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RECENT ANTI-DEPRESSANT MOLECULES FOR FUTURISTIC PHARMACOTHERAPEUTICS: DEEP INSIGHTS INTO THE MEDICINAL CHEMISTRY AND MECHANISM OF ACTIONS

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ABSTRACT

A serious health problem that affects individuals of all ages and genders, depression is more common in women than in men. It is one of the main causes of disability globally and affects 340 million people. By 2025, depression is expected to be the second-largest health burden, behind cardiovascular illnesses, according to the World Health Organisation. The regular physical, mental, and social lives of depressed people and their families may be disrupted by untreated, chronic, or recurring depression. In the worst situations, a depressive may also have suicidal inclinations and behaviours. Therefore, it's crucial to diagnose and treat this illness at an early stage. Reduced energy, a poorer mood, and a lack of interest and pleasure are among of this disorder's most prevalent symptoms. Along with this, additional symptoms include diminished focus and attention, feeling restless and agitated, avoiding other people, a drive to harm oneself or commit suicide, a gloomy outlook on the future, poor sleep, changes in eating and weight, and the notion of shame and unworthiness. Ethanol has been used as a self-medication for anxiety since ancient times. Today, individuals still utilise it for this purpose. Several safe treatment options are now available to treat anxiety disorders, however none of them are successful owing to insufficient pharmacodynamic and pharmacokinetic properties. As a result, new views on the ongoing endeavour known as "drug discovery" start to emerge. The most current anti-depressant/anti-anxiety compounds, together with their potential mechanisms of action, are presented in this review article.

KEYWORDS: Depression, Anti-anxiety, Anti-depressant, $5HT_3$, Synthesis, Mechanism of Action.

INTRODUCTION

A serious health problem that affects individuals of all ages and genders, depression is more common in women than in men. It is one of the main causes of disability globally and affects 340 million people.[1] By 2025, depression is expected to be the second-largest health burden, behind cardiovascular illnesses, according to the World Health Organization. The regular physical, mental, and social lives of depressed people and their families may be disrupted by untreated, chronic, or recurring depression.[2] In the worst situations, a depressive may also have suicidal inclinations and behaviours. Therefore, it's crucial to diagnose and treat this illness at an early stage. Reduced energy, a poorer mood, and a lack of interest and pleasure are among of this disorder's most prevalent symptoms.[3] Along with this, additional symptoms include diminished focus and attention, feeling restless and agitated, avoiding other people, a drive to harm oneself or commit suicide, a gloomy outlook on the future, poor sleep, changes in eating and weight, and the notion of shame and unworthiness.[4]

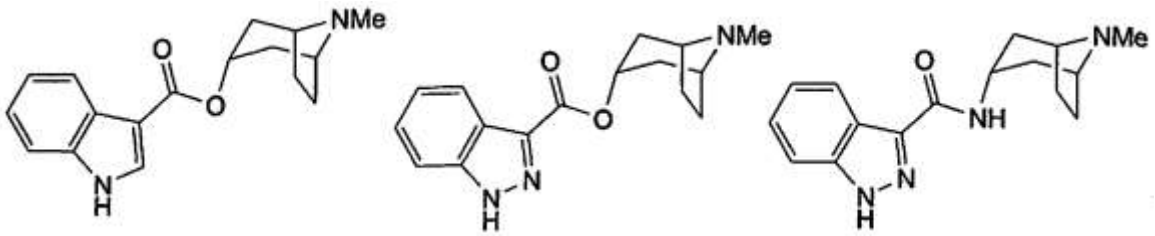
Many different 5-HT_3 receptor antagonists have been developed during the last four decades to combat the nausea and vomiting that might occur after cancer treatment with chemotherapy or radiation. Additionally, various therapeutically accessible and synthesised 5-HT_3 receptor antagonists have been explored for their potential positive benefits in a variety of mental health conditions, including but not limited to: depression, anxiety, migraine, cognition, irritable bowel syndrome, eating disorders, etc.[5,6] Cocaine and metoclopramide were the first substances shown to have a strong antagonistic effect on the 5-HT_3 receptor. Metaclopramide is an efficient anti-emetic, however it has serious extrapyramidal adverse effects since it blocks the D_2 receptor. As a solution, several compounds with bridging bicyclic amine or piperazine structures, which are derivatives of aromatic acids, have been synthesised and tested for their ability to block the action of 5-HT_3 receptors.[7]

Ethanol has been used as a self-medication for anxiety since ancient times. Today, individuals still utilise it for this purpose.[8] Several safe treatment options are now available to treat anxiety disorders, however none of them are successful owing to insufficient pharmacodynamic and pharmacokinetic properties.[9] As a result, new views on the ongoing endeavour known as "drug discovery" start to emerge. The most current anti-depressant/anti-

anxiety compounds, together with their potential mechanisms of action, are presented in this review article.

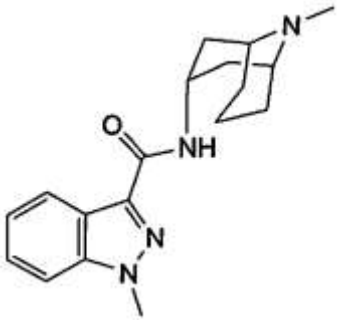
SPECIFIC REPORTS

Using indazole as a bioisostere of indole, Fludzinski *et al.* synthesised a series of indazole-3-carboxylic acid derivatives that are structurally similar to ICS 205-930, a 5-HT_3 receptor antagonist. In the B-J reflex test, the ED_{50} values for the analogue of ICS 205-930 (Compound **1**) that blocks the 5-HT_3 receptor were 0.004 mg/kg and 0.003 mg/kg, respectively. Among the synthesised compounds, the ED_{50} value for compound **2**, the amide counterpart of compound **1**, was the lowest, at 0.002 mg/kg i.v.[10]



ICS 205-930 **1** **2**

Several series of compounds containing aromatic pharmacophoric components such as imidazole, indolizine, and imidazopyridine were synthesised and shown to be antagonistic to the 5-HT_3 receptor by Bermudez *et al.* The pharmacophoric needs of metaclopramide were used as a starting point for the design of these compounds, with a few tweaks here and there, such as a conformational limitation on the side chain achieved by swapping out the (diethylamino)ethyl group for an azabicyclic tropane, and the phenyl group for the aforementioned heterocyclic nucleus. Neither dopamine antagonist nor gastric motility stimulatory activities were present in the obtained compounds, although they did show strong 5-HT_3 receptor antagonism. Substituting azabicyclic moieties like quinoclidine and isoquinoclinide for the tropane nucleus did not alter the antagonism of the resulting compounds towards the 5-HT_3 receptor. The most promising anti-emetic effect was shown in both ferrets and humans when testing the synthesised compounds, and this effect was identified in compound **3.**[11]



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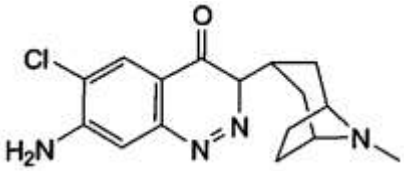
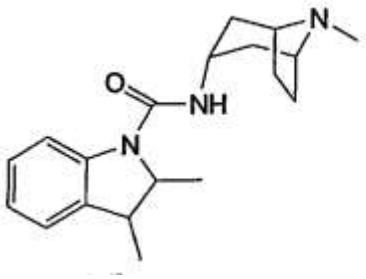


4

King *et al.* synthesised a series of benzotriazinones as antagonists for the 5-HT_3 receptor. The B-J reflex test revealed that among the synthesised compounds, **4** (ID_{50} = 0.17) was the most active.[12]

As antagonists for the 5-HT_3 receptor, Bermudez *et al.* synthesised two series of compounds: indoline carboxamides and indole carboxamides. Inhibition of the rat serotonin-induced B-J reflex was used to evaluate the antagonistic potential of the synthesised compounds. The most potent of the indoline carboxamides was compound **5** (ID_{50} = 0.5 pg/kg), whereas the most potent of the indoles was compound **6** (ID_{50} = 1.6 pg/kg). Given the preference for a "in plane" orientation of the carbonyl group, these findings imply that aromaticity of the 5-membered ring is not necessary for potency.[13]



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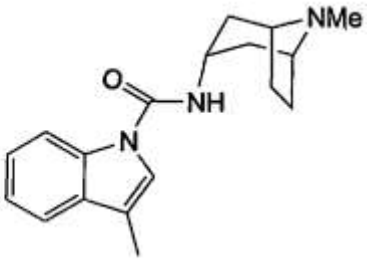
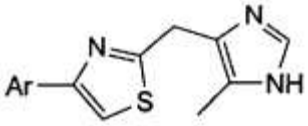
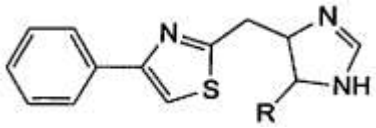


6

A series of thiazole-based compounds were synthesised by Rosen et al. and used as 5-HT_3 receptor antagonists. A thiazole linker was inserted between the aromatic group and the basic nitrogen region in lieu of the carbonyl group to improve interaction with 5-HT_3 receptors. High affinity for 5-HT_3 receptors was established for compounds **7** and **8** by the radioligand binding assay and the B-J reflex test, respectively.[14]

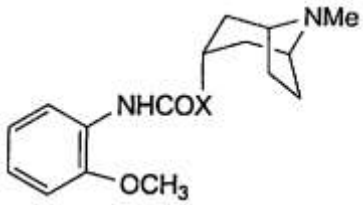




7 Ar = indolyl-3-yl; **8** Ar = 2-methoxyphenyl**9** R = CH_3; **10** R = H

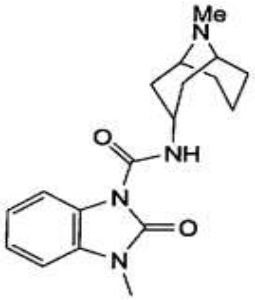
Thiazole was used as a connecting unit between an aromatic and basic nitrogen pharmacophoric ingredient in a series of compounds synthesised by Nagel *et al.* The thiazole ring was utilised as a bioisostere in place of the carbonyl group, and compound **9**, which was tested in a radioligand binding experiment, demonstrated strong antagonism (11.0 pg/kg) against 5-HT3 receptors. In contrast, agonistic action was seen in a desmethyl derivative of compound **9** (compound **10**).[15]

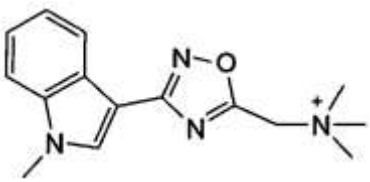
7'-substituted phenylureas were synthesised, and their ability to block the 5-HT_3 receptor was reported by Bermudez *et al.* The research confirmed that the absence of the *ortho* substituent on the aromatic moiety prevented the molecule from displaying antagonism. The most potent of the synthesised compounds were **11** and **12**, with ID_{50} values of 2.4 pg/kg and 2.5 pg/kg in the rat B-J reflex test, respectively.[16]

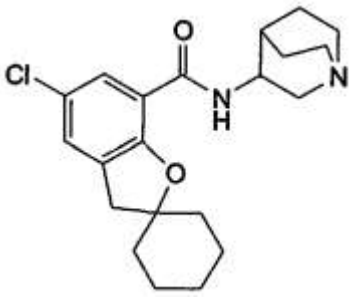


11 X = O; **12** X = NH

To create 5-HT_3 antagonists, Turconi *et al.* synthesised a series of 2,3-dihydro-2-oxo-1H-benzimidazole-1-carboxylic acid esters and amides. Compound **13** was found to be more potent than the reference antagonists MDL-72222 (Ki = 24.4 5.8 nM, ED_{50} = 195 nM/kg, i.v.) and ICS 205930 (Ki = 1.71 0.29 nM, ED_{50} = 2.1 nM/kg, i.v.).[17]





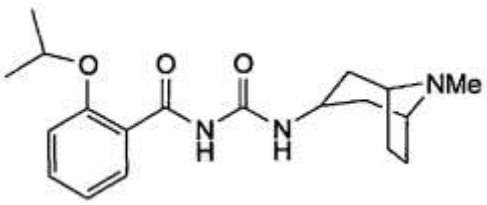


13 **14** **15**

It was shown by Swain *et al.* that indole/aryl compounds block the action of the 5-HT_3 receptor. The oxadiazole used as a carbonyl group in 5-HT_3 receptor antagonists is a linker between an aromatic residue and basic nitrogen. When tested for affinity to the 5-HT_3 receptor, drugs based on the indole ring performed better than their non-indazole counterparts. In contrast to the indole-based compounds, those with a hydroxyl (-OH) group on the phenyl ring exhibited almost equipotent affinity. Compound **14** was determined to be the most potent of the synthesised compounds, having a pIC_{50} value of 9.15. These findings imply that an aromatic group and a basic centre 8.4–8.9 A° apart will have the highest affinity for 5-HT_3 receptors.[18]

To counteract the effects of the 5-HT_3 receptor, Youssefyeh *et al.* developed a series of new benzamides. Compared to common antagonists like GR38032F, BRL43694, and metaclopramide, the *S*-isomer of Compound **15** was shown to be more selective. With a Ki value of 0.19 nM, the *S*-isomer of compound 2.15 was the most effective in blocking binding to 5-HT_3 receptor binding sites in rat entorhinal cortex. The ED_{50} in ferrets was 9 mg/kg p.o. for blocking cisplatin-induced vomiting.[19]

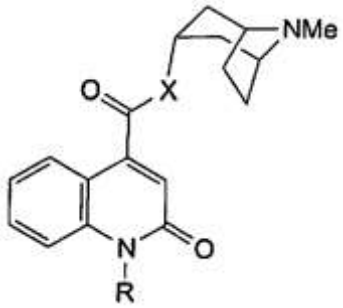
Using rat vagus nerve isolation, Bradley *et al.* synthesised a series of benzoyl urea derivatives as 5-HT_3 receptor antagonists and tested their effectiveness. Compounds with an alkoxy group on the *ortho*-position of the benzoyl function were shown to be the most potent 5-HT_3 receptor antagonists among those synthesised. Compound **16** showed stronger antagonism (pA2: 9.2) at the 5-HT_3 receptor than the reference drugs ondansetron (pA2: 8.7), zacopride (pA2: 9.1), and MDL 72222 (pA2: 7.8).[20]

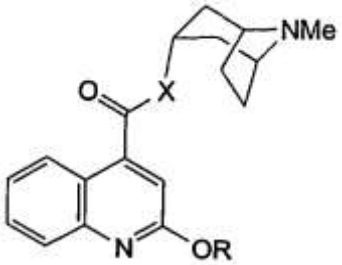


16

Using a 1-alkyl-2-oxo-1,2-dihydroquinoline-4-carboxylic acid or 2-alkoxyquinoline-4-carboxylic acid with a basic azabicycloalkyl residue, Hayashi *et al.* synthesised a variety of esters and amides. Affinities for [3H]quipazine-labeled 5-HT_3 receptors were measured. The antagonism of 5-HT_3 receptors was measured with the use of the serotonin-induced B-J reflex test. In comparison to ondansetron (1; Ki = 7.6 nM), the majority of the ester compounds

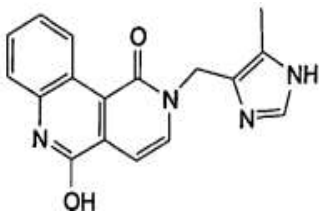
showed an affinity that was 10 times stronger. A higher affinity for the receptors was achieved by adding a hydrophobic substituent to the first or second position of the quinoline ring. In terms of affinity, compounds **17** and **18** were found to be the most potent (Ki = 0.32 nM and 0.31 nM, respectively). Carbonyl groups in Compound **19** (ester) and Compound **20** (amide) were found to deviate from the plane of an aromatic ring by more than 20 degrees, according to molecular modelling studies. However, we could not identify a robust correlation between the drugs' affinity for the 5-HT_3 receptors and their activity in the B-J reflex test. These findings suggest that the 5-HT_3 receptors in the brain and the heart are not identical, and that quinoline derivatives may interact with these receptors in a way different from that of the previously described 5-HT_3 receptor antagonists.[21]

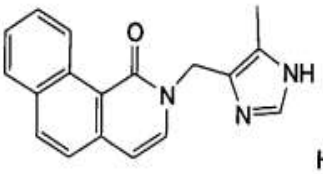


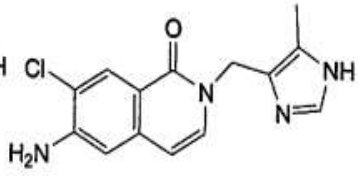


17 R = i-Pro, X = O; **19** R = CH_3, X = O; **20** R = CH_3, X = NH **18** R = i-Pro, X = O

Evidence from the B-J reflex test in rats showed that 1,2-dihydro-1-[(6-methyl-1-imidazol-4-yl)methyl]-2-oxopyridines (compound **21**) have the potential to be antagonists of the 5-HT_3 receptor, as established by Matsui *et al.* Inhibition of the B-J reflex and protection against emesis produced by the anti-cancer medication cisplatin were both significantly improved by compounds **22** and **23**, which were both orally efficacious and more powerful than ondansetron.[22]



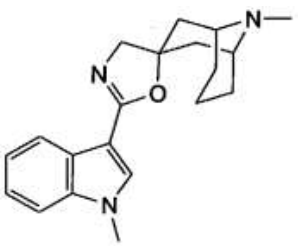




21 **22** **23**

Using oxazoline as a bioisostere for esters and amides, Swain *et al.* synthesised and biochemically evaluated a series of spirofused indole oxazoline as 5-HT_3 receptor antagonists. Steric constraints of the aromatic binding site were revealed by the impact of

substitution around the indole ring. The binding model, which included many well-established antagonists and agonists, was defined by including a wide range of azabicyclic systems inside a strict spirofused framework. Compounds with the basic nitrogen at the bridgehead position showed the strongest affinity. Lipophilic interactions may have a role in boosting affinity, as shown by the fact that Compound **24** (pIC_{50} = 8.95) is the most powerful analogue in this group's azabicyclic[3.3.1] system.[23]



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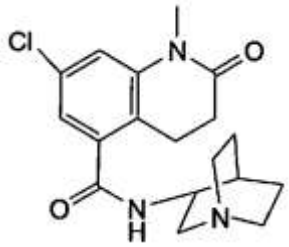
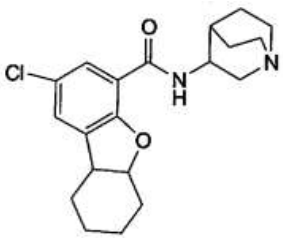


25

To create 5-HT_3 receptor antagonists, Kawakita *et al.* synthesised a series of 3,4-dihydro-3-oxo-1,4-benzoxazine-8-carboxamides. Compounds in this series with the 1-azabicyclo[2.2.2]oct-3-yl moiety with eighth position of benzoxazine exhibited the most antagonistic activity. Compound **25** showed the highest Ki = 2.9 nM affinity for 5-HT_3 receptors and the most promising antagonistic action in the B-J reflex test (ED_{50} =1.3 pg/kg i.v.). At a dosage of 0.1 mg/kg i.v., it also totally eliminates cisplatin-induced emesis in dogs.[24]

The two series of tricyclic carboxamides were reported by Youssefyeh *et al.* to be antagonists of the 5-HT_3 receptor. *In vitro* and *in vivo* experiments indicated that compounds **26** and **27** had the most promising antagonistic actions, and these molecules also blocked chemotherapeutic agent-induced emesis. Compound **26** had higher radioligand binding affinity (Ki = 0.17 nM) and antagonism (1 kg/kg i.v. in the B-J reflex test and 10'9 M in 5-HT-induced contraction of guinea-pig ileum) than the reference 5-HT_3 receptor antagonists.[25]



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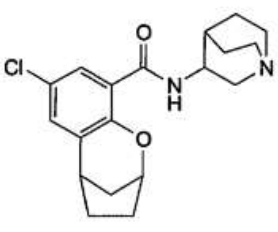
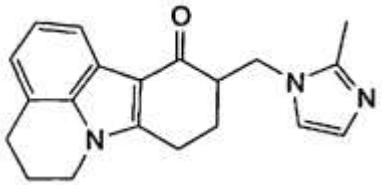


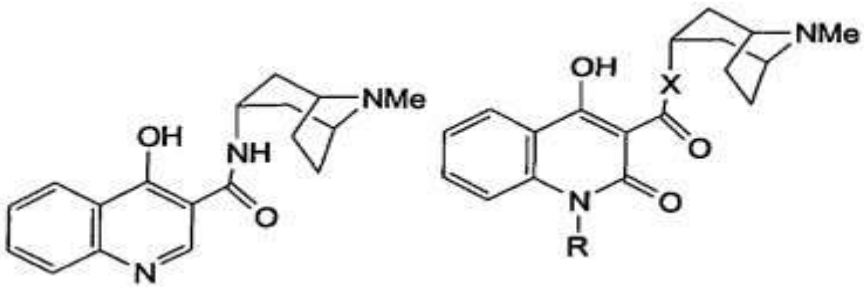
27

To create more 5-HT_3 receptor antagonists, Wijngaarden *et al.* modelled a series of 1,7-annelated indole compounds after the structures of the widely used antagonists ondansetron and GR65630. Compared to ondansetron and GR 65630, the annealed compounds showed increased efficacy. Compared to their dextro isomers, the *L*-isomers of the synthesised compounds were shown to be somewhat more effective. Compound **28** has a Ki of 340 nM for the 5-HT_3 receptor, 910 nM for the muscarine Mt receptor, 960 nM for the 5-HT_4 receptor, and a Ki of > 5000 nM for the other 37 receptor types.[26]



28

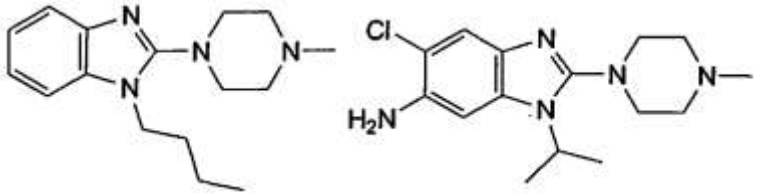
Derivatives of 4-hydroxy-3-quinolinecarboxylic acid and 4-hydroxy-2-oxo-1,2-dihydro-3-quinolinecarboxylic acid were synthesised by Hayashi *et al*. and shown to be potent antagonists of the 5-HT3 receptor. Molecular simulations revealed that carbonyl groups in 2-oxo-quinoline and 4-hydroxy-3-quinolinecarboxylic acid derivatives were not coplanar with aromatic residues, but were instead offset by 30 degrees. Although Compound **29** showed the highest activity in the B-J reflex test (ED_{50} = 0.1 pg/kg i.v.), other compounds, including Compounds **30** and **31** (Ki = 0.48 nM), showed greater affinities for the 5-HT_3 receptor in binding assay. In the B-J reflex test, chemicals made subsequently were not as effective as the reference compounds.[27]



29 **30** R = Phenyl, X = NH **31** R = Butyl, X = NH

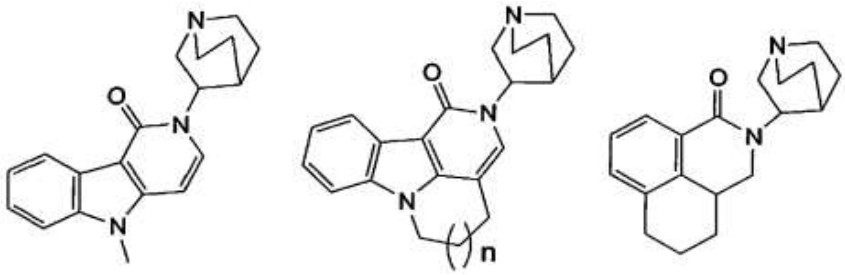
By comparing the serotonin and 5-HT_3 receptor antagonists, Hori *et al.* created a series of new 5-HT_3 receptor antagonists employing regular hexagonal grid templates in two dimensions. Compound **32**, one of the synthesised compounds, was found to be the most promising since it displayed 5-HT_3 receptor antagonism on par with granisetron. Compound

33 (KB 6933), an antagonist of the 5-HT_3 receptor, was obtained by quantitative structure-activity relationship optimisation of compound **32.**[28]



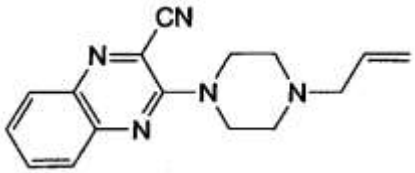
32 **33**

As antagonists for the 5-HT_3 receptor, Clark *et al*. synthesised a number of different series of chemicals. These included indole, pyridoindole, benzamide, pyridoindolone, and isoquinolone. The radioligand binding experiment revealed high affinities for compounds **34–36**, a class of pyridoindolone compounds, with pK/ values over 9. *S*-isomers of the synthesised compounds showed higher affinity than their corresponding R isomers, suggesting that they are the more functional of the two forms. The most powerful molecule, with a binding affinity of pK7 = 10.4, was determined to be (*S*,*S*)-**37** in a radioligand binding experiment. This compound substantially prevented cisplatin-induced emesis in ferrets and dogs and antagonised serotonin type-3 receptor-mediated bradycardia in the B-J reflex test.[29]



34 **35** n = 1 **36** n= 2 **37**

Piperazinyl quinoxaline was synthesised by Monge *et al.*, and its antagonistic potential at the 5-HT_3 receptor was described. The pA_2 values of 5-HT_3 receptor antagonism were determined in a LMMP preparation from guinea pig ileum in response to a standard 5-HT_3 agonist, 2-methyl-5-HT or serotonin. Cyanoquinoxalines with an alkyl group on the distal nitrogen of piperazine reacted more negatively than others. The most effective of the synthesised chemicals was determined to be compound **38**. In *in-vitro* functional testing, Compound **38** demonstrated stronger antagonism than the reference medicines tropisetron and ondansetron. However, the radioligand binding studies and the B-J reflex tests showed that this molecule was not as effective as conventional medicines.[30]



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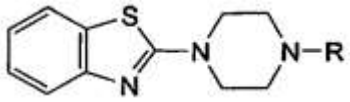
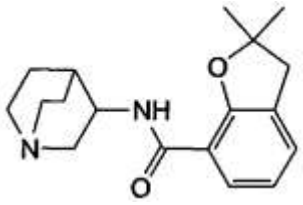
An array of 2-piperazinylbenzothiazole and 2-piperazinylbenzoxazole derivatives were synthesised by Monge *et al.* for use as 5-HT_3 antagonists. Functional assays in a guinea pig ileum LMMP preparation showed that compounds **39** and **40** had stronger antagonism than the gold standard medication ondansetron. However, in a radioligand binding experiment and a test of 5-HT_3 receptor antagonism, none of these drugs was as effective as ondansetron. These compounds, by virtue of their agonistic action at 5-HT_4 receptors, exhibited enhanced prokinetic effects comparable to cisapride. Using a preparation susceptible to activation of the 5-HT_4 receptor (isolated rat esophageal tunica muscularis mucosae), the agonistic activity of the chemical increased the twitch response in the LMMP preparation.[31]



39 R = Bn; **40** R = Piperonyl

The 5-HT_3 receptor antagonists azabicyclo-3-yl-2,3-dihydrobenzofuran-7-carboxamides were synthesised by Kuroita *et al.* Radioligand binding assays and the 5-HT_3 receptor antagonism in the B-J reflex test were used to determine the receptor affinity. The pharmacological activity of dihydrobenzofurans was shown to be enhanced by the introduction of methyl group(s) at the second position of the ring. When it came to the fundamental component, compounds with an *S*-1-azabicyclo[2.2.2]octan-3-yl moiety were superior to their contemporaries. Dimethyl > (2*S*)-methyl > (2*R*)-methyl > dihydro was the most effective of the four possible methyl groups at position 2 of the dihydrobenzofuran ring. These findings showed that the dihydrobenzofuran (2*S*)-methyl group was responsible for the improved pharmacological action. The B-J reflex test indicated that (*S*)-Compound **41** had the greatest affinity for the 5-HT_3 receptors (Ki = 0.055 nM) compared to granisetron (Ki = 0.41 nM) and zacopride (Ki = 0.18 nM) and the lowest effective dose (ED_{50} = 0.18 pg/kg, i.v.).[32]



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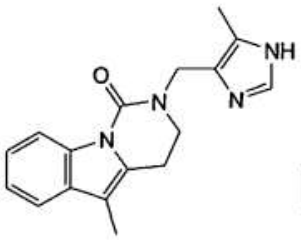

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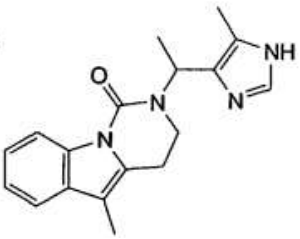
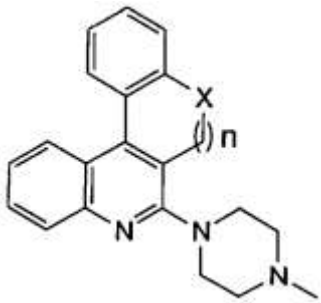


43

Synthesis and putative antagonistic effects on the 5-HT_3 receptor were documented for a series of pyrimido[1,6-a]indol-1(2H)-ones by Kato *et al.* High efficacy was found in compounds with methyl substituents on the pyridoindole and imidazole rings. The most effective antagonists in the B-J reflex test were compounds **42** and **43**, with ED_{50} values of 0.6 pg/kg and 0.8 pg/kg, i.v., respectively. Twenty to thirty times as effective as the gold standard medicine ondansetron, these molecules were.[33]

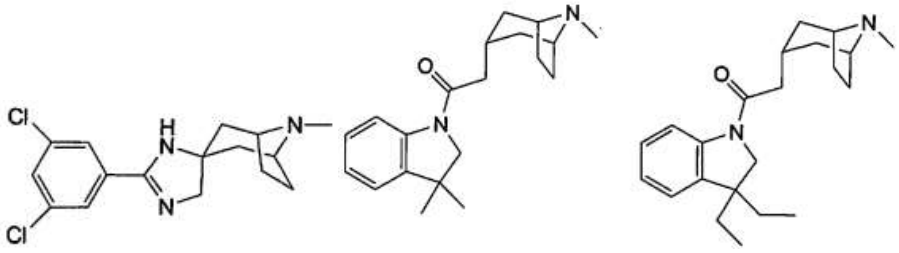
As antagonists for the serotonin type-5 (S5) receptor, Anzini *et al.* synthesised a series of fused quinoline derivatives with a basic nitrogen group on the second quinoline nucleus. Compound **44**, one of the synthesised compounds, had a Ki value for binding affinity towards the 5-HT_3 receptor that was comparable to quipazine's. In the B-J reflex test, this molecule demonstrated the same degree of strong 5-HT_3 receptor antagonism as the reference medicines ondansetron, tropisetron, and zacopride. The 5-HT_3 receptor affinity and antagonism of compounds **45-46** were equivalent to those of well-established 5-HT_3 receptor antagonists.[34]



44 X = O, n = 1; **45** X = O, n = 2; **46** X = CH_2, n = 2

A variety of tropane-3-spiro-4'(5')-imidazoline derivatives with antagonistic activity at the 5-HT_3 receptor were synthesised and tested by Waeber *et al.* Compound **47** was determined to be the most effective of this series, with an affinity for the 5-HT_3 receptor that was similar to that of radioligand binding assay and an antagonism of the 5-HT_3 receptor that was

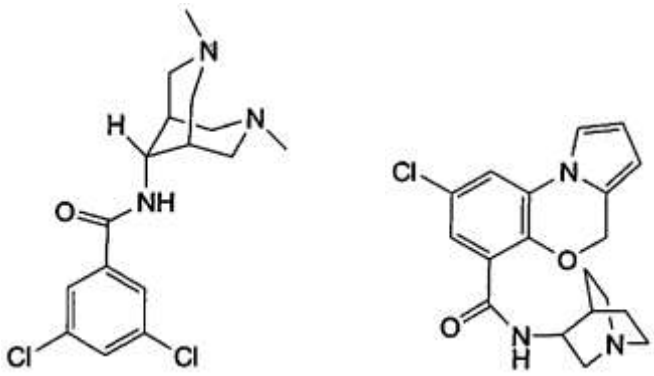
equivalent to that of metaclopramide in the B-J reflex test. In this research, it was shown that the carbonyl group of 5-HT_3 receptor antagonists may be replaced with a bioisosteric imidazoline nucleus.[35]



47 **48** **49**

Synthesis and SAR of 5-HT_3 receptor antagonists derived from a series of azabicycloalkaneacetic acid derivatives were reported by Kato *et al.* The B-J reflex test revealed strong antagonism of the 5-HT_3 receptor by compounds containing a 2,3-dihydroindole aromatic nucleus with a gem-dimethyl or gem-diethyl group at the third position. Among the synthetic drugs, **48** and **49** showed the most potent antagonism against the 5-HT_3 receptor. The potency of antagonism demonstrated by Compounds **48** (ED_{50} = 2.3 pg/kg i.v.) and **49** (ED_{50} = 1.7 pg/kg i.v.) was 10 times that of the reference medication, ondansetron (ED_{50} = 17.5 pg/kg i.v.). A novel bioisostere for the basic nitrogen region and a connecting carbonyl group has been identified: the acetyl group of an azabicycloalkane.[36]

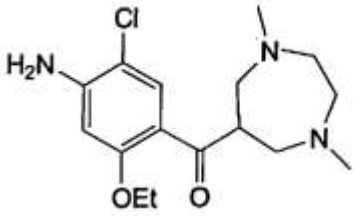
As antagonists for the 5-HT_3 receptor, Fernandez *et al.* synthesised a series of compounds based on the amide moiety of 3,7-dimethyl-3,7-bicyclo [3.3.1]nonan-9-amine. Compound **50**, the most powerful of the synthesised compounds, was shown to be just as effective as MDL-72222 in a radioligand binding experiment. At a dosage of 25 mg/kg, this test chemical similarly antagonised 5-HT_3 receptors in the B-J reflex test.[37]



50 **51**

Novel heterocyclic carboxamides have been shown to have antagonistic potential at the 5-HT_3 receptor, as described by Kato *et al.* Substituents (chloro/methyl) that are both tiny and lipophilic on the 8th position of the aromatic ring tend to retain their potency. However, compounds with heavy substituents showed little action. The antagonistic efficacy was somewhat diminished by the addition of a gemdimethyl group to the aromatic ring in the fourth position. When compared to other amine derivatives, the activity of compounds generated from the 1-azabicyclo[2.2.2]octan-3-amine was the highest. The B-J reflex test revealed that Compound **51**, with an ED_{50} of 0.4 pg/kg i.v., was the most effective antagonist, being 40 times more effective than ondansetron (ED_{50} = 17.5 pg/kg i.v.).[38]

Series of 2-alkoxy-4-amino-5-chlorobenzamides with five seven-membered heteroalicyclic rings as the basic area were synthesised by Harada *et al.*, and their 5-HT_3 receptor antagonistic potentials were described. Pyrrolidine, morpholine, piperidine, 1,4-thiazine, 1,4-thiazepine, azepine, 1,4-diazepine, and 1,4-oxazepine were all included among the heteroalicyclic compounds. Among them, 1,4-diazepine derivatives showed strong antagonism towards 5-HT_3 receptors. Compounds **52** and **53** demonstrated strong inhibition of the 5-HT_3 receptor, but little affinity for the 5-HT_4 receptor.[39]



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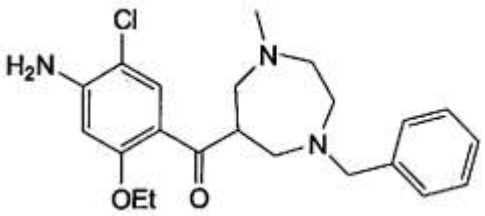
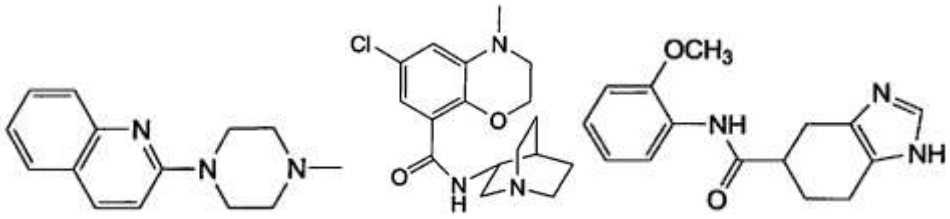


53

By using a radioligand binding experiment, Dukat *et al.* synthesised a range of aryl piperazines and guanidines and tested their affinity for the 5-HT_3 receptor. A higher affinity was shown for the arylpiperazines than for the guanidine derivatives. Substituents found in powerful arylpiperazines were incorporated into guanidine derivatives to increase their affinity for 5-HT_3 receptors. Unfortunately, in the B-J reflex test conducted on rats, the derived guanidine derivatives worked as agonists, but the arylpiperazines showed antagonism. Compound **54** showed the highest affinity for 5-HT_3 receptors among the synthesised compounds (Ki = 3.01 nM).[40]

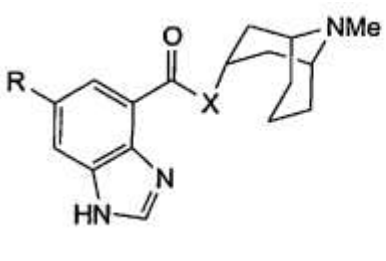


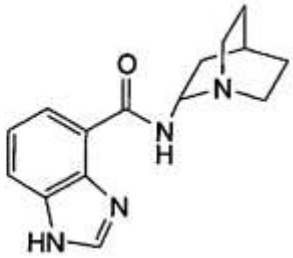
54 **55** **56**

Kuroita *et al.* showed that 6-chloro-3,4-dihydro-4-methyl-2H-1,4-benzoxazine-8-carboxamides are effective antagonists of the 5-HT_3 receptor. In radioligand binding experiments, the affinities of granisetron (Ki = 0.41 nM), zacopride (Ki = 0.18 nM), and azasetron (Ki = 0.54) for the 5-HT_3 receptor were much lower than those of Compound **55** (Ki = 0.051 nM). Potent antagonism (ED_{50} = 0.089 pg/kg, i.v.) was seen between the *S*-isomer and *R*-isomer in the B-J reflex test, whereas the corresponding *R*-isomer demonstrated an ED_{50} value of 0.73 pg/kg, i.v. ED_{50} values of 0.74 pg/kg, 0.5 pg/kg, and 1.3 pg/kg i.v. were observed for granisetron, zacopride, and azasetron, respectively, the reference compounds.[41]

The antagonistic action at the 5-HT_3 receptor was tested after a series of fused imidazole derivatives was synthesised by Ohta *et al.* The isolated guinea pig colonic contraction IC50 value for Compound **56** was 0.43 pM, and the ID_{50} value for the B-J reflex test was 0.32 pg/kg, making it the most effective of the synthesised compounds, making it roughly ten and two times potent than ondansetron, respectively.[42]

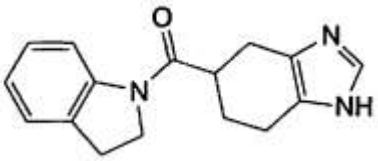
The series of benzimidazole-4-carboxylic acid derivatives, esters, and amides were synthesised, and their 5-HT_3 and 5-HT_4 receptor affinities were reported by Lopez-Rodriguez *et al.* The synthetic compounds showed low to moderate affinity for 5-HT_4 receptors and moderate to high affinity for 5-HT_3 receptors. Compounds **57–59** had the highest affinity for 5-HT_3 receptors among the synthesised compounds (Ki = 6.1 nM, 3.7 nM, and 4.9 nM, respectively). Radioligand binding experiments indicated that these drugs lacked considerable affinity for the other subtypes of the 5-HT receptor, 5-HT_4 and 5-HT_{1A} (Ki > 1000 nm and Ki > 10,000 nM, respectively). In a light-dark test, compound **59** showed antagonism towards 5-HT_3 receptors.[43]

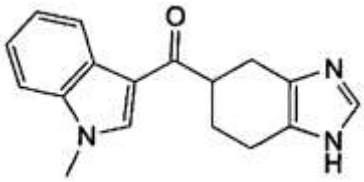




57 R = H, X = NH; **58** R = Cl, X = O **59**

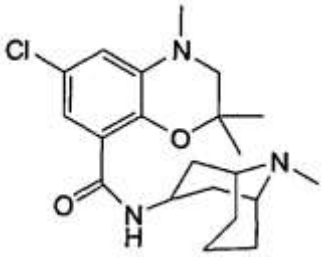
Synthesis and pharmacological assessment of 5-HT_3 receptor antagonists of 4,5,6,7-tetrahydro-1*H*-benzimidazole derivatives were disclosed by Ohta *et al.* For the 5-HT_3 receptor antagonism, the 5-HT_3 receptor binding affinity in the radioligand binding experiment, and the contraction of the isolated guinea pig colon, *R*-isomers have shown more activity than the comparable *S*-isomers. Inhibiting cisplatin-induced emesis in ferrets and restraint stress-induced increased faecal pellet production in rats, the *R*-isomer of Compounds **60-61** was shown to be several hundred times more powerful than ondansetron and granisetron when administered orally.[44]





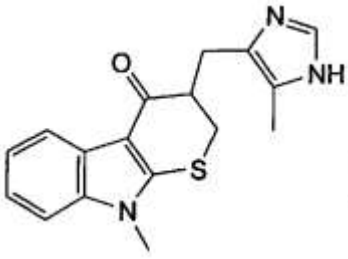
60 **61**

A series of 3,4-dihydro-2-H-1,4-benzoxazine-8-carboxamides were synthesised by Kuroita *et al.* for use as antagonists of the 5-HT_3 receptor. Substituting a 1,4-benzothiazine or seven-membered ring for the 1,4-benzoxazine ring in this series decreased their affinity for 5-HT_3 receptors. The antagonistic activity of 1,4-benzoxazine was improved by the introduction of a substituent at position-2. Compound **62** had the longest duration of 5-HT_3 receptor antagonism (3 hr) and the greatest affinity for 5-HT_3 receptors in the B-J reflex test.[45]



62

Novel 9-methylthiopyrino[2,3-b]indol-4-one, 9-methyl-2,3,4,9-tetrahydrothiopyrino[2,3-b]indol-4-one, and 3-methylene-9--methyl-2,3,4,9-tetrahydrothiopyrino[2,3-b]indol-4-one derivatives were synthesised by Suzuki *et al.* The B-J reflex test and an *in-vitro* functional experiment using guinea pig colon isolation were used to determine the antagonism of the synthesised compounds on the 5-HT_3 receptor. In the B-J reflex and the *in-vitro* functional experiment (IC_{50} = 0.0062 pM), compounds **63** and **64** showed 5-HT_3 receptor antagonism 79 and 126 times more powerful than ondansetron, respectively.[46]



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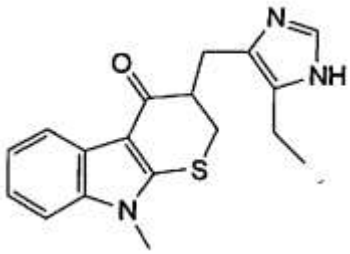
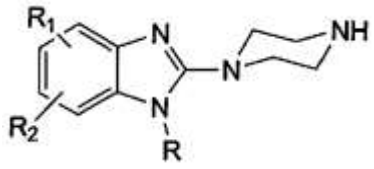


64

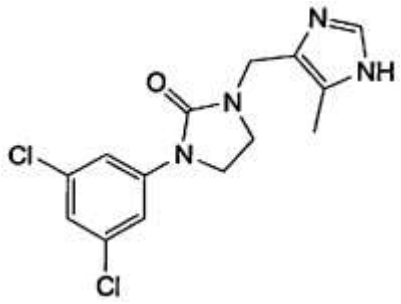
Several 2-piperazinylbenzimidazole compounds were described as 5-HT_3 receptor antagonists by Orjales *et al.* The antagonism of the 5-HT_3 receptor was measured using the serotonin-induced B-J reflex test in anaesthetized rats, and the radioligand binding assay was used to determine the affinities of the synthesised compounds for the 5-HT_3 receptor. Almost as effective as the reference medicines tropisetron and granisetron, majority of the synthesised compounds also demonstrated high affinity for the 5-HT_3 receptor. Structure-activity investigations revealed that high affinity for the 5-HT_3 receptor requires a substituent on the benzimidazole nitrogen. Substituent position on the aromatic residue also had a significant role in determining activity, with the 7-methoxy derivative **65** showing the greatest affinity for the 5-HT_3 receptor (pKi = 9.4) and the 4-methoxy derivative **66** showing the weakest affinity (pKi = 6.7). In the B-J reflex test, compound **65** also demonstrated potent 5-HT_3 receptor antagonism (ED_{50} = 0.7 pg/kg i.v.).[47]



65 R = Bn, R_1 = (7)OCH_3, R_2 = H; **66** R = Bn, R_1 = (4)OCH_3, R_2 = H

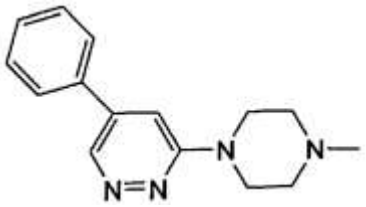
Based on the pharmacophoric properties present on the medicines, metaclopramide and zetidoline were modified on the aryl and basic nitrogen area to create a series of

phenylimidazolidin-2-ones that Heidempergher *et al.* created as 5-HT_3 receptor antagonists. The benzamido group and the azabicyclicalkyl/imidazolylalkyl residue of phenylimidazolidin-2-one have found use as bioisoteres. In comparison to their azabicyclicalkyl counterparts, imidazolylalkyl derivatives were shown to be more potent. When compared to standard 5-HT_3 receptor antagonists (ondansetron, tropisetron, granisetron, and BRL 46470), compound **67** demonstrated superior binding affinity (Ki = 0.038 nM) and 5-HT_3 receptor antagonism (Kb = 5.62 nM), respectively. Similar inhibition of the 5-HT_3 receptor was seen in the B-J reflex test when compound **67** was used.[48]



67

In order to better understand how to design Mt receptor agonists, Rival *et al.* created a pharmacophoric model based on already available powerful muscarinic receptor agonists. Most of the already available 5-HT_3 receptor antagonists contained an aromatic group, while muscurnic agonists did not. Because of this, Rival *et al.* reworked Mi receptor agonists to be 5-HT_3 receptor antagonists chemically. Four of the anticipated aminopyridiazines were synthesised and tested for affinity to the 5-HT_3 receptor. Compounds **68–71** showed nanomolar affinity for the 5-HT_3 receptor throughout the synthesis process.[49]



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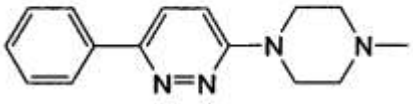

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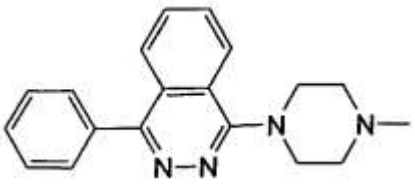

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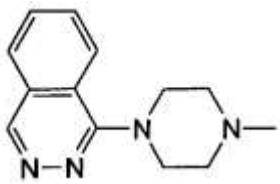
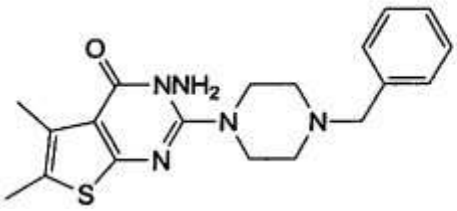


71

As antagonists for the 5-HT_3 receptor, Lopez-Rodriguez *et al.* synthesised a variety of benzimidazole-4-carboxylic derivatives, amides, and esters. Compounds having a nitro substitution at position-7 on the benzimidazole nucleus or no modification at position 6 showed higher affinity against 5-HT_3 receptor in a structure-activity relationship investigation. Compounds **72–74** had the highest affinity and antagonistic profile (pKa = 9.6, 9.9, and 9.1, respectively).[50]

72 $R_1 = R_2 = H$; **73** $R_1 = Cl$, $R_2 = H$; **74** $R_1 = Cl$, $R_2 = NO_2$

In order to bind to 5-HT_3 and 5-HT_4 receptors, Modica *et al.* synthesised thienopyridinopiperazine and piperazinylaminomethylthiophene derivatives and reported their binding affinities. In a radioligand binding experiment, the synthesised compounds with the highest affinities for 5-HT_3 and 5-HT_4 receptors were compounds **75** and **76.**[51]



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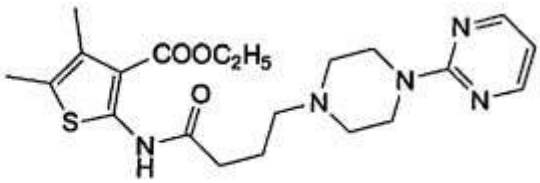
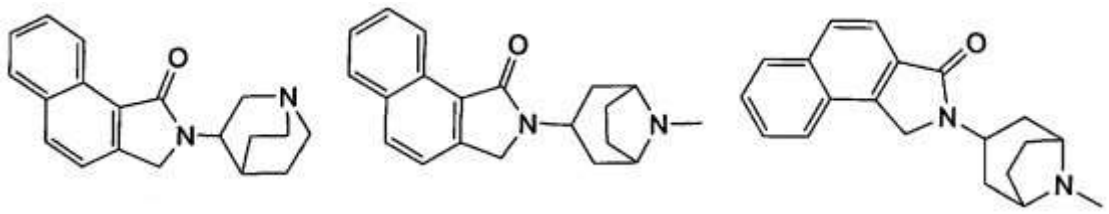


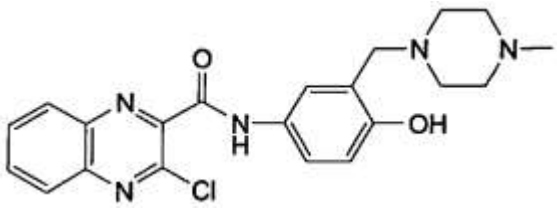
76

Using a radioligand binding assay, Cappelli *et al.* synthesised a series of conformationally constrained pyrrolidone based compounds to test as 5-HT_3 receptor antagonists. The series' most potent member, compound **77**, showed activity comparable to that of granisetron. In functional experiment, drugs based on tropane showed antagonistic qualities, whereas compounds based on quinuclidine showed agonistic properties. ID_{50} values of 2.8 pg/kg and 181 pg/kg were observed for Compound **78** and (S)-**77**, respectively, in the B-J reflex test. Select compounds **77–79** protected against amnesia produced by scopalamine in a passive avoidance test.[52]



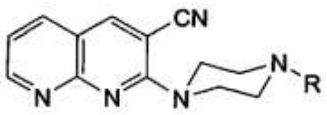
77 **78** **79**

To block the effects of the 5-HT_3 receptor, Mahesh *et al.* developed and synthesised a series of 3-chloroquinoxaline-2-carboxamides. The *p*-aminophenol-derived Mannich base connected the aromatic group to the basic nitrogen region. In a longitudinal muscular myenteric plexus produced from guinea pig ileum, pA_2 values for antagonism of the 5-HT_3 receptor by the 5-HT_3 agonist 2-methy-5-HT were determined. This antagonism was measured as a decrease in receptor activity. The most effective of the synthesised compounds was compound **80**, which had a pA_2 value of 6.4, making it competitive with the gold standard 5-HT_3 receptor antagonist, ondansetron (pKa 6.9).[53]



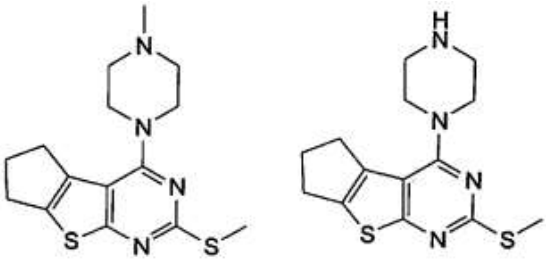
80

Mahesh *et al*. designed and synthesised a novel series of 2-(4-substituted piperazin-1-yl)-1,8-naphthyridine-3-carbonitriles as antagonists for the 5-HT_3 receptor. They then performed pharmacological testing on these compounds. The carbonyl group was not present in the molecules that were synthesised; in its place, the naphthyridine nitrogen was the component that was responsible for the interaction with the 5-HT_3 receptor. pAz values were employed in a preparation of guinea pig ileum myenteric plexus in order to make a comparison between the antagonism of the 5-HT_3 receptor and that of a reference 5-HT_3 agonist known as 2-methy-5-HT. Compounds **81–83**, which were also synthesised, displayed potent antagonism with pA_2 values higher than ondansetron (pA_2: 6.9), the gold standard medication in this class. The research team determined that compound **83** had the highest activity of the series. These findings imply that the antagonistic potential of napthyridine-3-carbonitriles is boosted by the presence of an aliphatic hydrophobic group on the distal nitrogen of piperazine.[54]



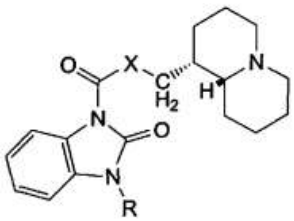
81 R = CH_3; **82** R = C_2H_5; **83** R = H

Piperazinyl substituted thienopyrimidine derivatives were synthesised by Modica *et al.* Using a ligand binding experiment, they determined the affinity of these drugs for the 5-HT_3 receptor. Compounds **84** and **85**, among those synthesised, exhibited selective potency at the 5-HT_3 receptor and poor potency at other receptor subtypes, especially the 5-HT_4 receptor. The inhibition of the 5-HT_3 receptor was shown in a noncompetitive manner by compounds **84** and **85** in an *in vitro* functional experiment.[55]

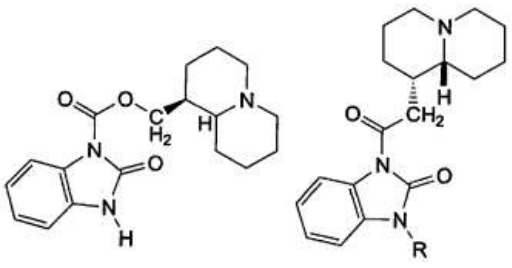


84 **85**

By using a radioligand binding assay, Tralongo *et al.* synthesised a number of 1-H-benzimidazole-carboxylic acid derivatives of epi-lupinine, lupinylamine and lupinine, tested their binding affinities for 5-HT_3 receptors and 5-HT_4 receptors. The synthesised compounds **86-92** were only moderately effective.[56]

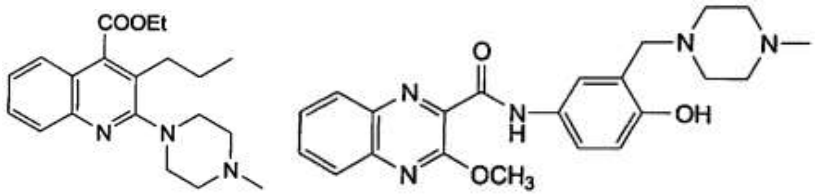


86 R = H, X = O; **87** R = C_2H_5, X = O; **88** R = H, X = NH; **89** R = C_2H_5, X = NH



90 **91** R = H; **92** R = C_2H_5

Lipophilic aryl-piperazine derivatives were synthesised by Cappelli *et al.*, and their affinity for the 5-HT_3 receptor was reported. Most of the synthesised compounds exhibited sub-nanomolar binding affinity towards 5-HT_3 receptors in a radioligand binding experiment. At picomolar concentrations (Ki = 0.080 nM), compound **93** was the most active.[57]



93 **94**

Three-substituted quinoxaline-2-carboxamides may function as antagonists of the 5-HT_3 receptor, as shown by research by Venkatesha and Mahesh. When developing these synthetic molecules, we took into account the pharmacophoric requirements of 5-HT_3 receptor antagonists. Mannich base (*p*-aminophenol derivatives) bridges the gap between the synthesised compounds' aromatic and basic nitrogen pharmacophores. To calculate the pA_2 value for the antagonism of the 5-HT_3 receptor by the 5-HT_3 agonist 2-methyl-5-HT, a preparation of the ileum myenteric plexus from a guinea pig was used. The antiemetic activity of ondansetron, the standard treatment, was not surpassed by any synthetic molecule. The highest *p*-value among the synthesised carboxamides was observed for compound **94.**[58]

CONCLUSION

The literature on the impact of contemporary antidepressants on cognitive performance is effectively reviewed. It is now generally accepted that SSRIs do not have any negative impact on mental capacity. Paroxetine has been linked to somewhat worse results on neurocognitive tests than other groups of SSRIs, although this is not conclusive. In addition, when compared to other SSRIs, sertraline routinely performs higher on cognitive tests. Few researches have looked at the impact of RIMAs and 2-receptor antagonists on mental acuity. The latter has been linked to potential cognitive impairments. Researchers have shown that reboxetine, bupropion, and SNRIs may be the most helpful antidepressants for improving mental acuity. It is uncertain, however, whether or whether these drugs may enhance cognitive performance to an extent beyond that which would be predicted from improvement in depressed symptomatology. When evaluating the efficacy of contemporary antidepressant medication on cognitive performance, it is essential to account for the influence of clinical, social, and emotional aspects.

Conflict of interest

No conflict of interest is declared.

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