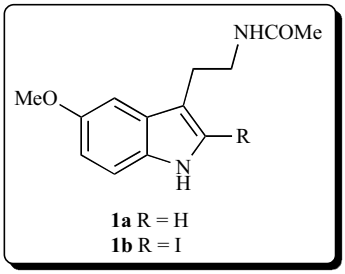
Abstract: The functions of melatonin, the hormone of the pineal gland, are of considerable current interest. Synthetic melatonin analogues as agonists and antagonists have been explored in some detail and the molecule can be considered as consisting of an indole core, acting mainly as a spacer, and the 5-methoxyl and 3-amidoethyl side chains acting as the functional components, as originally proposed by Heward and Hadley. This review focuses on the synthetic routes to these melatonin analogues, first of the core, then of the substituents that have been attached to the core, and finally those compounds with restricted conformations and those that are chiral. The importance of the various factors involved in the activity of the compounds as agonist or antagonists is indicated, as is the difference in activity of enantiomers.

INTRODUCTION

Melatonin (**1a**) [1, 2] is ubiquitous throughout the plant [3] and animal kingdoms and is the hormone of the pineal gland in mammals, including humans [4]. It plays a critical role in the regulation of reproduction in seasonally breeding mammals [5], where it has been commercially exploited [6]. It has a major role in the regulation of circadian rhythms in non-mammalian vertebrates and is a component of their regulation in mammals [7, 8]. A wide variety of invertebrates show daily rhythms in the concentration of melatonin [9, 10] and the sea pansy has a seasonal variation, maximal with gonadal maturation [11]. Cnidarians, to which the sea pansy belongs, have one of the most ancient nervous systems, indicating its long involvement as a neurohormone. Melatonin has a hypnotic action in animals [12] and humans [13-15] and there is considerable interest in its therapeutic action in sleep. Sleep problems are common in the elderly [16, 17] and the lack of melatonin, which decreases with age, may be a major factor. It also has therapeutic potential in Seasonal Affective Disorder [18] and as an agent in restoring circadian rhythms in the blind [19] and where these have been disturbed by shift-work [20] or jet-lag [21, 22]. Melatonin has also been implicated in Alzheimer's and other neurotic disorders [23-26], in certain cancers [27, 28] in Parkinson's disease [29] and as an antioxidant [30, 31].

The physiological actions of melatonin in regulating seasonal and circadian rhythms is mediated through a family of specific, high affinity, G-protein-coupled cell membrane receptors [32]. Radioligand binding studies using 2-[^{125}I]-melatonin (**1b**) have revealed a widespread distribution of binding sites throughout the nervous system [33]. The distribution of binding sites shows that they are particularly abundant in tissues that respond to melatonin, including the retina, suprachiasmatic nucleus (SCN), the *pars tuberalis* of the pituitary and cerebral and tail arteries [34]. Two receptor subtypes have been cloned in mammals, MT_1 (Mel_{1a}) and MT_2 (Mel_{1b}), and a third, Mel_{1c}, in chicken, the toad *Xenopus*, and zebra fish [35-37].



1a R = H
1b R = I

The way in which melatonin binds at these receptors and the possible therapeutic potential of melatonin in a wide variety of clinical conditions has led to a surge of interest in the synthesis of agonists and antagonists to its actions. The preparation of compounds that can discriminate between the receptor types is a major goal [38-41] since together with the genetic disruption of specific receptors [42] these could provide tools for targeting specific functions.

Melatonin receptors and their ligands have recently been reviewed [43-46]. This review will focus on the methods used to prepare the wide range of analogues now available. Melatonin will be considered as if composed of three parts, the indole core, the *N*-acetyl 3-ethylamine and 5-methoxy side chains, a concept originally suggested by Heward and Hadley [47]. Preparation of indole and bioisosteric core molecules will be described first, conformationally restricted and chiral compounds second, and compounds with substituted 3-side chains third.

1. CORE MOLECULES

1.1. Indole, Benzo[*b*]thiophene, Benzo[*b*]furan, Benzimidazoles, Indene and Indane

Although the indole core can largely be considered as a spacer [47], with the nitrogen atom not involved in receptor binding, nevertheless it features in the largest number of ana-

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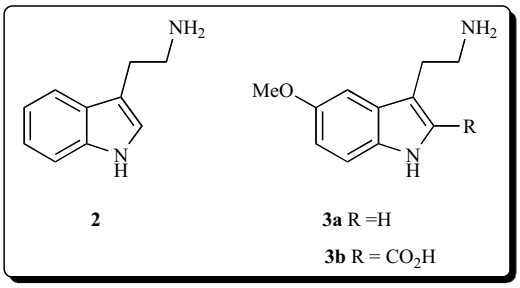
logues. Following the early work of Flaugh *et al*. [48], most syntheses are based on classic procedures [49-51]. Tryptamine (**2**) is commercially available for compounds without a 5-substituent.



5-Methoxytryptamine (**3a**) can be prepared by the Grandberg-Bobrova [52] modification of the Fischer indole synthesis, but has problems with further alkylation [53, 54]. The Japp-Klingemann reaction has been used, but this required a decarboxylation of the 2-carboxylate **3b**, which proceeds in only moderate yield. The best route to 5-methoxyindole (**4**) is probably *via* the Repke-Ferguson [55] modification of the Leimgruber-Batcho reaction [56], Fig. (**1**). The 3-side chain can be added in a variety of ways.

Both practical preparations [57-59] and an interesting radical synthesis [60] of melatonin have recently been reported. In the latter, the indoline ring of **5** is formed in a radical step, Fig. (**2**). Somei *et al.* [58, 59] introduced the 5-methoxyl group by reaction of *N*-acetyl 1-hydroxytryptamine with 20% BF_3 in methanol at reflux which gave **1a** in 80% yield.

Changing the C-3 substituent to *N*-1 and the C-5 methoxyl to C-6 gives a series of compounds comparable to melatonin [60-62]. 6-Methoxyindole (**7**) is readily available from 4-methoxy-2-nitroaniline (**6**) in *ca*. 40% yield by Meerwein arylation followed by reductive cyclisation, Fig. (**3**) [63].

Benzo[*b*]furan and benzo[*b*]thiophene can both be substituted for indole and reactivity is retained. A series of active benzo[*b*]furans has been prepared by Wallez *et al*. [64] from 3-oxo-2,3-dihydrobenzo[*b*]furans. 5-Methoxy-3-oxo-2, 3-dihydrobenzo[*b*]furan (**9**) was prepared from 4-methoxyphenol (**8**) by acylation with chloracetonitrile followed by cyclisation (Fig. **4**) [65].

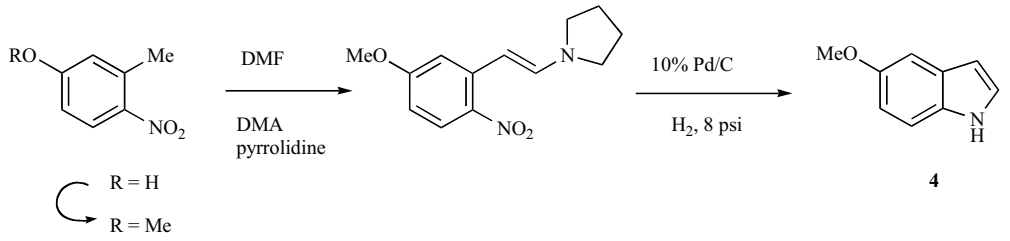


Fig. (1).

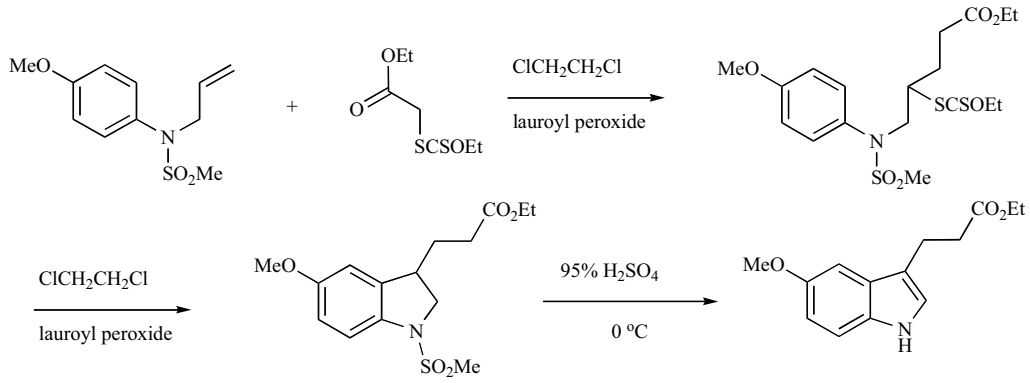


Fig. (2).

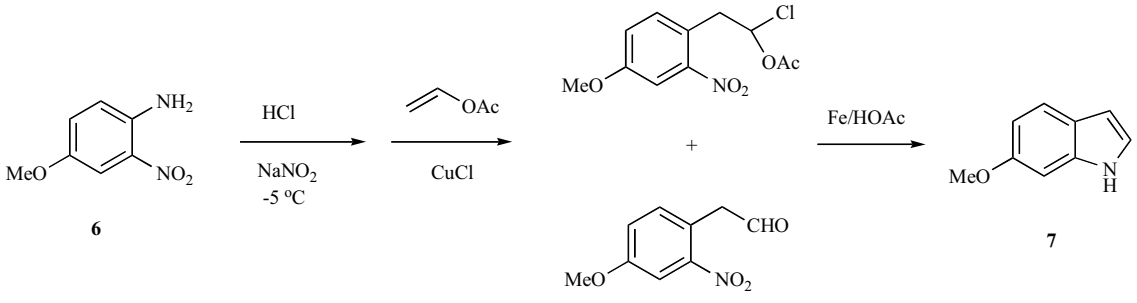


Fig. (3).

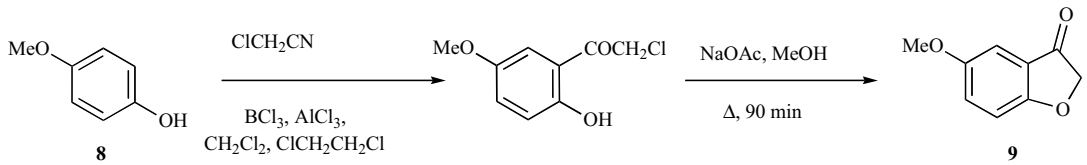


Fig. (4).

Sulfur was the earliest isosteric replacement for the nitrogen of indole [66, 67], and was prepared from 3-bromomethyl-5-benzoylbenzo[*b*]thiophene (**10**), prepared by the route shown in Fig. (**5**) [68, 69].

The benzimidazole analogue of melatonin is, like the C-6 methoxyl, *N*-1 side chain analogue, a melatonin agonist [70]. The core **11** was prepared from 3-chloro-4-nitroanisole with the C-3 side chain attached, as shown in Fig. (**6**).

Indane and indene derivatives are effective cores for melatonin agonists [71-74]. 2-Aminoindans are readily available by the method of Cannon *et al.* [75]. Uchikawa and coworkers syntheses start from either benzocyclopentan-1-ones (**12a** R = H) or 2,3-dihydrobenzo[*b*]furan (**13**), the latter being converted into 5,6-dimethyleneoxy-2,3-dihydroindanone (**14**), Fig. (**7**) [74]. Indanyl piperazine derivatives have also been prepared from **12b** (R = OMe) [76].

1.2. Benzene, Benzoxazole, Naphthalene, Tetralin, 6,7,8, 9-Tetrahydro-5*H*-benzene, Benzocycloheptane, Benzopyran, Chroman, Benzodioxane, Benzooxathiane, Benzodithiane

The phenyl ring is a sufficient core to provide compounds with significant potency as melatonin agonists [77-81]. The methoxyl and amide substituents have to be the appropriate distance apart. Benzoxazole derivatives have also been shown to act as melatonergic ligands, the oxygen atom mimicking the oxygen atom of the 5-methoxyl group [82]. The heterocyclic ring was synthesised after the 3-substituted side chain was partially in place, Fig. (**8**).

Melatonin analogues of high affinity and potency are obtained when naphthalene is substituted for indole, Fig. (**9**) [83, 84]. 2-(7-Methoxy-1-naphthyl)ethylamine, a key intermediate, was prepared from (7-methoxy-1-naphthyl)acetic acid (**16**), readily obtained from 7-methoxytetral-1-one (**15**)

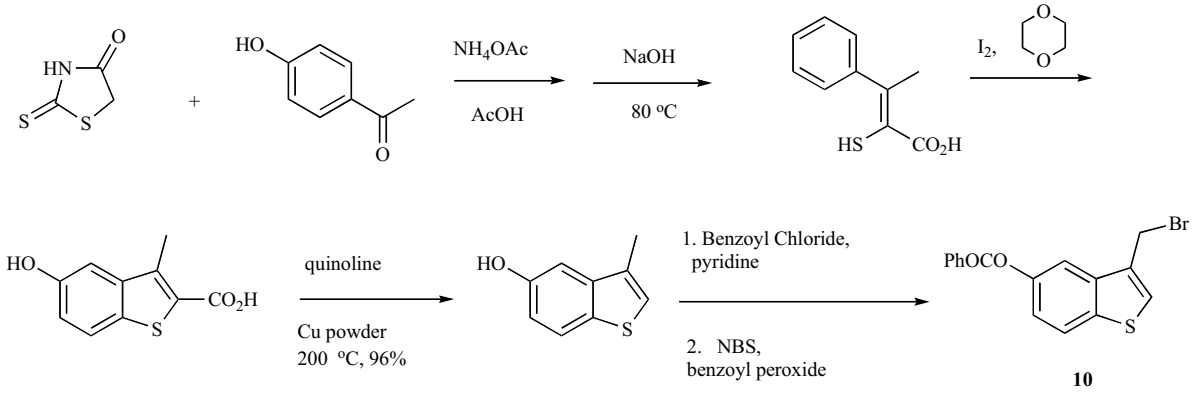


Fig. (5).

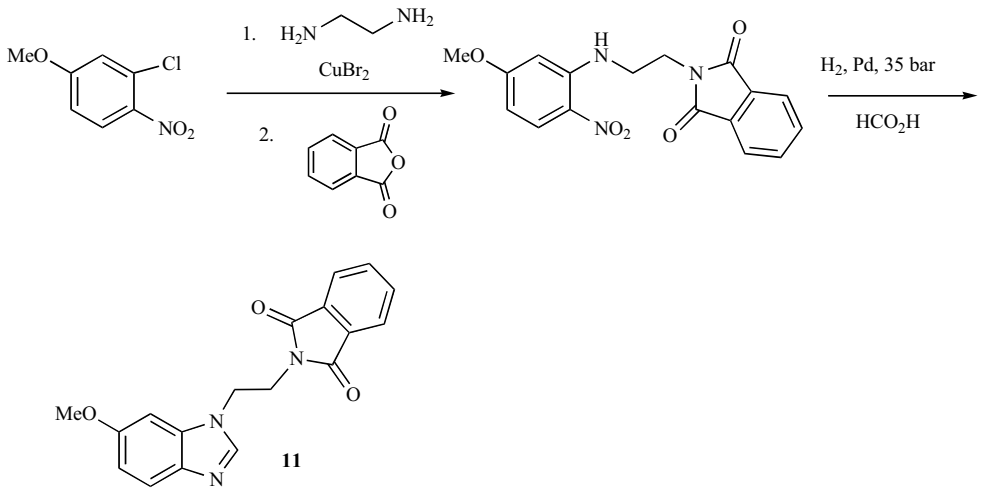


Fig. (6).

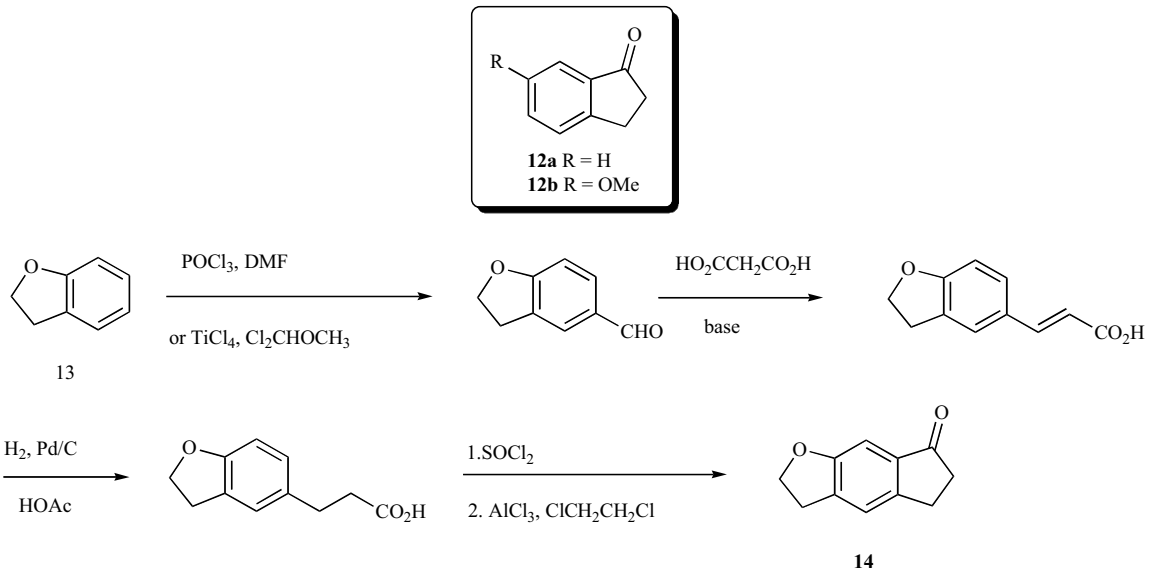


Fig. (7).

[85, 86]. The readily available ketones **17** also provide short routes to active compounds [87].

Tetralins also provide cores for active analogues [77]. The desired tetralones can usually be prepared by reduction of the appropriate methoxylated naphthalene by the method of Mathé-Allainmat *et al.* [87] but since 1,7-dihydroxynaphthalene was difficult to obtain commercially, Copinga *et al.* [77] pre-pared 8-methoxy-2-tetralone (**18**) from 2-methoxybenzal-dehyde following the method of Nichol *et al.* [88] as shown in Fig. (**10**). The key step is the rhodium (II)acetate catalysed cyclisation of the diazoketone followed by trifluoroacetic acid catalysed rearrangement [89]. The yield from this reaction was, however, poor and the authors reverted to the route from 1,7-dihydroxynaphthalene.

1-Phenyl-3-aminotetrahydronaphthalenes have been shown to be melatonin agonists, the *cis* derivative having higher binding affinity than the *trans* [90]. 1-Methoxy-8-amino-6,7,8,9-tetrahydrobenzocyclohexane (**19**) also provides a suitable core for melatonin agonists [71, 72].

Oxygenated heterocycles give active compounds when the substituents are correctly orientated [91]. The core structures are commercially available or readily prepared. For example, 5-bromomethyl-2,3-dihydro-1,4-benzodioxin (**20**) can be prepared from 3-methylcatechol as shown in Fig. (**11**).

Chroman (**21**) [92], benzopyran (**22**), benzothiopyran (**23**) and benzoxathiine (**24**) systems can all provide effective cores [91].

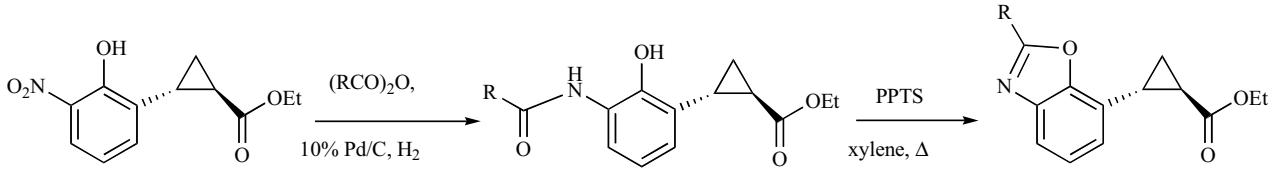


Fig. (8).

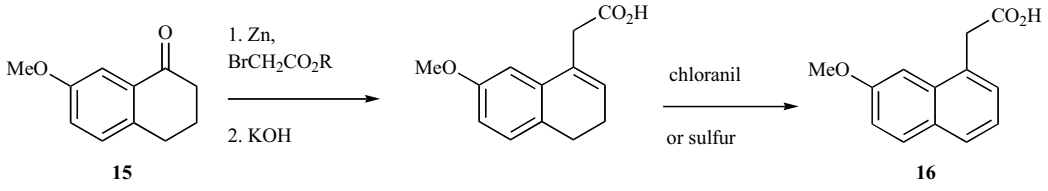
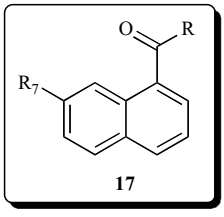


Fig. (9).



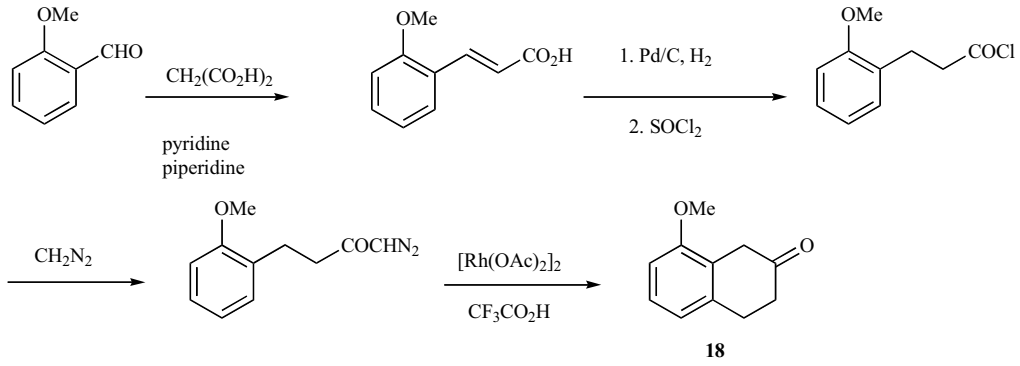


Fig. (10).

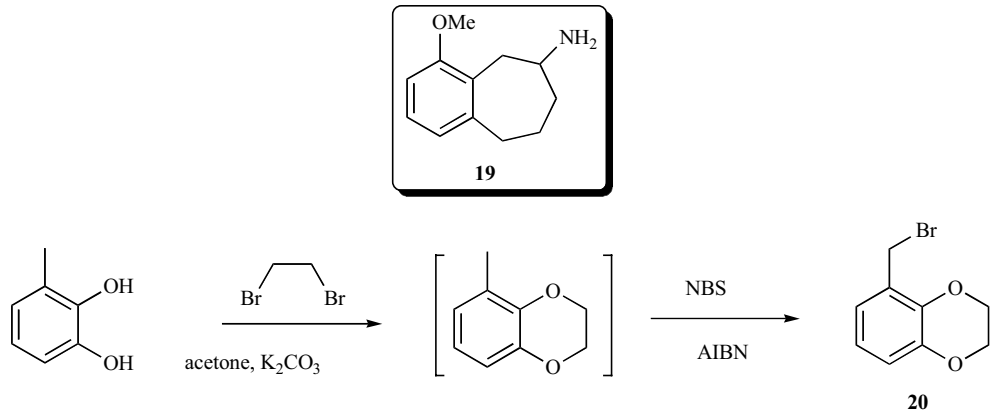


Fig. (11).

1.3. Tri- and Polycyclic Ring Systems

A wide range of tricyclic and larger systems have been investigated, based both on indole and the analogues described in section 1.1 and on the bicyclic compounds described in section 1.2. Tsotinis *et al.* [93] prepared 6,7,8,9-tetrahydropyridino[1,2-*a*]indole (**25**) using a free-radical insertion method developed by Caddick *et al.*, Fig. (**12**) [94].

Van de Poël *et al.* [95] prepared **27a** by a tributyl tin hydride catalysed radical insertion of the bromide **26**, following the method of Moody and Norton [96]. They also synthesised the oxygen analogue **27b** from the corresponding 2-keto-2,3-dihydrohydroxyindole by treatment with sodium hydride in DMF, Fig. (**13**).

Tetrahydrocarbazoles (**28b**) and the analogues with 5- (**28a**) and 7-membered (**28c**) rings replacing the 6-membered saturated ring were prepared by the Julia modification of the Bischler synthesis, Fig. (**14**) [97, 98]. Carbazole can also act as a core [99], although the compounds do not appear to be as active (however, different biological models were used).

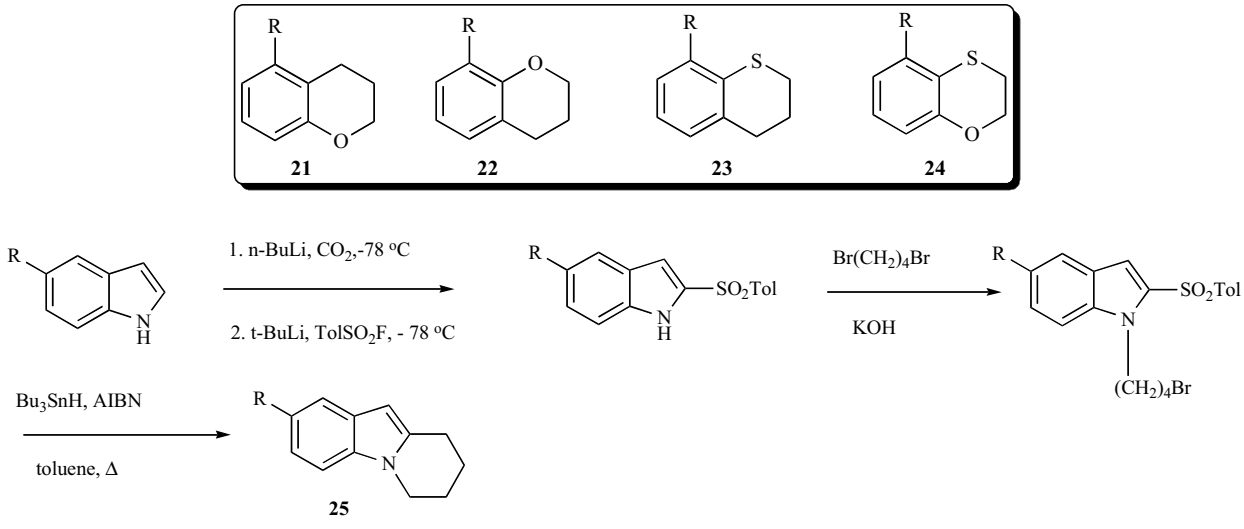


Fig. (12).

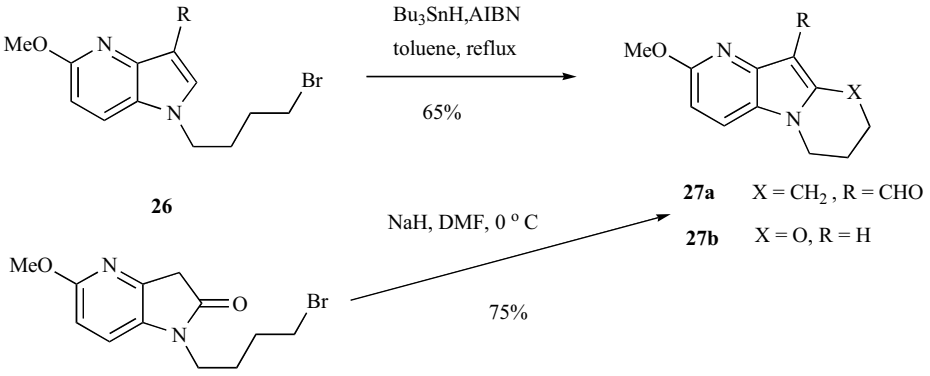


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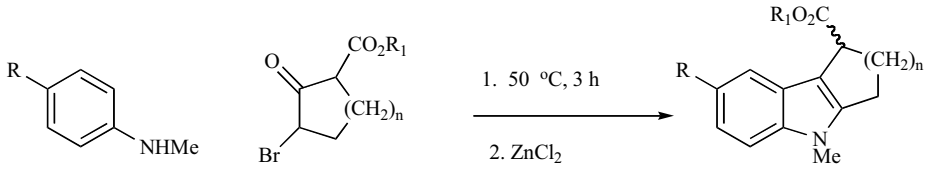
Fig. (13).



28a n =1
28b n = 2
28c n = 3

Fig. (14).

N-Acyl 3-aminotetrahydrocarbazoles were prepared by Garratt and co-workers [98, 100], the core **29** being obtained from *p*-substituted phenylhydrazine and 4-acetoxycyclohexanone by the Fischer synthesis following the procedure of Bird and Wee [101], Fig. (**15**). These compounds were much less active than the analogues **28b**.

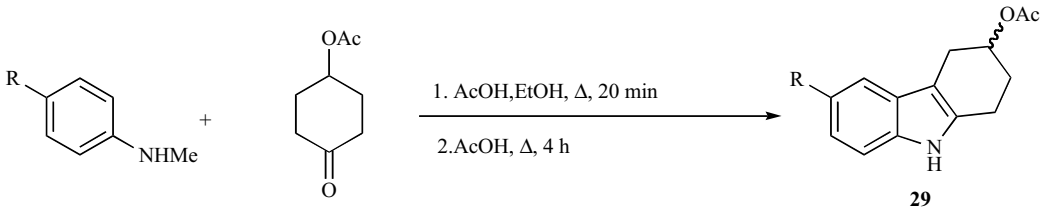


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Fig. (15).

Faust *et al.* [41] prepared isoindolo[2,1-*a*]indoles (**30a**) and benzo[*c*]azepino[2,1-*a*]indoles (**30c**) by application of the method of Kozikowski *et al.* [102, 103]. Formation of the isoindolo[2,1-*a*]isoquinolines (**30b**) required substitution of the corresponding tosylate for 2-(2-bromophenyl) bromoethane, since the latter eliminated under the reaction conditions, and the use of 3-formyl indoles, Fig. (**16**). The 5- (n = 1) and 6- (n = 2) membered ring compounds were agonists whereas the 7- (n = 3) membered ring compounds were antagonists.

Spadoni *et al.* [99] prepared 6-methoxy-4-nitro-1,3,4,5-tetrahydrobenz[*cd*]indole (**31**) by the method of Kruse and Meyer [104] and hydrogenated it to the amine, which was not isolated but acetylated to **32**, Fig. (**17**).

To synthesise the 3-substituted 1,3,4,5-tetrahydro[*cd*]indoles, the carboxylic acid **33** was cyclised with hot polyphosphoric acid to the ketone **34**. The cyclisation went with substantially higher yield (84% cf. 35%) when R was CO_2Me rather than H. The ketone was then converted to the cyanide **35** by reaction with 2,4,6-triisopropylbenzenesulfonyl hydrazide (TPSH) followed by heating the unpurified hydrazone with KCN in ethanol, Fig. (**18**).

Mathé-Allainmat *et al.* [105] prepared the tetrahydronaphthalene **36**, Fig. (**19**), by a route they had previously used for the synthesis of 8-OH-DPAT. The tetrahydrophenanthrene **37** was prepared in an analogous manner from 2-methoxy-3-(chloromethyl)naphthalene. They also prepared the tetrahydrophenylene derivative **40** by a Friedel-Crafts acylation of the azalactone **39** derived by acetylation of the glycine **38**, itself readily obtained from the appropriate chloromethylnaphthalene, Fig. (**20**).

1.4. Dimeric Cores

Coupling drug molecules together, either the same or different drug structure, has become a fashionable endeavour over the past few years, and it has been applied to melatonin analogues. It may also be important here as G-receptors often occur as dimmers or multimers, and this appears to be the

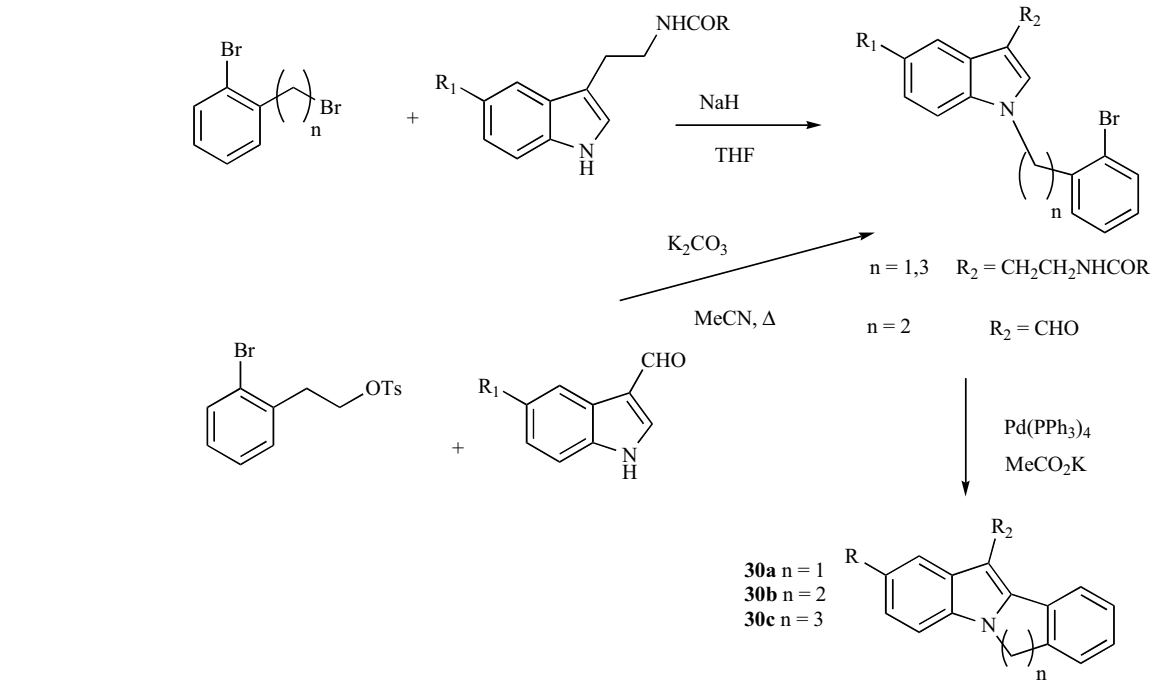


Fig. (16).

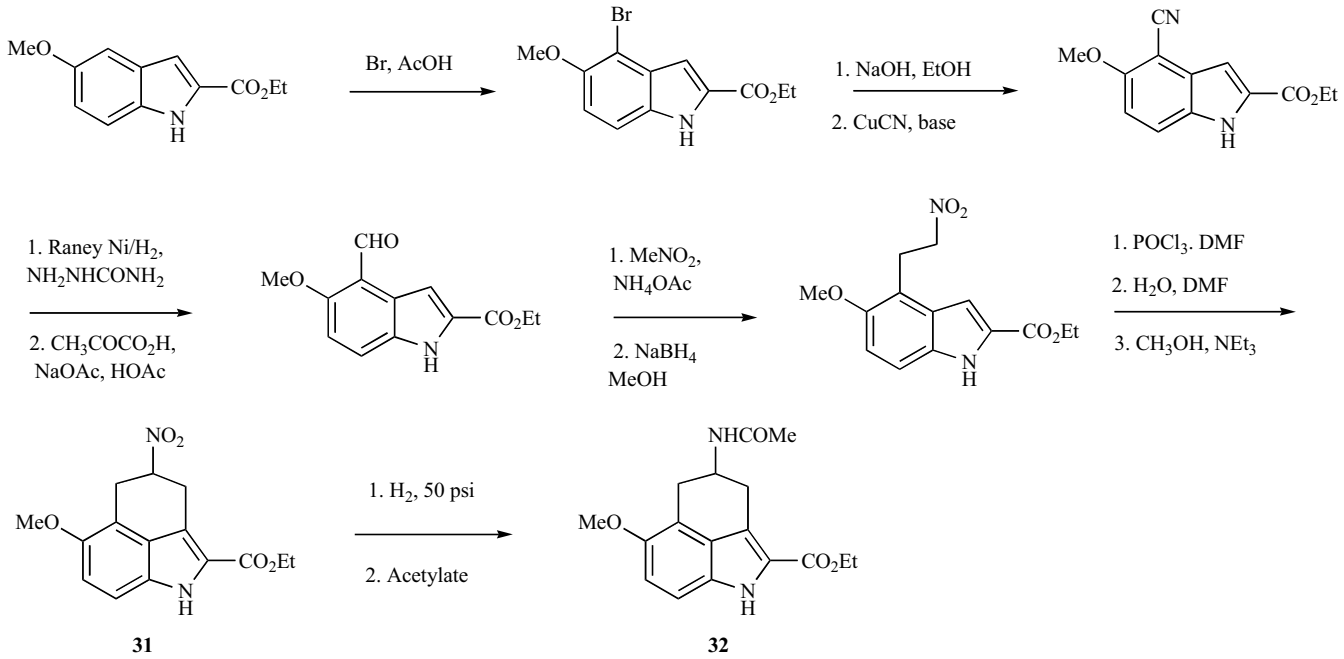


Fig. (17).

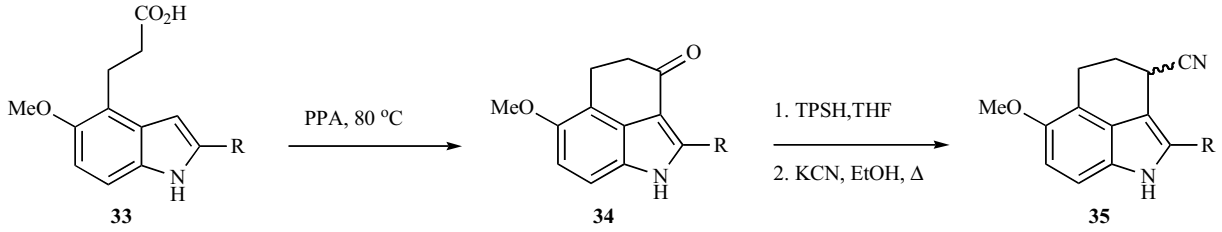


Fig. (18).

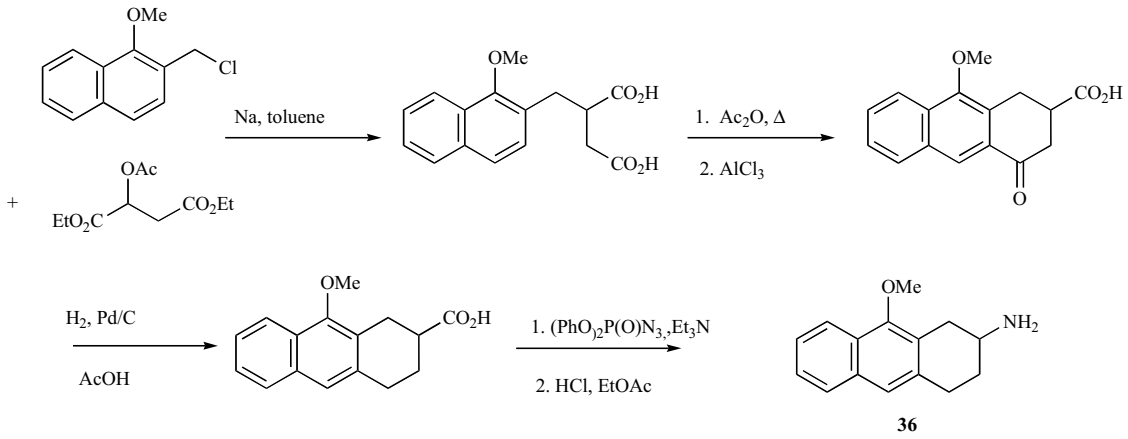


Fig. (19).

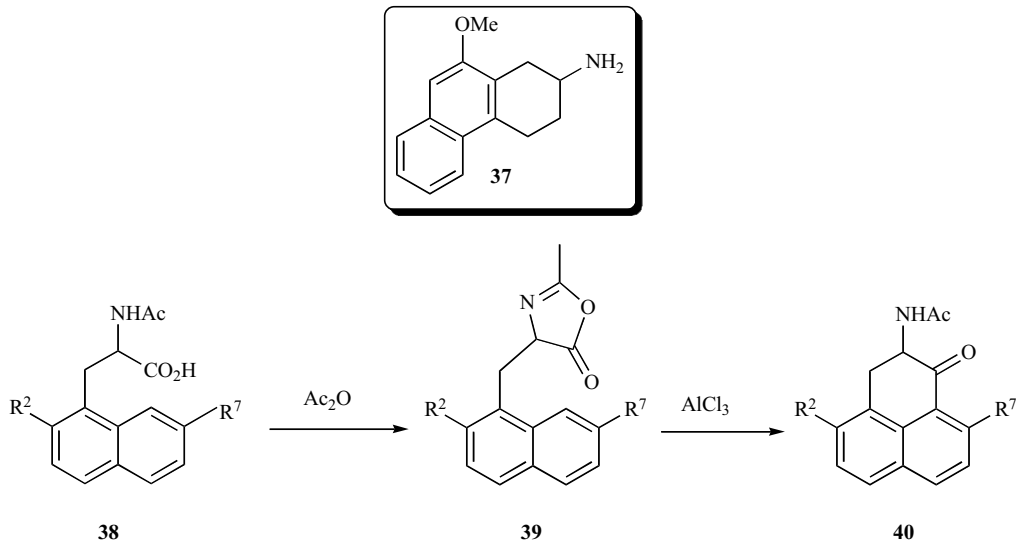


Fig. (20).

case for melatonin receptors. A simple method for melatonin or its analogues is to replace the methyl of the 5-OMe group by a methylene spacer to join two molecules [106-108]. Changing the number of methylene groups then readily varies the length of the spacer. Examples are shown in Fig. (**21**). Some of these compounds showed some preference for MT_1 over MT_2. Naphthalene dimers joined by C-C bonds have also been described.

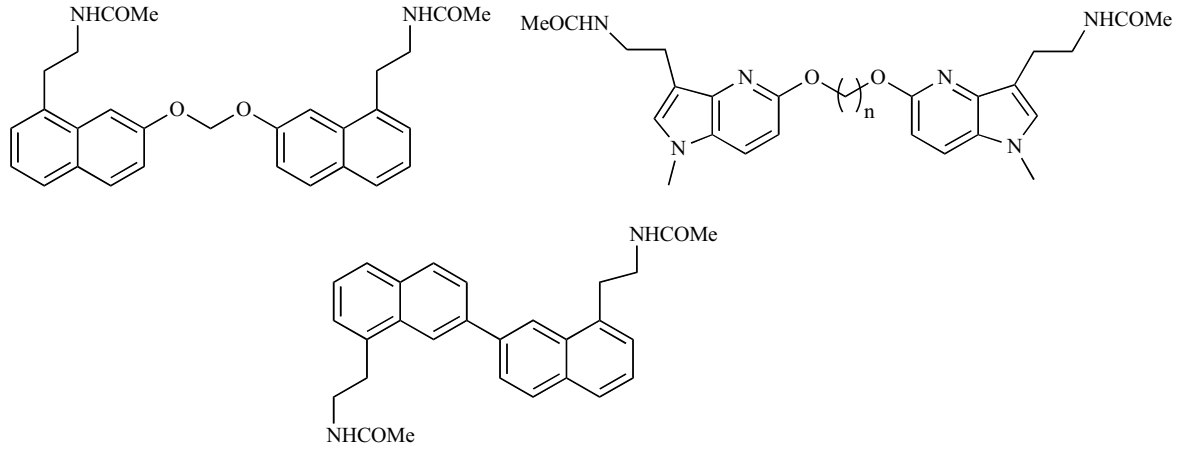


Fig. (21).

2. CHIRAL AND CONFORMATIONALLY RESTRICTED MELATONIN ANALOGUES

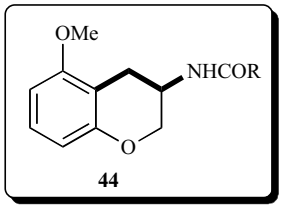
A number of the core structures described in section 2 lead naturally to compounds both with restricted conformations and compounds that are chiral. Such compounds allow the three dimensional structure of the melatonin receptors to be probed. Melatonin, though achiral and conformationally flexible [109], has to engage with a chiral reactive site which will differ for each melatonin receptor subtype. Conformational and chiral molecules may thus indicate ways in which compounds can be prepared to preferentially target a specific receptor subtype.

2.1. COMPOUNDS WITH RESTRICTED CONFORMATIONS

The flexibility of the side chain of optimum length attached to the indole nucleus make it difficult to prepare conformationally restricted compounds using indole as a core. Other bicyclic and polycyclic core structures more readily provide scaffolds for the construction of systems with various degrees of conformational rigidity. A series of methoxytetralins were prepared by Copinga *et al.* [77]. Condensation of a methoxy-2-tetralone with benzylamine followed by catalytic hydrogenation gave the benzylamine which was then debenzylated, Fig. (**22**). The resulting amine could then be acylated with either the anhydride or acyl chloride to give the chiral, conformationally restricted derivatives **41**. Similar types of systems were prepared with 5- (**42**) and 7-membered (**43**) rings. The 5-methoxychroman derivatives **44** reported by Sugden [92] have a similarly constrained configuration to the tetralin **41**.

The *E*- and *Z*-methyleneindane derivatives **45** have different, constrained configurations but have very similar binding affinities to the MT_1 receptor [72]. The compounds were obtained from the tetralone by a Wittig reaction with diethyl cyanomethylphosphonate, reduction of the cyanide to the amine and acylation.

The tetrahydocarbazole and 5- and 7-membered analogues provide two different types configurations, one derived from **29** resembling that for the tetralins and related compounds in Fig. (**22**) and the other derived from **28** with the methoxy and *N*-acylamide in closer proximity [98, 100].



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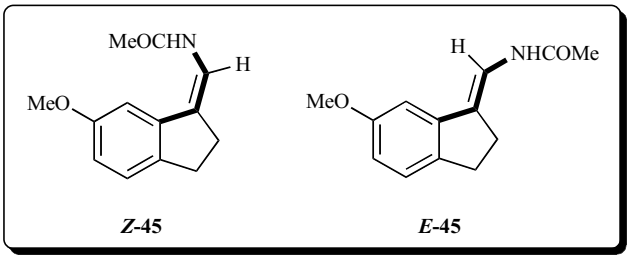
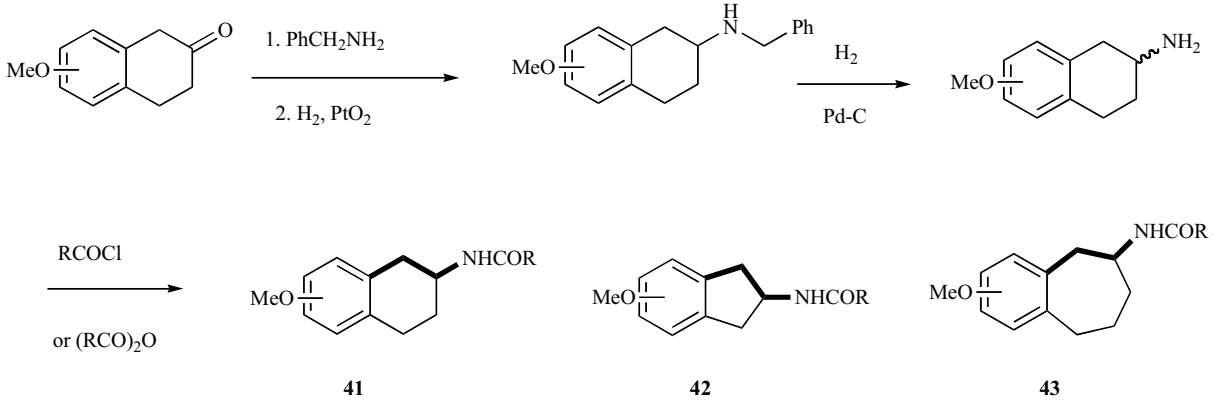
The latter compounds have much higher affinity for the receptor. The core molecule **28** was saponified to the acid, converted to the mixed anhydride which on ammonolysis gave the amide. The amides were reduced to the amine and acylated to give **46**, Fig. (**23**). These systems have more conformational mobility than those derived from **29** or the tetralins but are again chiral. The corresponding carbazole derivatives also have restricted conformations but are not chiral [98].



***Z*-45** ***E*-45**

Both **32** (Fig. **16**) and the amides derived from **34** have restricted conformations [99]. The cyanide **34** was converted to the acetylated amine by reduction in acetic anhydride, which was then saponified and decarboxylated to **47**, Fig. (**24**). Both series are chiral.

The tetrahydroanthracene, tetrahydrophenanthrene and dihydro-1*H*-phenylene derivatives prepared by Mathé-Allainmat *et al.* [105] have constrained conformations as shown in Fig. (**25**). All three derivatives differ only in the position of the second aromatic ring and the configuration is similar to that of the tetralin and chroman derivatives in Fig. (**22**). The introduction of a second methoxy group in the phenylene series has a similar effect to changing the *N*-acetyl group to *N*-propyl.



41 **42** **43**

Fig. (22).

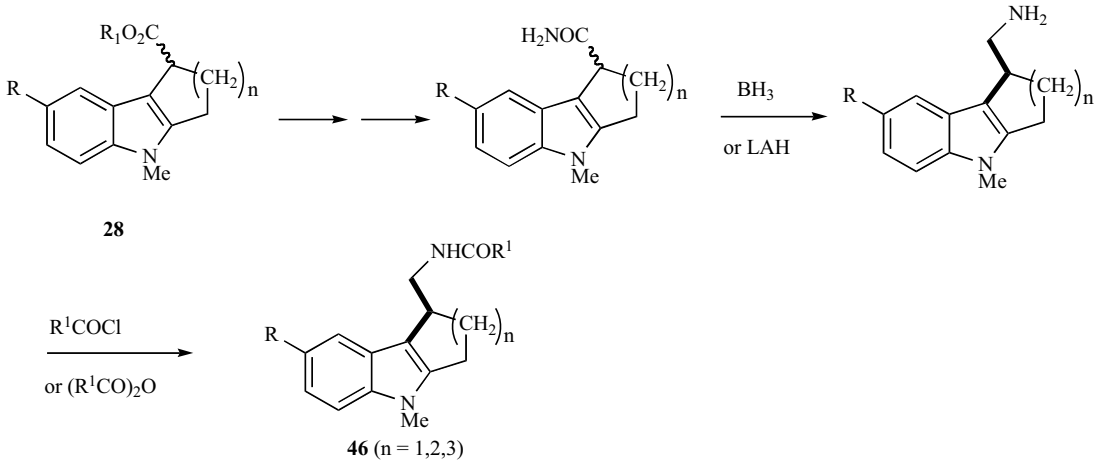


Fig. (23).

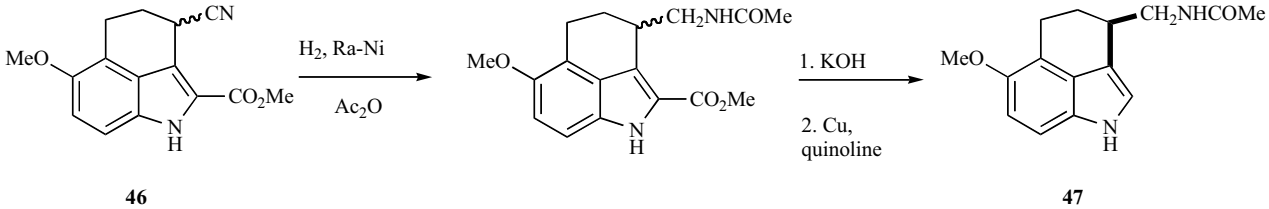


Fig. (24).

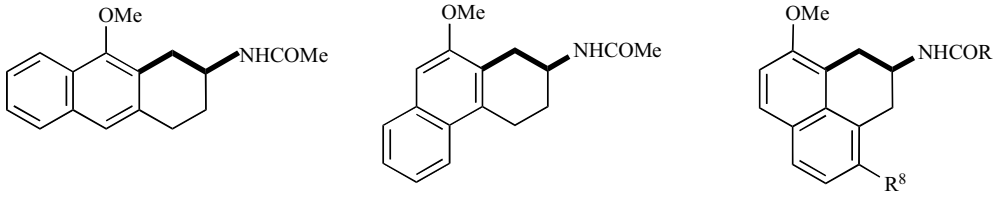
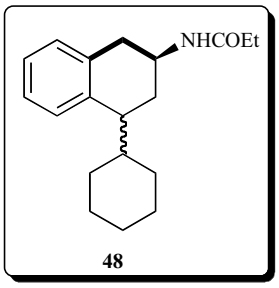


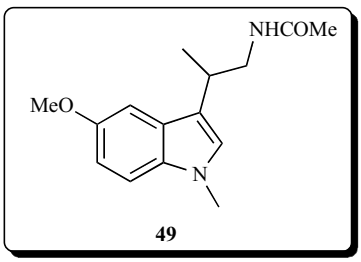
Fig. (25).

Cis- and *trans*-4-phenyl-2-propanylaminotetrahydronaphthalene derivatives **48** have different binding affinities at the human MT_1 and MT_2 receptors [90]. The compounds are chiral but the racemates were tested.

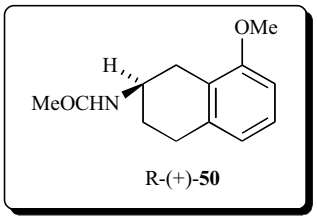


2.2. Chiral Compounds

As pointed out in section 2.1, many of the compounds with restricted conformations are also chiral. Most of these systems were prepared as racemates and then, in some cases, resolved. This has the initial advantage of providing both enantiomers for biological testing, although asymmetric syntheses may then be required if a larger amount of one enantiomer is desired. β-Methyl *N*-methyl substituted melatonin derivative **49** has been prepared and resolved by chiral HPLC, but the absolute configurations of the enantiomers are not known [110]. The (+)-enantiomer has a 10-fold higher potency for pigment aggregation in Xenopus and does not show selectivity between the MT_1 and MT_2 receptors, whereas the (-)-enantiomer, although binding more weakly, has a 28-fold selectivity for MT_2. The corresponding β-methylmelatonin has been prepared but not resolved, the racemate showing a small selectivity for MT_1.



The tetralin and related systems prepared by Jansen *et al.* [71] were resolved by HPLC using tri-acetylcellulose as the stationary phase. The *R*-tetralin **50** had been prepared by a



R-(+)-**50**

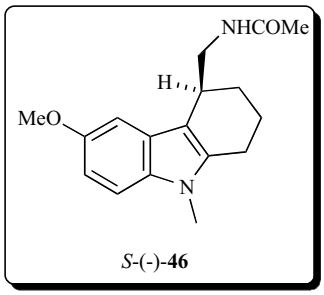
stereoselective synthesis [111] and had a positive optical rotation. This observation together with circular dichroism (CD) and other data was used to assign the related derivatives. The *S*-(-) enantiomers had higher binding affinities than the *R*-(+) [72].

The indanyl piperazine **51** [76], prepared from 6-methoxy-1-indanone by addition of piperazine, resolution and acylation, Fig. (**26**), has an unusual side chain for a melatonin agonist and is chiral. The absolute configuration was obtained by an X-ray crystallographic analysis. In this case *R*-**51** with a negative rotation is the most potent, this enantiomer having a similar 3D structure to *S*-(-)-**50** and *S*-(-)-**46** (n=2).

Asymmetric hydrogenation of *E*-**45** using binap (Ru $(OAc)_2$[*S*-2,2'-bis(diphenylphopsphino)-1,1'-binaphthyl] gave the *S*-(-) indane **52** with 95% ee [73]. The similar reduction of *Z*-**45** gave the *R*-(+)- enantiomer but only with 80% ee. The isomer with the double bond in the 5-membered ring proceeded with only low selectivity for the *S*-enantiomer. The *S*-enantiomer was converted into *S*-**53** (Ramelteon) by a 9-step sequence.

Ramelteon can also be prepared by asymmetric hydrogenation of **54** with binap $(Ru(OAc)_2$ to *S*-**55**, followed by reduction to the amine and acylation with propanoyl chloride, Fig. (**27**) [112].

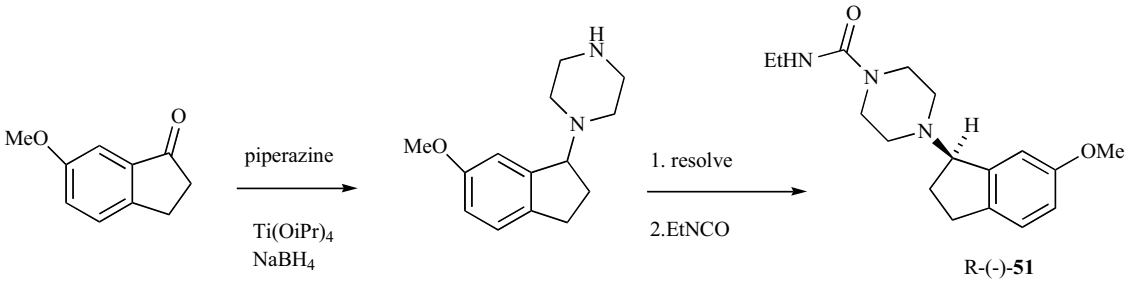
The enantiomers of **46** (n=2) were separated by HPLC on Chiral AD. The enantiomer with negative rotation was found bind more effectively and be more potent than the positive enantiomer [113]. The positive enantiomer was later shown to have the *R* configuration by X-ray crystallography [98].



S-(-)-**46**

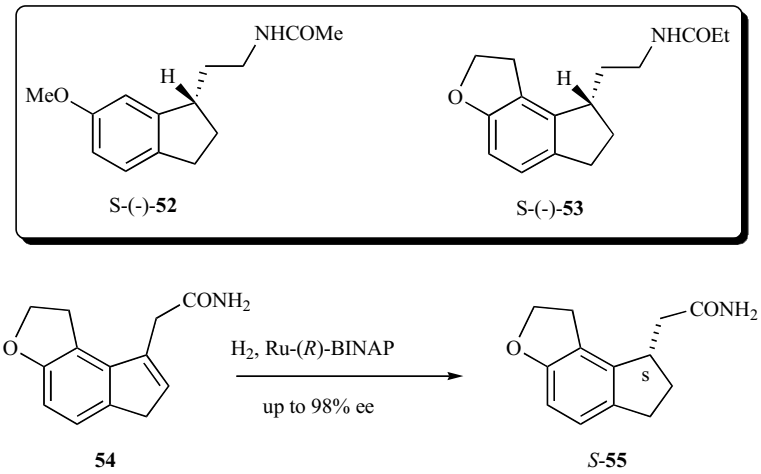
The chiral benzoxazole derivative **56** has a high binding affinity for both the MT_1 and MT_2 human melatonin receptors, but only data for the racemate has been reported [82].

Compound **47** has been resolved and the (+)-*S* enantiomer has about 500 times the affinity of the (-)-*R* enantiomer at MT_1 and MT_2 receptors, the highest discrimination between two enantiomers so far observed [114]. The (+)-*S* enantiomer is a full agonist, whereas the (-)-*R* enantiomer is a partial agonist.



R-(-)-**51**

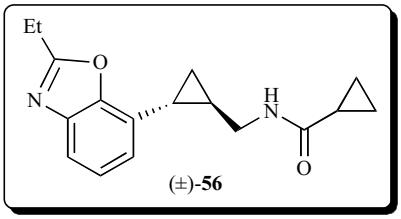
Fig. (26).



S-(-)-**52** S-(-)-**53**

54 *S*-**55**

Fig. (27).



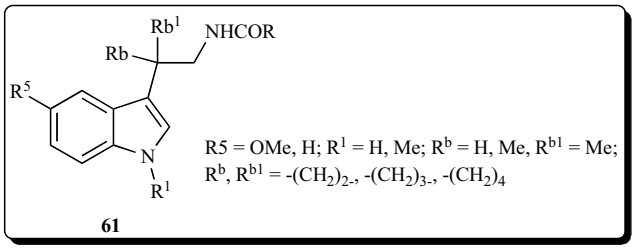
(±)-**56**

3. α- AND β-SIDE CHAIN SUBSTITUTED MELATONINERGICS

α–Substituted derivatives were first reported by Flaugh *et al*. [48], who prepared α-methyl-6-chloromelatonin (**58**) by reaction of the aldehyde **57** with nitroethane followed by reduction of the resulting nitronate with AlH_3 to the corresponding amine which was acetylated with acetic anhydride. (Fig. **28**).

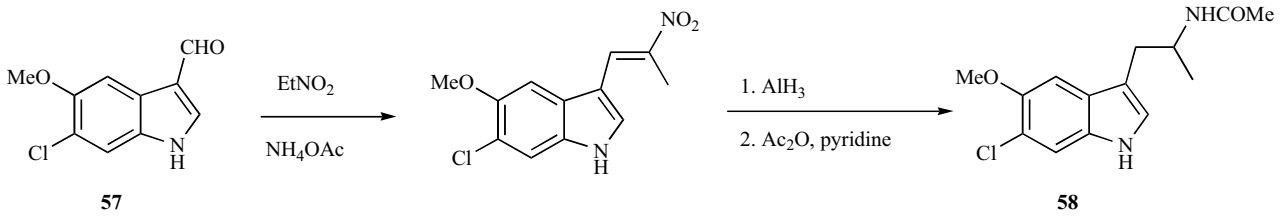
Substituents on the 3-side-chain, particularly at the β-position, should initially increase the preference for the active conformation but, as the size of the substituents is increased, the population of the preferred conformation may decline. This hypothesis has been investigated by assessing the melatoninergic potency of various compounds which bear in their side chain small to large substituents. A typical example of α- and β-methyl side chain functionalised molecules with enhanced activity is the *N*1-phenethyl-substituted indole derivatives **59** and **60** [113]. The synthetic routes followed for the preparation of these probes are depicted in Fig. (**29**).

Recently, the synthesis of a series of 5-methoxytryptamines and 5-methoxy-1-methyltryptamines substituted at the β-position by one or two methyl groups or by a three-, four-, or five-membered ring, has been reported [108], as illustrated by **61**. These compounds show a range of properties, from potent agonists to antagonists, with some having different activities at the human MT_1 and MT_2 receptors. Again, the enantiomers of chiral compounds show different affinities for the receptor.



61

Other examples of melatoninergic ligands substituted at the β-position of their side chain are the analogs **62**, **63** and



57 **58**

Fig. (28).

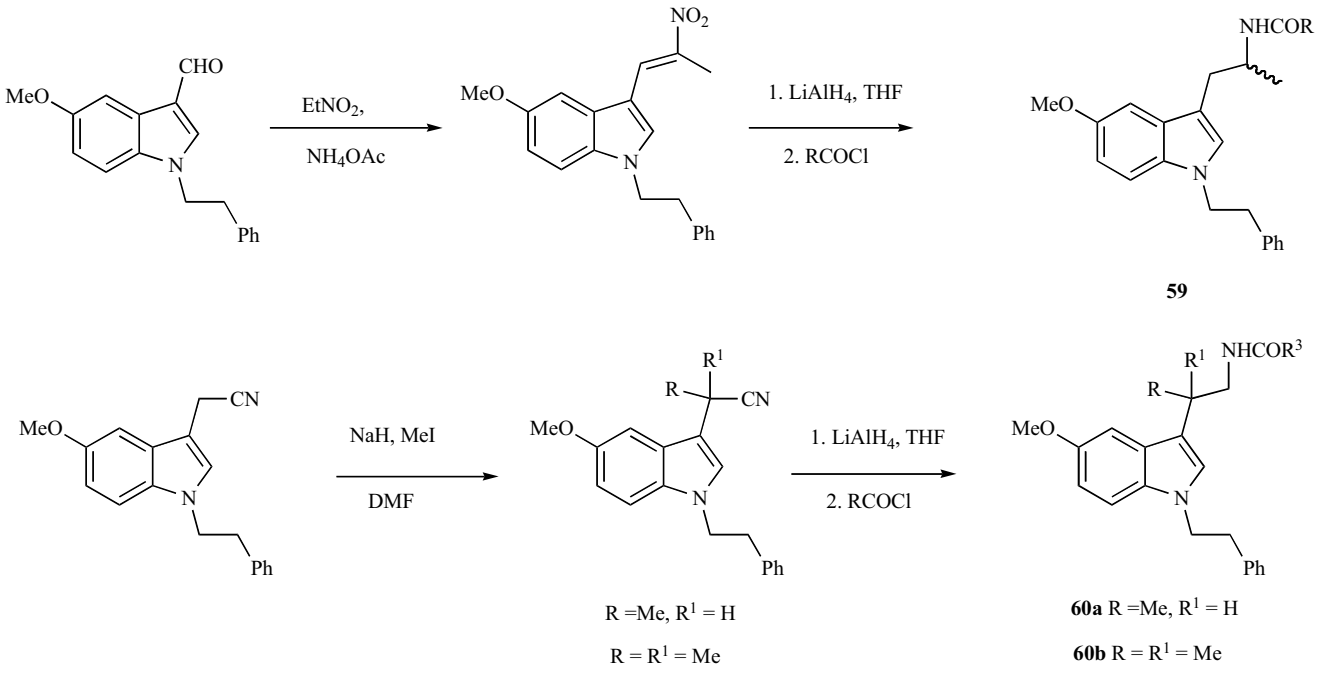
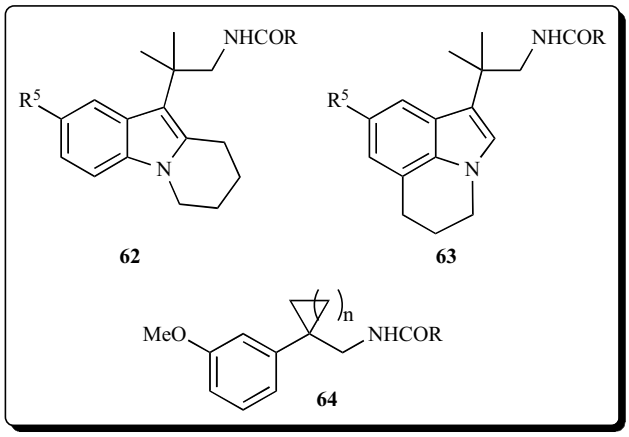


Fig. (29).

64, which were prepared in a similar way [115-117]. These compounds again show a range of activities, from agonists to antagonists.



CONCLUSIONS

Small molecules, such as melatonin, continue to have an important role in medicinal chemistry since they are easy to administer and are rapidly effective. Although much more needs to be understood about the various functions of melatonin and through which receptor type they are processed, treatments are already in use and melatonin analogues are now appearing as drugs. The range of small molecules having agonist or antagonist effects on the melatonin receptors is large and compounds with some selectivity towards either MT_1 or MT_2 are becoming available. The variety of synthetic strategies to melatonin analogues has been illustrated in this review, which should assist those wanting to explore the preparation of new compounds in this area.

ACKNOWLEDGEMENTS

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