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Effect of the replacement of the *o*-methoxyphenyl moiety with nitrogen-containing aromatic rings within N-phenyl-piperazine and phenoxy-ethylamine-based 1,3-dioxo/oxathio/dithiolanes as α_1 and 5-HT_{1A} receptor ligands

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ABSTRACT

In the present work, nineteen analogues of 1-[(2,2-Diphenyl-1,3-dioxolan-4-yl)methyl]-4-(2-methoxyphenyl) piperazine **5** and N-[2-(2-Methoxyphenoxy)ethyl]-2,2-diphenyl-1,3-dioxolane-4-methanamine **18** were synthesized. The compounds were tested for binding affinity at 5-HT_{1A}R and α_1-AR subtypes. They were also tested using functional assays as α_1-AR antagonists and the most promising were tested for functional activity at 5-HT_{1A}R, where they were shown to behave as agonists. The results highlight that the replacement of the 1,3-dioxolane ring with a 1,3-oxathiolane or a 1,3-dithiolane moiety leads to an overall reduction in *in-vitro* affinity at the α_1-AR, while affinity, potency and efficacy were strongly enhanced at the 5-HT_{1A} receptor. Overall, the nitrogen-containing aromatic moieties scarcely affect the affinity at the 5-HT_{1A} receptor, while reducing potency and increasing efficacy. The oxidation of the sulphur atom in the 1,3-oxathiolane to give sulfoxides and solfones has a negative effect on affinity and potency at both receptor systems. Regardless of the effect on the other parameters, selectivity toward 5-HT_{1A}R with respect to the α_1-AR is often favoured, but never the contrary. The most striking result is the inversion of selectivity. In fact, while the lead **5** is 100-fold selective for α_1-AR, the new derivatives, although to differing degrees, are selective for 5-HT_{1A}R.

1. Introduction

The 5-HT_{1A} receptor (5-HT_{1A}R) is the most studied among 5-HT subtypes. Its pharmacology has been extensively studied through the development of a large number of selective ligands, also designed to identify possible new drugs. In fact, 5-HT_{1A}R represents an attractive target for drug discovery [1]. In particular, agonists and partial agonists have been considered potentially useful in the treatment of anxiety, depression, and psychosis [2–7]. 5-HT_{1A}R agonists have shown neuroprotective properties, indicating their possible use in the treatment of ischemic stroke [1,8–19]. Moreover, 5-HT_{1A}Rs are also targeted by new analgesic substances. In fact, a possible correlation between the peripheral 5-HT_{1A}Rs producing antinociception in the formalin test and the 5-HT_{1A}R subtype was recently established, suggesting that its agonists may rival opioids in pain relief therapy [20–26].

Among the 5-HT_{1A}R ligands that have been extensively studied over the years, a 1-arylpiperazine scaffold, linked using an alkyl chain of variable length to a terminal group (imides, amides, alkyl, arylalkyl, or heteroarylalkyl derivatives and tetralines), is present in a large number of known ligands [1,27]. In most cases, the 1-arylpiperazine scaffold has an o-methoxy-phenyl group.

We recently reported the synthesis and biological evaluation of compound **5,** a potent and selective α_1-adrenoreceptor (α_1-AR) antagonist, with affinity also for 5-HT_{1A}R, where it has been shown to be a very potent partial agonist [28]. Taking compound **5** as starting point, we synthesized ten analogues of this lead compound by replacing the *o*-methoxy group with different nitrogen-containing aromatic rings. Buspirone is an example of a 5-HT_{1A}R ligand containing this structural

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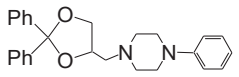
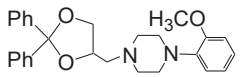
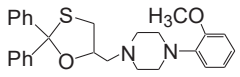
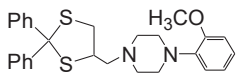
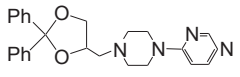
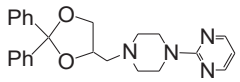
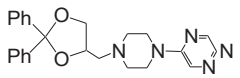
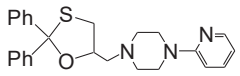
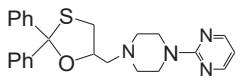
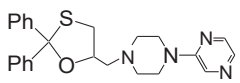
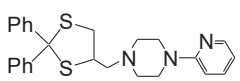
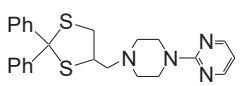
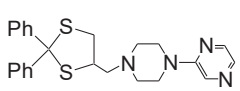
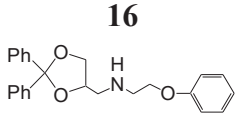
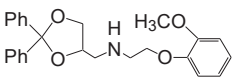
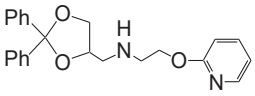
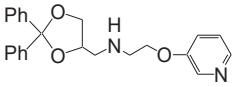
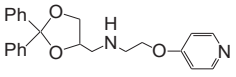
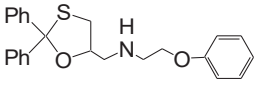
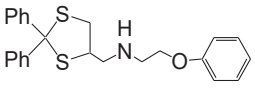
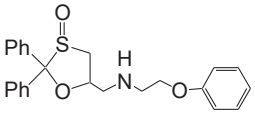
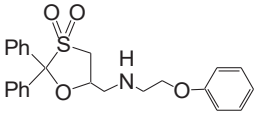
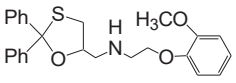
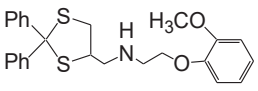
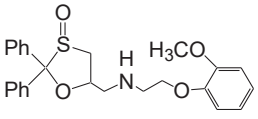
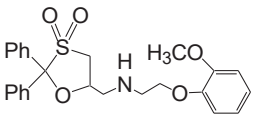
Table 1
Binding affinity and selectivities at cloned human α_1-AR and 5-HT_{1A}R subtypes and functional studies at 5-HT_{1A}R.

Compound	pKi*human cloned									
	α_{1a}	α_{1b}	α_{1d}	α_{1d}/α_{1a}	α_{1d}/α_{1b}	α_{1a}/α_{1b}	5-HT_{1A}	pD2	%max	5-HT_{1A} /α
 **4**	7.42	6.88	6.94	0.3	1	3	7.21			0.6
 **5**	9.58	8.17	9.09	0.3	8	26	7.64	8.3	16	0.01
 **6**	8.69	8.05	8.40	0.5	2	4	8.18			0.3
 **7**	7.24	**<6**	6.64	0.3	>4	>17	8.26	6.27	41	11
 **8**	7.24	**<6**	6.56	0.2	>4	>17	7.82	6.64	72	4
 **11**	6.54	**<6**	**<6**	<0.3	1	>3	7.22	6.09	65	5
 **14**	**<6**	**<6**	**<6**	1	1	1	**<6**			–
 **9**	6.62	**<6**	**<6**	<0.2	1	>2	7.76	6.62	70	14
 **12**	**<6**	**<6**	**<6**	1	1	1	7.46	6.10	63	>30
 **15**	**<6**	**<6**	**<6**	1	1	1	**<6**			.
 **10**	6.53	**<6**	**<6**	<0.3	1	>3	7.62	6.67	60	12
 **13**	6.40	**<6**	**<6**	<0.4	1	>3	6.75			1
 **16**	**<6**	**<6**	**<6**	1	1	1	**<6**			–
 **17**	7.43	7.20	7.94	3	5	2	8.45	8.8	24	3

(*continued on next page*)

Table 1 (*continued*)

Compound	pKi*human cloned									
	α_{1a}	α_{1b}	α_{1d}	α_{1d}/α_{1a}	α_{1d}/α_{1b}	α_{1a}/α_{1b}	5-HT_{1A}	pD2	%max	5-HT_{1A} /α
 **18**	7.71	7.33	8.03	2	5	2	9.22	7.36	32	15
 **21**	6.92	7.01	7.66	5	4	1	7.80	7.27	57	1
 **22**	8.52	7.67	8.03	0.3	3	7	8.87	7.61	61	2
 **24**	<6	<6	<6	1	1	1	5 1E-6 M			–
 **25**	6.88	6.61	7.79	8	15	2	8.55	8.03	92	6
 **27**	6.89	6.62	7.30	3	5	2	8.61	8.04	88	20
 **29**	6.52	6.61	7.00	3	2	1	8.24	7.52	49.6	15
 **31**	<6	<6	<6	1	1	1	6.69	–	–	>5
 **26**	7.68	7.00	9.28	40	190	5	8.99	8.94	76	0.5
 **28**	7.45	6.93	7.69	2	6	3	9.89	7.76	20	158
 **30**	6.35	6.60	8.14	62	35	0.6	8.30	8.10	54	1
 **32**	<6	<6	6.62	>4	>41		7.03	–	–	3

*Each experiment was performed in triplicate.
The data are expressed as means of 2–3 separate experiments performed in duplicate;
Standard deviation is within ± 10% of the value.

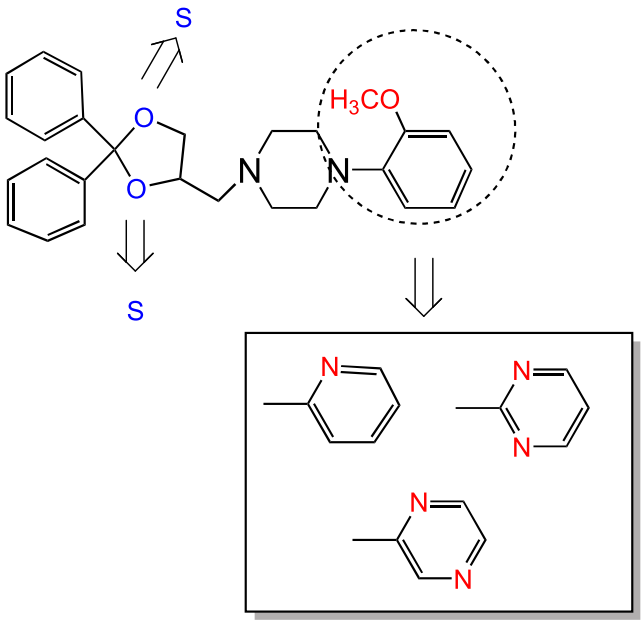


Chart 1. Aim of the work for the *o*-methoxyphenyl piperazine series.

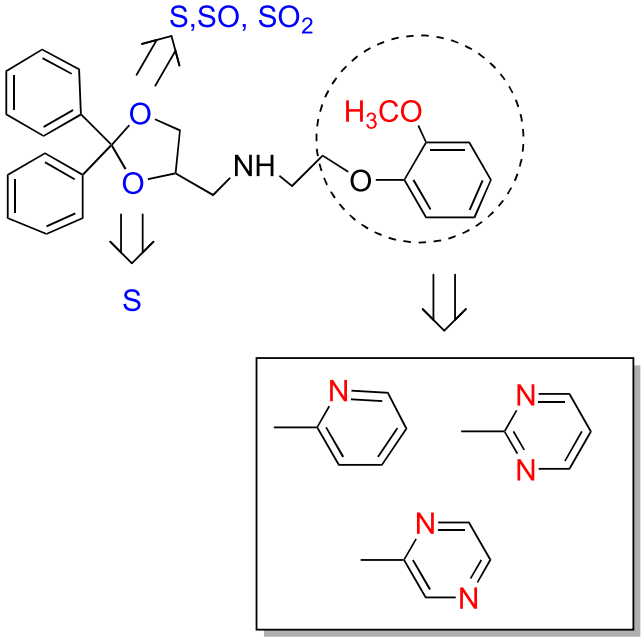
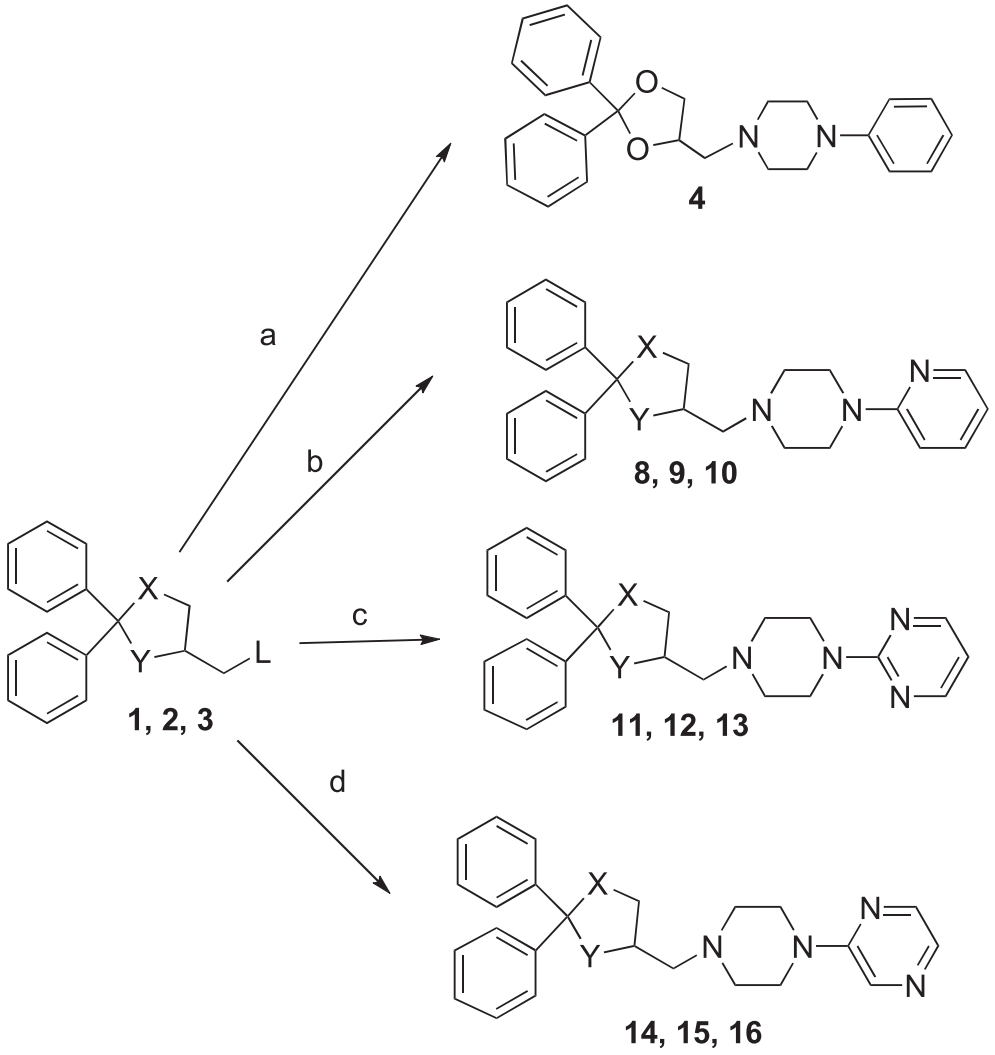


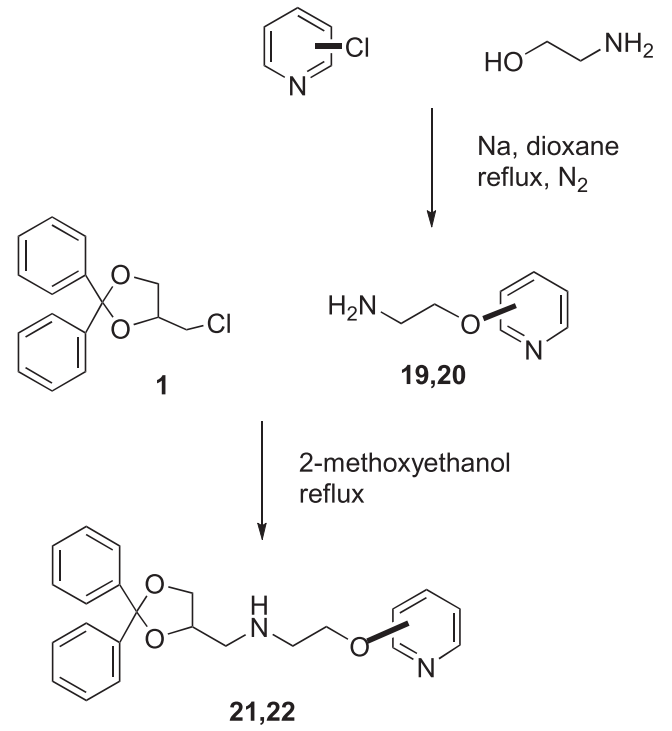
Chart 2. Aim of the work for the *o*-methoxyphenoxy ethylamine series.



1: X =Y=O; L=Cl
2: X=S; Y=O; L=OTs
3: X=Y=S; L=Cl
8: X=Y=O
9: X=S; Y=O
10: X=Y=S
11: X=Y=O
12: X=S; Y=O
13: X=Y=S
14: X=Y=O
15: X=S; Y=O
16: X=Y=S

a: 1-phenyl-piperazine,KI, 2-methoxyethanol, reflux, 35%
b: 1-(2-pyridyl)piperazine, KI, 2-methoxyethanol, reflux, 75%(8), 80% (9), 33% (10)
c: 1-(2-pyrimidyl)piperazine, KI, 2-methoxyethanol, reflux, 38%(11), 68% (12), 55% (13)
d: 1-(2-pyrazinyl)piperazine, KI, 2-methoxyethanol, reflux, 89%(14), 68% (15), 25% (16)

Scheme 1. Reaction conditions and yields.



Scheme 2. Reaction conditions.

motif. This variation was also combined with the replacement of the 1,3-dioxolane ring, with 1,3-oxathiolane and 1,3-dithiolane (Chart 1).

The same structural modifications were carried out for another series of 5-HT_{1A}R ligands, developed by the authors, where the o-methoxy-phenyl-piperazine was replaced with the *o*-methoxy-phenoxy-ethyl-amine moiety, as for compounds **17** and **18** [29]. For these compounds, the oxidation of a sulphur atom was also studied and nine new analogues were obtained (Chart 2).

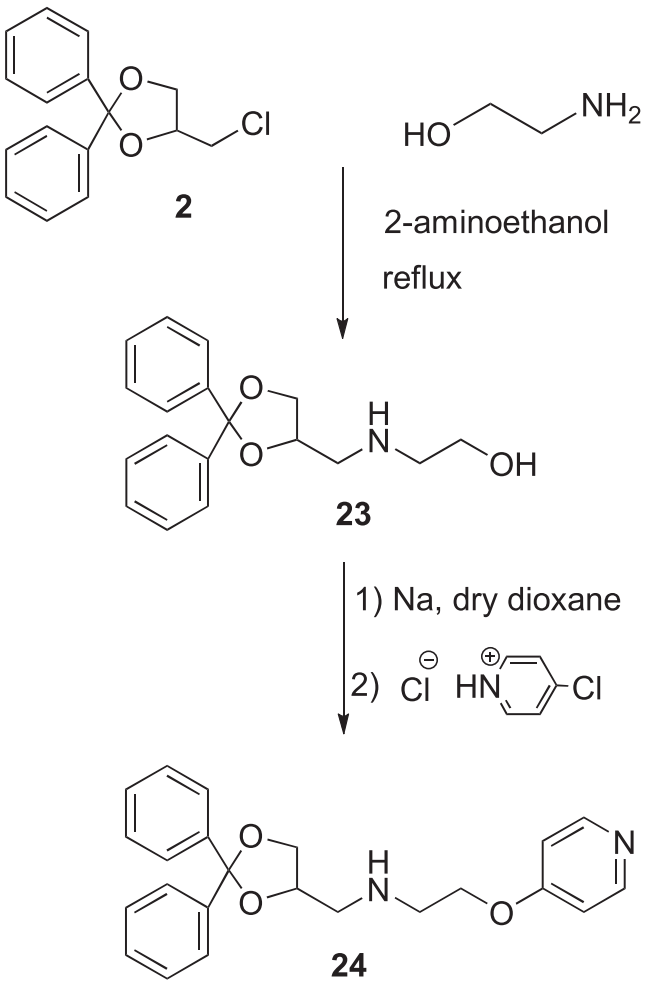
2. Results and discussion

2.1. Synthesis

The intermediates 1–3 and the final compounds 5–**7** [28], **17** and **18** [29], **26 and 28** [30] were obtained as previously reported. The synthesis of compounds **4**, **8**–**16**, **21**, **22**, **24, 25**, **27**, **29**–**32** was carried out as depicted in Schemes 1-4. The N-alkylation of the commercially available 1-phenyl-piperazine, 1-(2-pyridyl)-piperazine, 1-(2-pyrimidyl)-piperazine, 1-(2-pyrazinyl)-piperazine, 2-aminoethanol or of the synthesized 2-(pyridin-2/3-yloxy)/2-(phenoxy)ethanamines was performed by the proper chloro- or tosyl-derivative **1**–**3**. The 2-(phenoxy)ethanamines [29], 1,3-dioxolane **1** [29], oxathiolane **2** and dithiolane **3** [31] were prepared as previously reported.

2.2. Pharmacology

The pharmacological profile of the compounds under study and BMY-3748, as a reference compound, were evaluated using radioligand binding assays with [^{3}H]prazosin to label cloned human α_1-ARs expressed in CHO cells [32], and [^{3}H]8-OH-DPAT to label cloned human 5-HT_{1A}R expressed in HeLa cells [33]. The functional characterization of the most active compounds (**4**, **5**, **7**–**12**, **21**, **22**, **24**–**30**) at the 5-HT_{1A}R



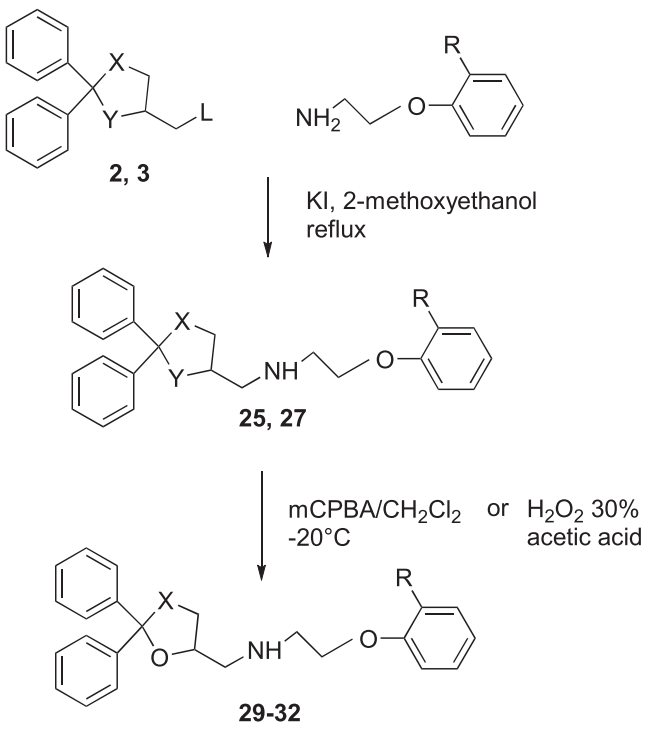
Scheme 3. Reaction conditions.

was performed according to the Stanton and Beer [34–37] method, using [^{35}S]GTPγS binding, in cell membranes from HeLa cells transfected with the human cloned 5-HT_{1A}R. Stimulation of [^{35}S]GTPγS binding was expressed as the percentage increase in binding above the basal value; the maximum stimulation observed with serotonin was established as 100%. The binding affinity and selectivities at cloned human α_1-AR and 5-HT_{1A}R and the functional studies at 5-HT_{1A}R are reported in Table 1. The functional antagonism at the α_{1A}AR subtypes was determined for all the compounds in the male rat isolated tissue, such as the Prostatic Portion of the Vas Deferens [38], Spleen [39] and Aorta [40]The results are reported in Table 2.

3. Structural-affinity and structural-activity relationships

3.1. Piperidine derivatives

In a previous work, we reported the compounds **5**–**7** that enabled us to study the effect on affinity, selectivity and potency at α_1-AR and 5-HT_{1A}R. In the present study, using a ligand-based approach, we expanded the SAR in order to verify the effect on activity of the replacement of the *o*-methoxy-phenyl group with nitrogen containing aromatics such as pyridine, pyrimidine and pyrazine. Compound **4** was also prepared, which enabled the comparison of the *o*-methoxy



25: X=O, Y=S, R=H, 72%
27: X=Y=S, R=H, 58%
29: X=SO, R=H, 39%
30: X=SO, R= OCH_3, 47%
31: X=SO_2, R=H, 9%
32: X=SO_2, R=OCH_3, 13%

Scheme 4. Reaction conditions and yields.

derivative with the unsubstituted one and therefore study the effect of the methoxy group in the ortho position.

A comparison of **4** and **5** clearly shows that the methoxy group strongly increases affinity and antagonist potency at the $\alpha_{1a/b/d}$ AR subtypes. At the 5-HT_{1A}R an increase is also observed, although to a lesser extent. The isosteric replacement of the ring oxygen atom with sulfur negatively affects affinity and the antagonist potency at the $\alpha_{1a/b/d}$ -AR subtypes, as already reported, while at 5-HT_{1A}R the affinity is increased. Comparing the agonist activity, it is evident that there is a strongly negative effect on potency (pD_2 8.18 vs 6.27) with an increase in efficacy (16% vs 41%).

Comparing the pyridine derivative **8** with the phenyl derivative **4,** the affinities at the α_1-AR subtypes are scarcely affected. This variation shows a negative trend, more pronounced for the α_{1B} -AR subtype. Similarly, for the antagonist potency, with the exception of the α_{1B}-AR subtype, an approximately 10-fold increase is observed (pk_b 6.49 vs 5.68). At the 5-HT_{1A}R, the affinity is increased (pKi = 7.82 vs 7.21). With respect to the methoxy derivative **5,** a large decrease in affinity and potency are observed at the three α_1-AR subtypes, while at 5-HT_{1A}R the affinity is similar and the agonist potency is decreased by 80–100-fold and efficacy is increased (72% vs 16%). It is worth noting that by replacing the 2-methoxy-phenyl moiety with a 2-pyridin one, an inversion of selectivity is obtained. While compound **5** is 100-fold more selective for the α_1-AR subtypes, compound **8** is more selective for 5-HT_{1A}R, although to a lesser extend, that is, about 4-fold. The insertion of a second nitrogen atom to give pyrimidine **11** and pyrazine **14** causes a further reduction in affinity and potency at both receptor systems, with compound **14** showing the largest reduction in affinity of about one order of magnitude (pKi = 7.22 vs < 6) at 5-HT_{1A}R. For these derivatives, the 1,3-oxathiolane (**12**, **15**) and 1,3-dithiolane (**13**, **16**) analogues were also prepared. In all cases, no significant variations were observed. This is contrary to what was observed with precursors **6** and **7,** for which a negative effect was seen at the α_1 -AR subtypes for both affinity and antagonist potency, while at 5-HT_{1A}R the affinity and efficacy were increased and the potency was decreased. It is worth noting that, in terms of selectivity, the 2-pyridil derivatives **9** and **10** and the 1,3-dithiolane **12** show the best selectivity index towards 5-HT_{1A}R of 14, 12 and 30, respectively.

3.2. *Aryloxyethylamine derivatives*

Similarly to the piperazine derivatives, within the phenoxyethylamine series the phenyl or *o*-methoxy-phenyl moiety of **17** and **18** were firstly replaced with a nitrogen-containing aromatic ring, such as pyridine ones. Compounds **17** and **18** had already been reported in a previous paper by the authors [29]. The two compounds proved to have excellent α_{1D}R functional selectivity (**17** pA_2 = 8.37; α_{1D}/α_{1A} 162; α_{1D}/α_{1B} 323), 15-fold selectivity and high affinity (pKi = 9.22) for 5-HT_{1A}R (**18**), where it behaves as a medium potency partial agonist (pD_2 = 7.36; E_{max} = 32%). As shown in Table 2, by replacing the phenyl- with pyridine ring (**21**), the functional selectivity at α_{1D} is lost. The affinities at the α_1R subtypes is decreased as well as at 5-HT_{1A}R (pKi = 7.80 vs 8.45). The decrease in 5-HT_{1A} agonist potency is more consistent (pD_2 = 7.27 vs 8.80), but is compensated by an increase in efficacy, which is more than doubled (E_{max} = 57% vs 24%). An additional drawback is the lack of 5-HT_{1A} /α_1-AR selectivity. By moving the nitrogen atom to position 3 (**22**), a significant decrease in antagonism potency at α_1-AR subtypes is observed, but which was not supported by binding studies, where the affinities are increased. Also at the 5-HT_{1A}R, the affinity is increased by a factor of 10 (pKi = 8.87 vs 7.80). Agonist potency (pD_2 = 7.61) and efficacy (E_{max} = 61%) are similar to those of compound **21**. The nitrogen atom in position 4 (**24**) is detrimental to all the parameters considered for both receptor systems.

Isosteric substitution O/S, to give 1,3-oxathiolane and 1,3-dithiolane derivatives and oxidation of the sulfur atom to give sulfoxide and sulfone were also studied. Compound **25** retained α_{1D} functional selectivity (α_{1D}/α_{1A} = 112; α_{1D}/α_{1B} = 19), although to a lesser extent compared with compound **17**. However, this large selectivity was not confirmed by binding studies where the affinity values for the three α_1R subtypes decreased. At the 5-HT_{1A}R, the affinity was maintained while the agonist potency decreased about 6-fold: the contrary was observed for the efficacy, where the Emax is 4-fold higher (92% vs 24%).

The substitution of the second oxygen atom with sulfur to give 1,3-dithiolane **27,** slightly decreases antagonist potency at α_1R subtypes with similar functional selectivity (α_{1D}/α_{1A} = 89; α_{1D}/α_{1B} = 13). In binding studies, affinities at the α_1-AR subtypes and affinity, agonist potency and efficacy at the 5-HT_{1A}R remain the same. Regardless of the small variation observed, the selectivity at the 5-HT_{1A}/α_1 increased up to 20-fold.

The *o*-methoxy-phenoxy derivatives **26** and **28** were reported in a previousl paper by the authors [30] and are included here for comparison with the desmethoxy derivatives **25** and **27,** and also to study the effect of sulfur oxidation, as in the case of the desmethoxy series.

Table 2
Functional studies at α_1-AR subtypes.

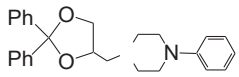
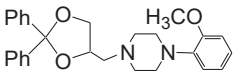
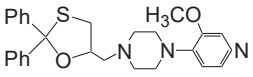
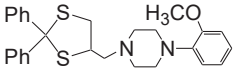
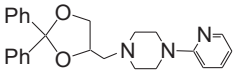
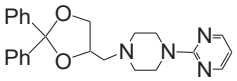
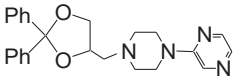
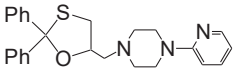
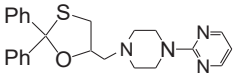
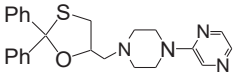
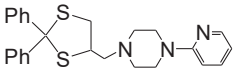
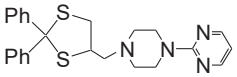
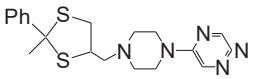
Compound	pK_b					
	α_{1A}	α_{1B}	α_{1D}	α_{1D}/α_{1A}	α_{1D}/α_{1B}	α_{1A}/α_{1B}
 **4**	6.06	5.68	6.97	8	20	2
 **5**	8.24	6.69	8.14	1	28	35
 **6**	7.35	6.21	7.33	1	13	14
 **7**	6.04	6.79	7.52	30	5	0.2
 **8**	6.14	6.49	6.14	1	1	1
 **11**	5.58	5.15	6.28	5	14	3
 **14**	5.30	5.89	6.56	18	5	0.3
 **9**	5.74	6.62	<5	<0.2	<0.02	0.1
 **12**	5.21	5.94	5.96	6	1	0.2
 **15**	5.54	5.12	6.40	7	19	3
 **10**	5.61	5.51	6.04	3	3	1
 **13**	5.62	5.68	6.29	5	4	1
 **16**	6.60	6.32	5.70	0.1	0.2	2

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Table 2 (*continued*)

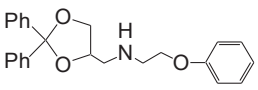
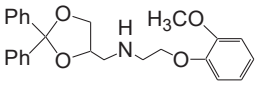
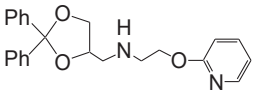
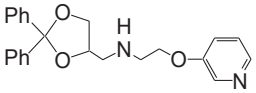
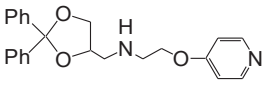
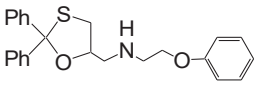
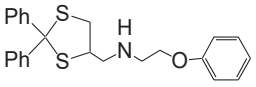
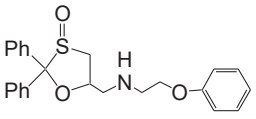
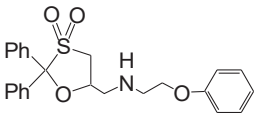
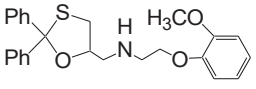
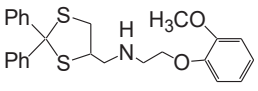
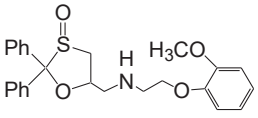
Compound	pK_b					
	α_{1A}	α_{1B}	α_{1D}	α_{1D}/α_{1A}	α_{1D}/α_{1B}	α_{1A}/α_{1B}
 **17**	6.16	5.86	8.37	162	323	2
 **18**	7.53	7.36	8.65	13	19	1
 **21**	6.26	6.96	6.95	5	1	0.2
 **22**	5.36	6.35	5.96	4	0.4	0.1
 **24**	5.25	6.16	5.84	4	0.5	0.1
 **25**	5.32	6.08	7.37	112	19	0.2
 **27**	5.10	5.92	7.05	89	13	0.2
 **29**	5.56	6.35	6.50	9	1	0.2
 **31**	<5	5.82	6.40	>25	4	>0.6
 **26**	6.71	8.44	8.68	93	2	0.02
 **28**	5.80	5.87	7.50	50	43	1
 **30**	6.23	6.43	6.43	2	1	0.6

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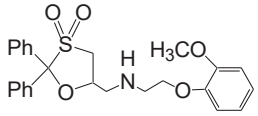
Table 2 (*continued*)

Compound	pK_b					
	α_{1A}	α_{1B}	α_{1D}	α_{1D}/α_{1A}	α_{1D}/α_{1B}	α_{1A}/α_{1B}
 **32**	5.49	5.97	6.28	6	2	0.3

α_{1A}: rat vas deferens, α_{1B}: rat spleen, α_{1D}: rat thoracic aorta.
The data are expressed as means of 2–3 separate experiments. Standard deviation is within ± 10% of the value.

The progressive substitution of O/S to give sulfoxide **29** and sulfone **30** has a similar negative effect seen for the same variations made on the desmethoxy derivative **25** to give **31** and **32**. This negative effect is more pronounced at the α_1-AR subtypes with sulfones **31** and **32**, the exception being sulfoxide **30** with a $pKi\alpha_{1D} = 8.14$ and a selectivity index $\alpha_{1D}/\alpha_{1A} = 62$ and $\alpha_{1D}/\alpha_{1B} = 35$. A similar decrease was observed at the 5-HT_{1A}R in terms of affinity and potency. Sulfoxide **29** appears to be the most interesting oxidation product maintaining a significant 5-HT_{1A} /α_1AR selectivity of about 15-fold.

3.3. Conclusion

The results presented in this work show that the replacement of the 1,3-dioxolane ring with a 1,3-oxathiolane or a 1,3-dithiolane moiety leads to an overall reduction in *in-vitro* affinity at the α_1-AR, while affinity, potency and efficacy were strongly enhanced at the 5-HT_{1A}R. Overall the nitrogen-containing aromatic groups scarcely affect the affinity at 5-HT_{1A}R, while reducing potency and increasing efficacy. The most striking result is the inversion of selectivity. In fact, while the lead **5** is 100-fold more selective for the α_1-AR, the new derivatives, although to differing degrees, are selective for the 5-HT_{1A}R. The oxidation of the sulphur atom in the 1,3-oxathiolane to give sulfoxides and sulfone has a negative effect on affinity and potency in both receptor systems. Regardless of the effect on the other parameters, selectivity toward the 5-HT_{1A}R with respect to the α_1-AR is often favoured.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rechem.2022.100425.

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