Bioorganic & Medicinal Chemistry 18 (2010) 6496–6511

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Design, synthesis, and pharmacological effects of structurally simple ligands for MT_1 and MT_2 melatonin receptors

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ARTICLE INFO

Article history:
Received 17 February 2010
Revised 22 June 2010
Accepted 29 June 2010
Available online 3 July 2010

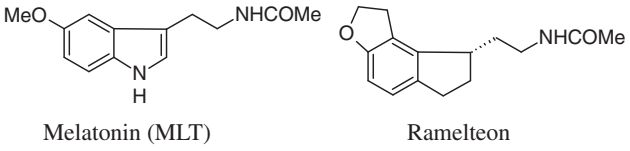
Keywords:
Melatonin
MT_1 and MT_2 receptors
Bioisosteres
Phenoxyalkyl amides

ABSTRACT

A series of phenoxyalkyl and phenylthioalkyl amides were prepared as melatoninergic ligands. Modulation of affinity of the newly synthesized compound by applying SARs around the terminal amide moiety, the alkyl chain, and the methoxy group on the aromatic ring provides compounds with nanomolar affinity for both melatonin receptor subtypes. Affinity towards MT_1 and MT_2 receptors were modulated also exploiting chirality. The investigation of intrinsic activity revealed that all the tested compounds behave as full or partial agonists.

1. Introduction

Melatonin (*N*-acetyl-5-methoxytryptamine, MLT, Fig. 1) is a neurohormone secreted primarily by the pineal gland, the highest levels occurring during the period of darkness.[1] It plays a major role in the regulation of circadian rhythms and the control of seasonal cycles.[2] Extensive studies have demonstrated that administration of MLT alleviates jet-lag and regulates delayed sleep phase syndrome.[3] Furthermore, exogenous MLT acts as sleep promoter, chronohypnotic and/or chronobiotic.[4,5] Neuroprotective,[6] free radical scavenging, antioxidant,[7–9] and immunomodulatory[10] properties of MLT have also been reported. Recently, MLT has been investigated for its potential use as anticancer,[11–13] antinflammatory,[14] antihypertensive,[15] radioprotector in radiotherapy,[16] and it has been even postulated the existence of a possible link between it and type 2 diabetes.[17] The obvious impact of MLT is actually underlined by more than 14,000 articles. Many of its physiological actions are mediated through G-protein coupled receptors[18] expressed in a wide variety of tissues. Cloning studies have revealed at least three MLT receptor subtypes, two of which have been found in mammals, MT_1 (Mel_{1a}) and MT_2 (Mel_{1b}),[19] localized in the central nervous system and in peripheral tissues.[20,21] Recently, another MLT binding site (MT_3) has been described in hamster as homologue of the cytoplasmic quinone reductase 2.[22] The way in which MLT binds at these receptors and the possible therapeutic potential of MLT in a wide variety of clinical conditions has led to a rising interest in the development of compounds capable of mimicking the effects of MLT, also considering that the use of MLT as a drug is limited by its short biological half-life, poor oral bioavailability, and ubiquitous action.[23]



Melatonin (MLT) Ramelteon

Figure 1. Chemical structures of MLT and Ramelteon.

Thus, during the past decade, a great number of structurally different MLT receptor ligands, which range from simple indole derivatives and their bioisosteres to phenylalkyl amides and constrained melatoninergic agents, have been reported in the literature.[24] It is noteworthy that nearly all these compounds present an amido group and an alkoxyaryl moiety that seem to be critical in determining the binding affinity and biological activity of these melatoninergic ligands.[25] Some MT_1/MT_2 agonists are currently under clinical evaluation or have been approved for their hypnotic properties; ramelteon (Fig. 1) is at the present the only non selective MLT receptors agonist marketed in the US for the treatment

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doi:10.1016/j.bmc.2010.06.100

of insomnia.[26,27] Other MT_1/MT_2 agonists, such as LY-156735[28] or tasimelteon (VEC-162),[29] are undergoing clinical trials for the treatment of sleep disorders. Agomelatine, an MT_1/MT_2 agonist and 5-HT_{2c} antagonist, is under evaluation for the treatment of unipolar depression.[30]

Several years ago, basing on results obtained on a series of phenylalkyl amides by Garratt et al.[31] we examined several substituted phenoxyalkyl amides by exploiting the well known isosteric relationship between the methylene group and the oxygen atom.[32] From structure–activity relationships (SARs) on these compounds, it appeared that the phenoxy moiety is a sufficient core to provide compounds with significant potency as MLT agonists. In this paper, we report the synthesis, the binding data, and activity results for human MT_1 and MT_2 receptors of *N*-(phenoxyalkyl)amides and their thioisologues, novel non-indolic MLT-like compounds, that could be considered simplified models of MLT (Fig. 2). Starting from *N*-(2-phenoxyethyl)acetamide as a scaffold we investigated in detail: (i) the role and the optimal position of the methoxy group on the aromatic moiety in structures that do not show the indole nucleus; (ii) the effect of isosteric substitution of the side chain; (iii) the effect of formal introduction of a methyl group on the alkyl chain; and (iv) the effect of a slight modulation of the acyl group. Starting from the observation that both indole[33,34] and non-indole[35,36] chiral MT_1 and MT_2 ligands can show stereoselectivity in terms of affinity and efficacy, we speculated that affinity towards MLT receptors might be modulated exploiting chirality; thus, we decided to synthesize and test our chiral compounds in their optically active form.

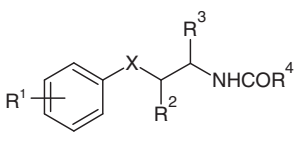
2. Results and discussion

2.1. Chemistry

Compound **20**[37] in its racemic and enantiomeric forms and (*R*)- and (*S*)-**23c**[38] were prepared as previously described.[37,38] Racemic propylacetamides **7a**,**b** were prepared via the synthetic route shown in Scheme 1. Alkylation of the suitable phenol (**1a**,**b**) with racemic ethyl 2-bromopropanoate **2** gave **3a**,**b** which were hydrolyzed and then converted into the corresponding amides (**5a**,**b**). Reduction of the amides and successive N-acetylation with acetic anhydride afforded the target compounds.

Ethylacetamides (**12a**–**h**) were prepared either by condensation of the phthalimido alcohol **8** with the appropriate phenol (**1a**–**d**) under Mitsunobu conditions[39] or by a Williamson reaction of *N*-(2-bromoethyl)phthalimide (**9**) with the suitable thiophenol (**1e**–**h**), followed by hydrazinolysis[40] of the corresponding phthalimido derivatives (**10a**–**h**) and N-acylation of amines **11a**–**h** with acetic anhydride (Scheme 2).

Racemic propyl *N*-alkanamides (**7c**–**e**, **15d**–**e**, and **16d**–**e**) were prepared according to Scheme 3. Alkylation of the suitable phenol or thiophenol (**1c**–**e**) with racemic **2** gave the esters (**3c**–**e**) which were submitted to reduction. The alcohols obtained (**13c**–**e**) were condensed with phthalimide following a typical Mitsunobu procedure. Hydrazinolysis run on the resulting phthalimido derivatives (**14c**–**e**) gave the corresponding amines **6c**–**e**. N-Acylation of the crude amines with acetic or *n*-butyric anhydride or with cyclopropanecarbonyl chloride provides the desired MLT ligands.



X = O, S
R^1 = H, OMe
R^2, R^3 = H, Me
R^4 = Me, c-Pr, *n*-Pr

Figure 2. General structures of the newly synthesized compounds.

Optically active propyl *N*-alkanamides (**7d**,**e**, **15d**,**e**, and **16d**,**e**) were prepared according to the same route followed for the synthesis of racemic propyl *N*-alkanamides except for the first step where the alcohols **13d**,**e** were obtained by condensation of the appropriate phenol or thiophenol (**1d**,**e**) with enantiomerically pure methyl 2-hydroxypropanoates [(*R*)- and (*S*)-**17**] under Mitsunobu conditions (Scheme 4).

1-Methylethylacetamides (**23c**,**d**) in their racemic and optically active forms were prepared according to the synthetic route reported in Scheme 5, which involved the Mitsunobu reaction of 2-aminopropanols (**19**), efficiently protected with phthalic anhydride, with the appropriate phenol (**1c**,**d**). Hydrazinolysis of the resultant phthalimido derivatives (**21c**,**d**) and N-acylation of the obtained amines (**22c**,**d**) with acetic anhydride gave the desired acetamides.

Phenylthio methylethylacetamides (**23e**,**f**), in their racemic and optically active forms, were prepared as reported in Scheme 6, by modifying a one-pot literature procedure,[41] which involved the reaction of the appropriate thiol (**1e**,**f**) with 2-aminopropanol and acetic acid.

Enantiomeric excess (ee) values for all the homochiral compounds were determined either by chiral HPLC or GC analyses.

2.2. Structure–affinity and structure–intrinsic activity relationships

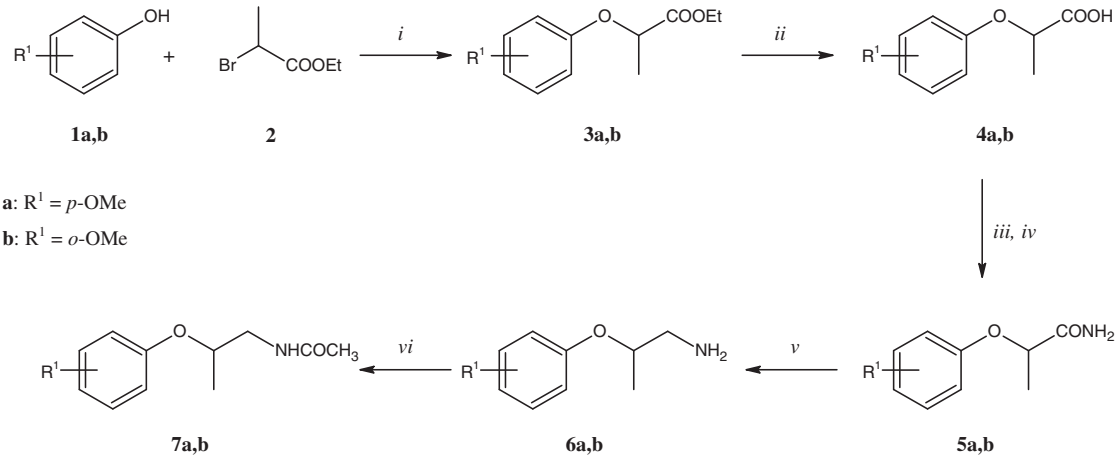
The binding affinities of *N*-(phenoxyalkyl)amides and *N*-(phenylthioalkyl)amides for human MT_1 and MT_2 receptors measured by competition binding analysis using the radioligand 2-[^{125}I]-iodomelatonin are shown in Table 1.

Comparison of phenoxyethyl acetamides **12a**–**d** reveals clearly that the isomer with the methoxy group in the *meta*-position of the aromatic moiety (**12d**) has the highest binding affinity; these results agree with the data obtained by Garratt et al.[31] in the corresponding series of phenylpropyl acetamides, which demonstrated the superiority of compounds with methoxy groups in the *meta*-position over their isomers. It is noteworthy that the unsubstituted phenoxy derivative **12c** shows a slightly higher affinity than the corresponding *ortho*- and *para*-methoxy derivatives **12a**,**b**. Furthermore, **12d** behaves as full agonist, whereas compounds **12a**–**c** are partial agonists.

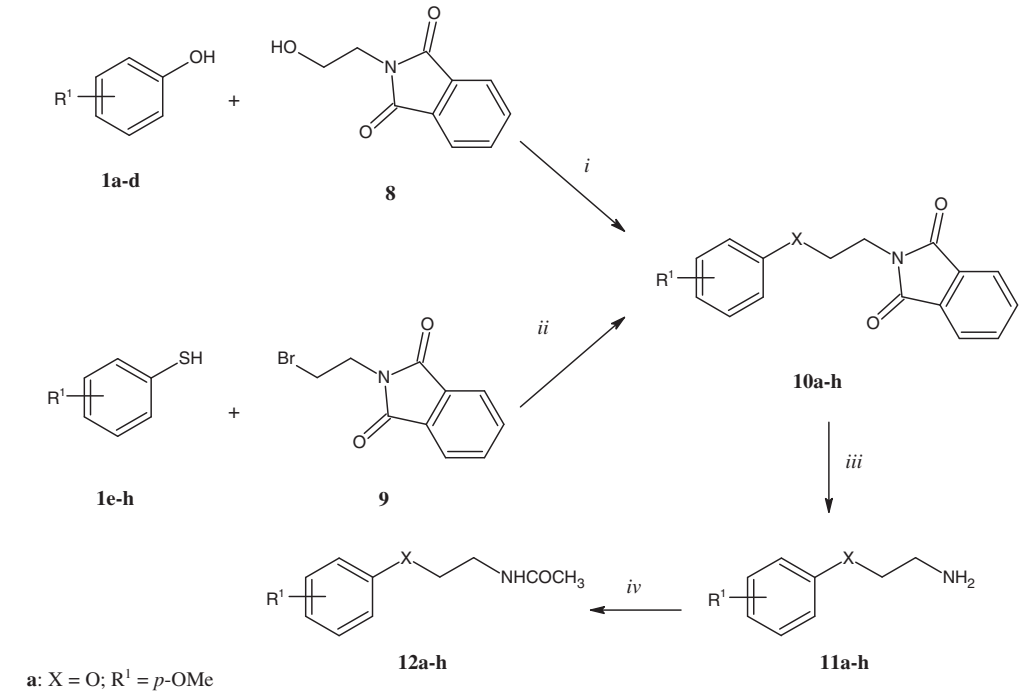
Results for compounds **7a**–**d**, in which a methyl group has been formally introduced into the position adjacent to the oxygen atom of the alkyl chain, reveal an interesting increase of binding affinity at both receptor subtypes for all derivatives of this series when compared to the related compounds **12a**–**d**. Also in this case, the highest binding affinity occurs for the *meta*-methoxy derivative **7d**, followed by the unsubstituted derivative **7c**.

On the other hand, the formal introduction of a methyl group into the position adjacent to the nitrogen atom, as in **23c**,**d**, leads to a decrease in MT_1 and MT_2 binding affinity (**23d** vs **12d**) or has no effect (**23c** vs **12c**). In order to optimize the biological profile of the highest-affinity ligand **7d**, we modulated the acyl chain by replacing the methyl group with substituents that are often present in other MLT ligands, such as cyclopropyl or *n*-propyl, obtaining **15d** and **16d**, respectively. The replacement of the methyl group in **7d** with a cyclopropyl gave the most interesting compound of the series, **15d**, which showed an excellent binding affinity for MT_1 receptors ($pK_i = 9.03$) close to that of MLT ($pK_i = 9.48$) with a MT_2/MT_1 selectivity ratio of 13. On the other hand, MT_1 and MT_2 binding affinities were substantially unaffected by substitution of the methyl group with a *n*-propyl as in **16d**. The most potent compounds (**7d**, **15d**, and **16d**) act as full agonists.

In order to probe the lipophilic and electronic requirements of the receptors binding pocket accommodating the aromatic moiety, we replaced the oxygen atom of the alkyl chain by a sulphur.



Scheme 1. Reagents and conditions: (i) Na, EtOH, 70 °C; (ii) KOH, EtOH/H_2O, reflux; (iii) $SOCl_2$, Py, THF, rt; (iv) conc NH_4OH, reflux then rt; (v) $LiAlH_4$, THF, reflux then rt; (vi) Ac_2O, Et_3N, THF, 0 °C.

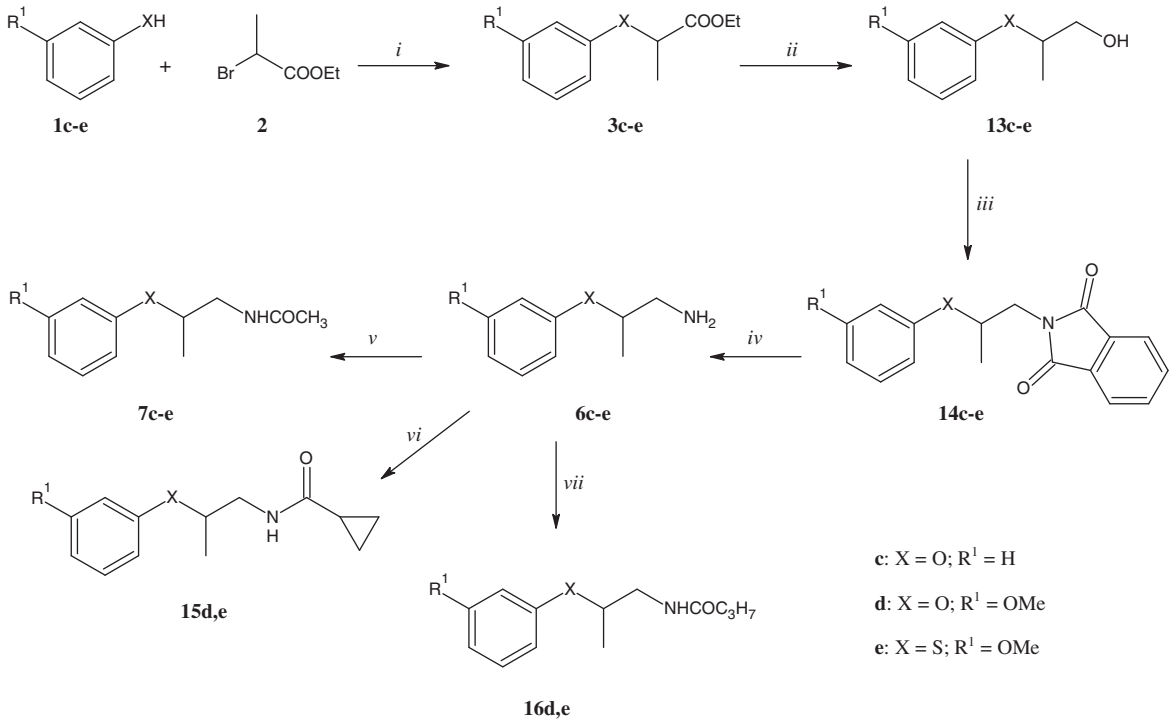


a: X = O; R^1 = *p*-OMe
b: X = O; R^1 = *o*-OMe
c: X = O; R^1 = H
d: X = O; R^1 = *m*-OMe
e: X = S; R^1 = *m*-OMe
f: X = S; R^1 = H
g: X = S; R^1 = *p*-OMe
h: X = S; R^1 = *o*-OMe

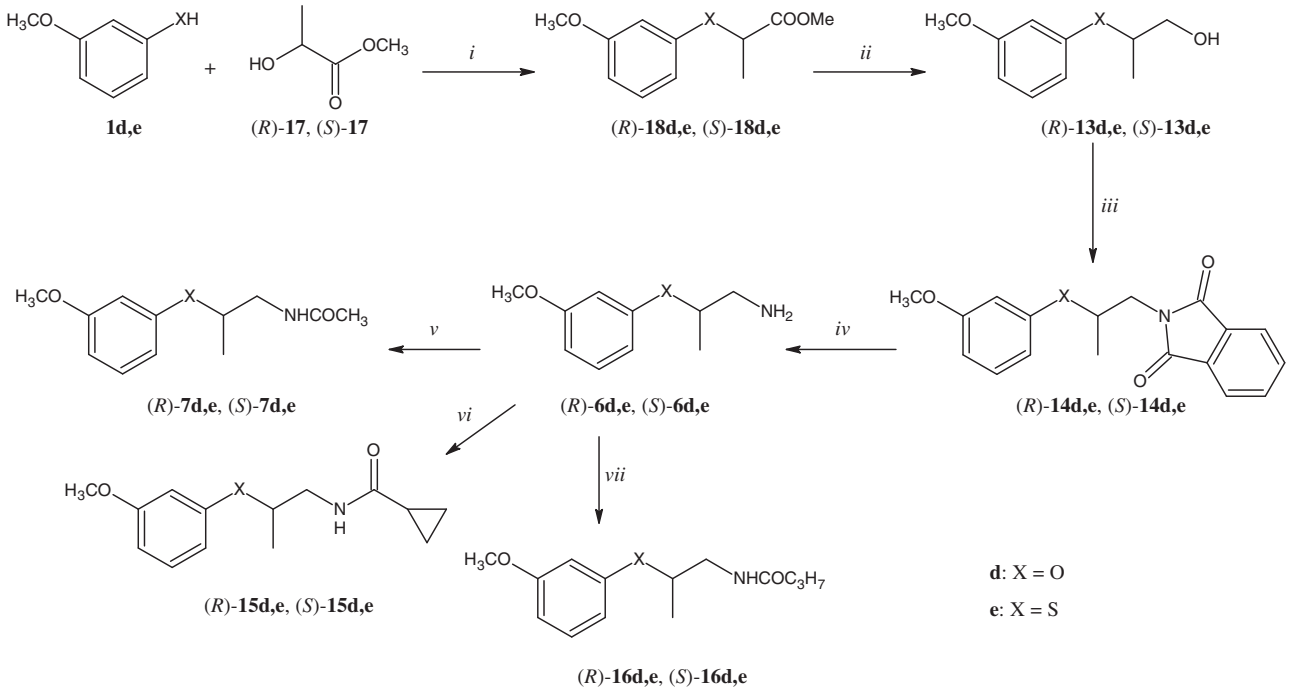
Scheme 2. Reagents and conditions: (i) DEAD, PPh_3, THF, rt; (ii) K_2CO_3, DMF, reflux; (iii) aq N_2H_4, AcOH, MeOH, reflux; (iv) Ac_2O, Et_3N, THF, 0 °C.

Despite a slight increase or no significant difference in affinity showed by phenylthioethyl acetamides **12e–h** with respect to the corresponding phenoxyethyl acetamides **12a–d**, the same modifications to the alkyl chain as were carried out for the phenoxyethyl derivatives generally reduces the affinity for both MT_1 and MT_2 receptors (see **7e**, **15e**, **16e**, and **23e** vs **7d**, **15d**, **16d**, and **23d**, respectively). Functional analysis on MT_1 and MT_2 receptors of the most potent sulphurated isologues (**12e** and **16e**) showed them to be full agonists except for compound **15e** which behaves as partial agonist.

Furthermore, in order to investigate the stereochemical requirements for the binding site, the enantiomers of the chiral compounds were prepared in their highly optically enriched enantiomeric forms and examined for their binding affinity. As expected, a significant difference between the enantiomers was observed; in particular, among the most potent compounds, the



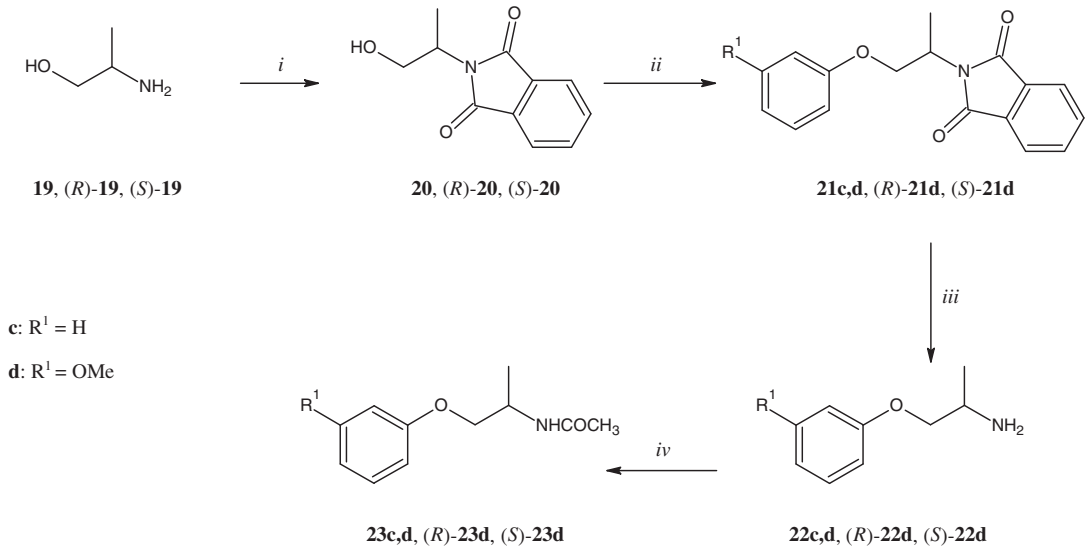
Scheme 3. Reagents and conditions: (i) Na, EtOH, 70 °C; (ii) $LiAlH_4$, THF, reflux then rt; (iii) phthalimide, DEAD, PPh_3, THF, rt; (iv) aq N_2H_4, AcOH, MeOH, reflux; (v) Ac_2O, Et_3N, THF, 0 °C; (vi) cyclopropanecarbonyl chloride, Et_3N, toluene, reflux; (vii) butyric anhydride, Et_3N, THF, reflux.



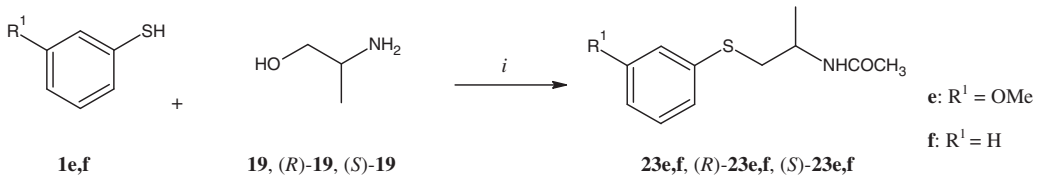
Scheme 4. Reagents and conditions: (i) DEAD, PPh_3, THF, rt; (ii) $LiAlH_4$, THF, reflux; (iii) phthalimide, DEAD, PPh_3, THF, rt; (iv) aq N_2H_4, AcOH, MeOH, reflux; (v) Ac_2O, Et_3N, THF, 0 °C; (vi) cyclopropanecarbonyl chloride, Et_3N, toluene, reflux; (vii) butyric anhydride, Et_3N, THF, reflux.

S-enantiomers behave as eutomers. The highest stereoselectivity was observed for the thioderivative **7e**, being K_i distomer/K_i eutomer ratio of 460 and 94 for MT_1 and MT_2 receptors, respectively. It is noteworthy that the most potent compound of the series (*S*)-**15d** shows a certain degree of selectivity in favour of MT_1 with a MT_2/MT_1 selectivity ratio of 6. As regards the intrinsic activity, all the most potent homochiral compounds behave as agonists, with the exception of compounds **15e** and **16e** for which the eutomers (*S*-enantiomers) are full agonists, whereas the distomers are partial agonists.

In summary, a novel series of *N*-(phenoxyalkyl)amides and their thioisologues were prepared in order to investigate structure–affinity and structure–intrinsic activity relationships for MT_1 and MT_2 receptors. Within this series, the effect of bioisosteric



Scheme 5. Reagents and conditions: (i) phthalic anhydride, Et_3N, toluene, reflux; (ii) phenol (**1c** or **1d**), DIAD, PPh_3, THF, rt; (iii) aq N_2H_4, AcOH, MeOH, reflux; (iv) Ac_2O, Et_3N, THF, 0 °C.



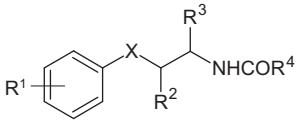
Scheme 6. Reagents and conditions: (i) AcOH, HCl, Zn, benzene, reflux.

substitution of the indole nucleus, the role of the methoxy group and changes in the *N*-acyl side chain were considered. Furthermore, in order to gain more insight into the receptor stereochemistry, we have examined the affinities of the single enantiomers of the chiral compounds. Our experience establishes the substituted phenoxy and phenylthio moieties as novel bioisosteres for the indole nucleus of the endogenous ligand and its close analogues. The data highlight that derivatives with a methoxy group (**12d** vs **12a–c**, **12e** vs **12f–h**, and **7d** vs **7a–c**) placed in a position that can be easily superposed to position 5 of the indole ring of MLT usually have the highest binding affinity, a behaviour consistent with what was observed for other series of MLT receptor ligands.[31,42] Shift of the methoxy group from the *meta*- to the *para*- or *ortho*-positions, in fact, greatly reduces binding affinity and intrinsic activity at both receptor subtypes; the pK_i values obtained for these compounds are even lower than those of the unsubstituted analogues. These data are in agreement with the results obtained on MLT derivatives in which the shift of the methoxy group from position 5 to position 6 led to a drastic reduction in binding affinity and to partial agonist behaviour.[43] Reduction of binding affinity and intrinsic activity because of the shifting of the methoxy group has also been observed in other series of MLT receptor ligands.[44] The effect of acyl chain modulation has been evaluated on the basis of compounds **15d**,**e** and **16d**,**e**. The *N*-propyl substituent is tolerated at both receptor subtypes. Interestingly, pursuing a similar substitution pattern with the cyclopropyl derivatives **15d** resulted in the achievement of subnanomolar MT_1 affinity. The positive effect of cyclopropyl group had already been observed for other MLT ligands.[45] Our experience evidenced a stereoselective behaviour of the most potent compounds both in phenoxyalkyl and phenylthioalkyl series; in all cases the *S*-enantiomers were found to be more potent agonists than the *R*-ones. In general, replacement of the ether function with a thioether one slightly influences receptor binding affinity, but provides compound **7e** which shows the highest stereodifferentiation especially for MT_1 subtype. A reasonable interpretation of this result could be related to the different lipophilic and electronic properties of oxygen and sulphur atoms.

3. Conclusions

SARs have been defined around the terminal amide moiety, the alkyl chain, and the methoxy group on the aromatic ring of a new series of phenoxyalkyl and phenylthioalkyl amides as novel melatoninergic ligands. A methoxy group in the *meta*-position is crucial for receptor binding affinity. Intrinsic activity and affinity towards MT_1 and MT_2 receptors can be modulated by replacing the methyl group of the acyl function with a propyl one. On the other hand, receptor binding affinity strongly depends on the presence and the location of a methyl group on the alkyl chain. Affinity towards MT_1 and MT_2 receptors can be modulated also exploiting chirality. These chemical modifications have afforded potent nanomolar compounds for both receptor subtypes. The highest level of stereoselectivity was found in the series of the thioisologues for compound **7e** (K_i distomer/K_i eutomer ratio: 457 for MT_1 subtype). Of particular interest, compound (*S*)-**15d** shows a binding affinity for the MT_1 receptors ($pK_i = 9.14$) close to that of MLT ($pK_i = 9.48$). These findings establish the *meta*-methoxyphenoxy or *meta*-methoxyphenylthio ring as a novel bioisostere for the alkoxyaryl moiety of the endogenous ligand. The synthetic procedures used are facile and versatile and allow insertion on the alkyl chain of groups of different size and shape and, in general, modification of the scaffold according to classical medicinal chemistry procedures, thus envisaging further development of the present study.

Table 1
Experimental binding affinity and relative intrinsic activity (IA_r) of newly synthesized compounds for human MT_1 and MT_2 melatonin receptors stably expressed in NIH3T3 cells



Compd	X	R^1	R^2	R^3	R^4	MT_1		MT_2	
						pK_i[a]	$IA_r \pm SEM$[b]	pK_i[a]	$IA_r \pm SEM$[b]
MLT						9.48 ± 0.06	1.00 ± 0.18	9.21 ± 0.09	1.00 ± 0.07
7a	O	*p*-OMe	Me	H	Me	4.37 ± 0.27	0.15 ± 0.01	4.90 ± 0.10	0.13 ± 0.01
7b	O	*o*-OMe	Me	H	Me	4.98 ± 0.04	0.19 ± 0.01	5.29 ± 0.17	0.45 ± 0.02
7c	O	H	Me	H	Me	5.86 ± 0.14	0.48 ± 0.02	5.94 ± 0.06	0.69 ± 0.03
7d	O	*m*-OMe	Me	H	Me	8.44 ± 0.41	1.01 ± 0.03	8.02 ± 0.71	1.01 ± 0.07
(*R*)-**7d**	O	*m*-OMe	Me	H	Me	7.31 ± 0.37	0.79 ± 0.04	6.96 ± 0.38	0.93 ± 0.20
(*S*)-**7d**	O	*m*-OMe	Me	H	Me	8.77 ± 0.43	1.01 ± 0.06	8.33 ± 0.49	1.09 ± 0.07
7e	S	*m*-OMe	Me	H	Me	6.96 ± 0.05	nd[c]	6.58 ± 0.22	nd[c]
(*R*)-**7e**	S	*m*-OMe	Me	H	Me	5.56 ± 0.23	nd[c]	6.18 ± 0.09	nd[c]
(*S*)-**7e**	S	*m*-OMe	Me	H	Me	8.24 ± 0.08	nd[c]	8.15 ± 0.13	nd[c]
12a	O	*p*-OMe	H	H	Me	4.21 ± 0.18	0.26 ± 0.02	4.34 ± 0.13	0.44 ± 0.03
12b	O	*o*-OMe	H	H	Me	4.43 ± 0.32	0.23 ± 0.01	5.18 ± 0.15	0.22 ± 0.01
12c	O	H	H	H	Me	4.94 ± 0.07	0.31 ± 0.03	5.26 ± 0.18	0.50 ± 0.03
12d	O	*m*-OMe	H	H	Me	7.39 ± 0.22	0.81 ± 0.06	7.17 ± 0.01	0.80 ± 0.05
12e	S	*m*-OMe	H	H	Me	7.26 ± 0.16	0.85 ± 0.03	7.40 ± 0.17	0.81 ± 0.04
12f	S	H	H	H	Me	5.42 ± 0.30	0.22 ± 0.02	6.47 ± 0.23	0.50 ± 0.05
12g	S	*p*-OMe	H	H	Me	5.55 ± 0.46	0.48 ± 0.02	5.62 ± 0.38	0.56 ± 0.02
12h	S	*o*-OMe	H	H	Me	5.44 ± 0.38	0.27 ± 0.01	6.30 ± 0.25	0.56 ± 0.03
15d	O	*m*-OMe	Me	H	*c*-Pr	9.03 ± 0.01	0.91 ± 0.04	7.89 ± 0.49	1.02 ± 0.02
(*R*)-**15d**	O	*m*-OMe	Me	H	*c*-Pr	8.11 ± 0.16	0.90 ± 0.03	7.68 ± 0.18	0.77 ± 0.01
(*S*)-**15d**	O	*m*-OMe	Me	H	*c*-Pr	9.14 ± 0.05	1.01 ± 0.06	8.36 ± 0.15	1.26 ± 0.06
15e	S	*m*-OMe	Me	H	*c*-Pr	8.07 ± 0.02	0.77 ± 0.01	8.01 ± 0.23	0.63 ± 0.09
(*R*)-**15e**	S	*m*-OMe	Me	H	*c*-Pr	6.92 ± 0.02	0.49 ± 0.09	7.31 ± 0.01	0.59 ± 0.05
(*S*)-**15e**	S	*m*-OMe	Me	H	*c*-Pr	8.27 ± 0.02	0.80 ± 0.05	8.17 ± 0.01	0.80 ± 0.05
16d	O	*m*-OMe	Me	H	*n*-Pr	8.38 ± 0.01	1.04 ± 0.03	8.43 ± 0.01	1.12 ± 0.12
(*R*)-**16d**	O	*m*-OMe	Me	H	*n*-Pr	7.09 ± 0.03	1.06 ± 0.13	7.17 ± 0.06	0.86 ± 0.06
(*S*)-**16d**	O	*m*-OMe	Me	H	*n*-Pr	8.51 ± 0.07	1.01 ± 0.05	8.56 ± 0.12	1.07 ± 0.18
16e	S	*m*-OMe	Me	H	*n*-Pr	8.04 ± 0.01	1.02 ± 0.08	8.30 ± 0.05	0.99 ± 0.03
(*R*)-**16e**	S	*m*-OMe	Me	H	*n*-Pr	7.15 ± 0.03	0.59 ± 0.05	7.58 ± 0.08	0.64 ± 0.07
(*S*)-**16e**	S	*m*-OMe	Me	H	*n*-Pr	8.41 ± 0.06	0.99 ± 0.07	8.22 ± 0.12	0.96 ± 0.10
23c	O	H	H	Me	Me	4.92 ± 0.17	0.04 ± 0.01	5.42 ± 0.19	0.15 ± 0.01
(*R*)-**23c**	O	H	H	Me	Me	4.20 ± 0.18	0.17 ± 0.02	4.27 ± 0.13	0.11 ± 0.01
(*S*)-**23c**	O	H	H	Me	Me	4.68 ± 0.31	0.05 ± 0.01	5.34 ± 0.14	0.26 ± 0.03
23d	O	*m*-OMe	H	Me	Me	6.45 ± 0.20	0.63 ± 0.03	6.46 ± 0.08	0.71 ± 0.05
(*R*)-**23d**	O	*m*-OMe	H	Me	Me	4.44 ± 0.26	0.35 ± 0.02	5.31 ± 0.14	0.43 ± 0.02
(*S*)-**23d**	O	*m*-OMe	H	Me	Me	6.46 ± 0.22	0.75 ± 0.05	6.52 ± 0.21	0.80 ± 0.06
23e	S	*m*-OMe	H	Me	Me	4.92 ± 0.10	nd[c]	5.88 ± 0.13	nd[c]
(*R*)-**23e**	S	*m*-OMe	H	Me	Me	4.94 ± 0.07	0.29 ± 0.01	4.91 ± 0.12	0.32 ± 0.02
(*S*)-**23e**	S	*m*-OMe	H	Me	Me	6.32 ± 0.12	0.30 ± 0.02	6.58 ± 0.16	0.50 ± 0.02
23f	S	H	H	Me	Me	4.50 ± 0.46	0	5.17 ± 0.13	0.20 ± 0.03
(*R*)-**23f**	S	H	H	Me	Me	4.13 ± 0.13	−0.05 ± 0.01	4.19 ± 0.11	−0.04 ± 0.01
(*S*)-**23f**	S	H	H	Me	Me	5.43 ± 0.24	−0.07 ± 0.01	5.36 ± 0.25	0.25 ± 0.03

[a] pK_i values were calculated from IC_{50} values obtained from competition curves by the method of Cheng and Prusoff,[52] and are the mean of at least three determinations performed in duplicate.
[b] The relative intrinsic activity values were obtained dividing the maximum analogue-induced G-protein activation by that of MLT.
[c] nd: not determined.

4. Experimental

4.1. Chemistry

General experimental methods. All chemicals, including chiral starting materials of known absolute stereochemistry, were purchased from Sigma-Aldrich or Lancaster. Yields refer to purified products and were not optimized. The structures of the compounds were confirmed by routine spectrometric analyses. Only spectra for compounds not previously described are given. Melting points were determined on a Gallenkamp melting point apparatus in open glass capillary tubes and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer (Norwalk, CT) Spectrum One FT spectrophotometer and band positions are given in reciprocal centimeters (cm^{-1}). ^1H NMR and ^{13}C NMR spectra were recorded on a Varian VX Mercury spectrometer operating at 300 and 75 MHz for ^1H and ^{13}C, respectively, using $CDCl_3$ as solvent. Chemical shifts are reported in parts per million (ppm) relative to solvent resonance: $CDCl_3$, δ 7.26 (^1H NMR) and δ 77.3 (^{13}C NMR). *J* values are given in Hertz. EIMS spectra were recorded on a Hewlett–Packard 6890–5973 MSD gas chromatograph/mass spectrometer at low resolution. Elemental analyses were performed with a Eurovector Euro EA 3000 analyzer. Optical rotations were measured on a Perkin-Elmer (Norwalk, CT) model 341 spectropolarimeter; concentrations are expressed in g/100 mL, and the cell length was 1 dm, thus $[\alpha]_D^{20}$ values are given in units of 10^{-1} deg cm^2 g^{-1}. HPLC analyses were performed with an Agilent chromatograph (model 1100) equipped with a diode array detector. Ee values were determined either by direct HPLC analysis on a Daicel Chiralpak IA column, or by GC analysis with Varian GC-3800 gas-chromatograph on CP-Chirasil DEX CB (25 × 0.25 mm, 0.25 μM thickness). Chromatographic separations were performed on silica gel columns by flash

chromatography (Kieselgel 60, 0.040–0.063 mm, Merck, Darmstadt, Germany) as described by Still et al.[46] TLC analyses were performed on precoated silica gel on aluminum sheets (Kieselgel 60 F_{254}, Merck).

4.2. General procedure for the preparation of esters 3a–e

The method adopted for the synthesis of ethyl 2-(4-methoxyphenoxy)propanoate (**3a**) is described. Sodium (0.93 g, 40.4 mmol) was added in small pieces to absolute EtOH (62 mL) and the mixture was heated at 70 °C. After completion of sodium dissolution, a solution of 4-methoxyphenol (**1a**) (5.0 g, 40.4 mmol) in absolute EtOH (20 mL) was added dropwise. After 30 min, a solution of ethyl 2-bromopropanoate (**2**) (7.3 g, 40.4 mmol) in absolute EtOH (32 mL) was added dropwise and the mixture was heated at reflux for 5 h. The solid residue was filtered off, the solvent was evaporated in vacuo and the residue was taken up with Et_2O, washed with 2 N NaOH and dried (Na_2SO_4). Removal of the solvent under vacuo gave 5.70 g (63%) of **3a** as a slightly yellowish oil. Spectroscopic data were in agreement with those reported in the literature for the (+)-isomer.[47]

4.2.1. Ethyl 2-(2-methoxyphenoxy)propanoate (3b)

Prepared as reported above for (**3a**) starting from **1b**. Yield: 81%; slightly yellowish oil. Spectroscopic data were in agreement with those reported in the literature for the (+)-isomer.[47]

4.2.2. Ethyl 2-phenoxypropanoate (3c)

Prepared as reported above for **3a** starting from **1c**. Yield: 52%; slightly yellowish oil; IR (neat): 1753 (C=O) cm^{-1}; ^1H NMR δ 1.25 (t, 3H, J = 7.1 Hz, CH_3CH$_2$), 1.62 (d, 3H, J = 6.9 Hz, CH_3CH), 4.22 (q, 2H, J = 7.1 Hz, CH_2), 4.74 (q, 1H, J = 6.9 Hz, CH), 6.83–6.92 (m, 2H, Ar), 6.92–7.02 (m, 1H, Ar), 7.22–7.32 (m, 2H, Ar); ^{13}C NMR δ 14.3 (1C), 18.8 (1C), 61.5 (1C), 72.9 (1C), 115.3 (2C), 121.8 (1C), 129.7 (2C), 157.8 (1C), 172.5 (1C); MS (70 eV) m/z (%) 194 (M^+, 42), 121 (100).

4.2.3. Ethyl 2-(3-methoxyphenoxy)propanoate (3d)

Prepared as reported above for **3a** starting from **1d**. Yield: 69%; slightly yellowish oil; IR (neat): 1754 (C=O) cm^{-1}; ^1H NMR δ 1.25 (t, 3H, J = 7.0 Hz, CH_3CH$_2$), 1.60 (d, 3H, J = 6.9, CH_3CH), 3.77 (s, 3H, CH_3O), 4.21 (q, 2H, J = 7.1 Hz, CH_2), 4.73 (q, 1H, J = 6.8 Hz, CH), 6.40–6.55 (m, 3H, Ar), 7.15 (apparent t, 1H, Ar); ^{13}C NMR δ 14.4 (1C), 18.8 (1C), 55.5 (1C), 61.5 (1C), 72.8 (1C), 101.9 (1C), 107.0 (1C), 107.6 (1C), 130.2 (1C), 159.0 (1C), 161.1 (1C), 172.4 (1C); MS (70 eV) m/z (%) 224 (M^+, 48), 151 (100).

4.2.4. Ethyl 2-[(3-methoxyphenyl)thio]propanoate (3e)

Prepared as reported above for **3a** starting from **1e**. Yield: 95%; slightly yellowish oil; IR (neat): 1732 (C=O) cm^{-1}; ^1H NMR δ 1.19 (t, 3H, J = 7.1 Hz, CH_3CH$_2$), 1.49 (d, 3H, J = 7.1 Hz, CH_3CH), 3.75–3.83 (m overlapping s at 3.79, 1H, CH), 3.79 (s overlapping m at 3.75–3.83, 3H, CH_3O), 4.13 (q, 2H, J = 7.1 Hz, CH_2), 6.77–6.86 (m, 1H, Ar), 6.96–7.08 (m, 2H, Ar), 7.21 (apparent t, 1H, Ar); ^{13}C NMR δ 14.3 (1C), 17.7 (1C), 45.4 (1C), 55.5 (1C), 61.5 (1C), 114.0 (1C), 117.9 (1C), 124.9 (1C), 129.9 (1C), 134.9 (1C), 159.9 (1C), 172.9 (1C); MS (70 eV) m/z (%) 240 (M^+, 75), 167 (100).

4.3. General procedure for the preparation of carboxylic acids 4a,b

The method adopted for the synthesis of 2-(4-methoxyphenoxy)propanoic acid (**4a**) is described. Compound **3a** (5.45 g, 24.3 mmol) was dissolved in a solution of KOH (2.73 g, 48.6 mmol) in H_2O/EtOH (15 mL/15 mL) and the reaction mixture was refluxed for 45 min. After evaporation of the solvent, the residue was dissolved in H_2O and extracted with Et_2O, then the aqueous phase was acidified with 2 N HCl and extracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give 4.40 g (92%) of **4a** as a white solid: mp 92–94 °C. Spectroscopic data were in agreement with the literature.[48]

4.3.1. 2-(2-Methoxyphenoxy)propanoic acid (4b)

Prepared as reported above for **4a** starting from **3b**. Yield: 85%; white solid: mp 76–77 °C. Spectroscopic data were in agreement with the literature.[48]

4.4. General procedure for the preparation of amides 5a,b

The method adopted for the synthesis of 2-(4-methoxyphenoxy)propanamide (**5a**) is described. Compound **4a** (2.50 g, 12.7 mmol) was dissolved in $SOCl_2$ (6 mL) at the temperature of 90 °C. After stirring for 1.5 h, excess $SOCl_2$ was evaporated in vacuo. The residue was taken up with THF (50 mL) and concentrated NH_4OH (50 mL) was added dropwise while cooling at 0 °C. The mixture was refluxed for 1 h and stirred at room temperature overnight. After evaporation of the solvent the residue was taken up with EtOAc, washed with a saturated $NaHCO_3$ solution and dried (Na_2SO_4). Evaporation of the solvent gave 1.50 g (61%) of a white solid: mp 108–110 °C; IR (KBr): 3390, 3184 (NH_2), 1661 (C=O) cm^{-1}; ^1H NMR δ 1.54 (d, 3H, J = 6.9 Hz, CH_3CH), 3.75 (s, 3H, CH_3O), 4.54 (q, 1H, J = 6.7 Hz, CH), 6.09 (br s, 1H, NHH), 6.47 (br s, 1H, NHH), 6.75–6.90 (m, 4H, Ar); ^{13}C NMR δ 18.8 (1C), 55.9 (1C), 75.9 (1C), 115.1 (2C), 117.0 (2C), 151.2 (1C), 155.0 (1C), 175.7 (1C); MS (70 eV) m/z (%) 195 (M^+, 88), 124 (100).

4.4.1. 2-(2-Methoxyphenoxy)propanamide (5b)

Prepared as reported above for **5a** starting from **4b**. Yield: 50%; white solid: mp 112–113 °C; IR (KBr): 3398, 3220 (NH_2), 1634 (C=O) cm^{-1}; ^1H NMR δ 1.63 (d, 3H, J = 6.9 Hz, CH_3CH), 3.86 (s, 3H, CH_3O), 4.63 (q, 1H, J = 6.8 Hz, CH), 5.99 (br s, 1H, NHH), 6.80–7.05 (m partially overlapped to br s at 7.09 ppm, 4H, Ar), 7.09 (br s, 1H, NHH); ^{13}C NMR δ 19.0 (1C), 56.0 (1C), 77.6 (1C), 112.4 (1C), 117.4 (1C), 121.4 (1C), 123.6 (1C), 147.0 (1C), 150.3 (1C), 175.7 (1C); MS (70 eV) m/z (%) 195 (M^+, 96), 151 (100). Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.85; H, 6.72; N, 7.23.

4.5. General procedure for the preparation of amines 6a,b and alcohols 13c–e, (*R*)- and (*S*)-13d,e

The method adopted for the synthesis of 2-(4-methoxyphenoxy)propan-1-amine (**6a**) is described. To a stirred suspension of $LiAlH_4$ (0.06 g, 1.58 mmol) in dry THF (20 mL) under N_2 atmosphere and in an ice-bath, a solution of **5a** (0.15 g, 0.77 mmol) in dry THF (20 mL) was added dropwise. After the addition, the mixture was stirred at reflux for 2 h. After cooling at 0 °C, cold H_2O was added dropwise to destroy the excess hydride. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was taken up with Et_2O and the product was extracted with 2 N HCl. The aqueous extracts were combined, brought to pH alkaline with 2 N NaOH and extracted with Et_2O. The combined organic layers were dried (Na_2SO_4). The filtrate was concentrated to yield 0.08 g (57%) of **6a** as a yellow oil: IR (neat): 3372 (NH_2) cm^{-1}; ^1H NMR δ 1.23 (d, 3H, J = 6.0 Hz, CH_3CH), 2.02 (br s, exch D_2O, 2H, NH_2), 2.86 (d, 2H, J = 5.5 Hz, CH_2), 3.76 (s, 3H, CH_3O), 4.22 (apparent sextet, 1H, CH), 6.75–6.90 (m, 4H, Ar); ^{13}C NMR δ 17.5 (1C), 47.7 (1C), 55.9 (1C), 76.9 (1C), 114.9 (2C), 117.8 (2C), 152.2 (1C), 154.3 (1C); MS (70 eV) m/z (%) 181 (M^+, 21), 124 (100).

4.5.1. 2-(2-Methoxyphenoxy)propan-1-amine (6b)

Prepared as reported above for **6a** starting from **5b**. Yield: 20%; slightly yellowish oil; IR (neat): 3375 (NH_2) cm^{-1}; ^1H NMR δ 1.29

(d, 3H, J = 6.3 Hz, CH_3CH), 2.19 (br s, 2H, NH_2), 2.84–2.88 (m, 2H, CH_2), 3.84 (s, 3H, CH_3O), 4.22–4.36 (m, 1H, CH), 6.82–7.0 (m, 4H, Ar); ^{13}C NMR δ 17.8 (1C), 47.6 (1C), 56.0 (1C), 78.1 (1C), 112.3 (1C), 117.4 (1C), 121.1 (1C), 122.3 (1C), 147.6 (1C), 150.9 (1C); MS (70 eV) m/z (%) 181 (M^+, 12), 58 (100).

4.5.2. 2-Phenoxypropan-1-ol (13c)

Prepared as reported above for **6a** starting from **3c**. Yield: 29%; transparent oil; IR (neat): 3392 (OH) cm^{-1}; ^{1}H NMR δ 1.27 (d, 3H, J = 6.0 Hz, CH_3), 2.04 (br s, exch D_2O, 1H, OH), 3.65–3.82 (m, 2H, CH_2), 4.45–4.56 (m, 1H, CH), 6.90–7.05 (m, 3H, Ar), 7.25–7.35 (m, 2H, Ar); ^{13}C NMR δ 16.0 (1C), 66.6 (1C), 75.0 (1C), 116.4 (2C), 121.5 (1C), 129.8 (2C), 157.9 (1C); MS (70 eV) m/z (%) 152 (M^+, 19), 94 (100).

4.5.3. 2-(3-Methoxyphenoxy)propan-1-ol (13d)

Prepared as reported above for **6a** starting from **3d**. Yield: 57%; slightly yellowish oil; IR (neat): 3414 (OH) cm^{-1}; ^{1}H NMR δ 1.27 (d, 3H, J = 6.0 Hz, CH_3CH), 2.08 (br s, 1H, OH), 3.68–3.76 (m, 2H, CH_2), 3.78 (s, 3H, CH_3O), 4.42–4.54 (m, 1H, CH), 6.46–6.56 (m, 3H, Ar), 7.18 (apparent t, 1H, Ar); ^{13}C NMR δ 16.0 (1C), 55.5 (1C), 66.5 (1C), 75.0 (1C), 102.8 (1C), 106.9 (1C), 108.4 (1C), 130.2 (1C), 159.2 (1C), 161.1 (1C); MS (70 eV) m/z (%) 182 (M^+, 41), 124 (100).

4.5.4. (−)-(*R*)-2-(3-Methoxyphenoxy)propan-1-ol [(−)-(*R*)-13d]

Prepared as reported above for **6a** starting from (*R*)-**18d**. Yield: 90%; slightly yellowish oil; $[\alpha]_D^{20}$ = −48 (c 2, $CHCl_3$). Spectroscopic and spectrometric data were in agreement with those reported for the (*S*)-isomer.

4.5.5. (+)-(*S*)-2-(3-Methoxyphenoxy)propan-1-ol [(+)-(*S*)-13d]

Prepared as reported above for **6a** starting from (*S*)-**18d**. Yield: 90%; slightly yellowish oil; $[\alpha]_D^{20}$ = +41 (c 2, $CHCl_3$); IR (NaCl): 3408 (OH) cm^{-1}; ^{1}H NMR δ 1.26 (d, 3H, J = 6.3 Hz, CH_3CH), 2.07 (s, 1H, OH), 3.68–3.74 (m, 2H, CH_2), 3.78 (s, 3H, CH_3O), 4.42–4.53 (m, 1H, CH), 6.45–6.56 (m, 3H, Ar), 7.17 (apparent t, 1H, Ar); ^{13}C NMR δ 16.0 (1C), 55.5 (1C), 66.4 (1C), 74.9 (1C), 102.7 (1C), 106.9 (1C), 108.3 (1C), 130.2 (1C), 159.1 (1C), 161.1 (1C); MS (70 eV) m/z (%) 182 (M^+, 47), 124 (100).

4.5.6. 2-[(3-Methoxyphenyl)thio]propan-1-ol (13e)

Prepared as reported above for **6a** starting from **3e**. Yield: 88%; transparent oil; IR (neat): 3391 (OH) cm^{-1}; ^{1}H NMR δ 1.31 (d, 3H, J = 6.9 Hz, CH_3CH), 2.12 (apparent br t, 1H, exch D_2O, OH), 3.33 (apparent sextet, 1H, CH), 3.46–3.66 (m, 2H, CH_2), 3.79 (s, 3H, CH_3O), 6.75–6.85 (m, 1H, Ar), 6.95–7.05 (m, 2H, Ar), 7.21 (apparent t, 1H, Ar); ^{13}C NMR δ 17.8 (1C), 46.7 (1C), 55.5 (1C), 65.7 (1C), 113.4 (1C), 118.1 (1C), 125.0 (1C), 130.0 (1C), 134.8 (1C), 160.0 (1C); MS (70 eV) m/z (%) 198 (M^+, 82), 167 (100), 140 (99).

4.5.7. (−)-(*R*)-2-[(3-Methoxyphenyl)thio]propan-1-ol [(−)-(*R*)-13e]

Prepared as reported above for **6a** starting from (*R*)-**18e**. Yield: 63%; transparent oil; $[\alpha]_D^{20}$ = −9.6 (c 1, $CHCl_3$); IR (neat): 3391 (OH) cm^{-1}; ^{1}H NMR δ 1.31 (d, 3H, J = 6.9 Hz, CH_3CH), 1.84 (br s, 1H, OH), 3.27–3.41 (m, 1H, CH), 3.52 (dd, 1H, J = 11.4, 6.2 Hz, CHH), 3.61 (dd, 1H, J = 11.3, 5.2 Hz, CHH), 3.80 (s, 1H, CH_3O), 6.76–6.84 (m, 3H, Ar), 6.95–7.05 (m, 2H, Ar), 7.22 (apparent t, 1H, Ar); MS (70 eV) m/z (%) 198 (M^+, 82), 167 (100), 140 (88). ^{13}C NMR was identical to the one of the racemate.

4.5.8. (+)-(*S*)-2-[(3-Methoxyphenyl)thio]propan-1-ol [(+)-(*S*)-13e]

Prepared as reported above for **6a** starting from (−)-(*S*)-**18e**. Yield: 90%; transparent oil; $[\alpha]_D^{20}$ = +10.8 (c 1, $CHCl_3$); MS (70 eV) m/z (%) 198 (M^+, 82), 167 (86), 140 (100). Spectroscopic and spectrometric data were in agreement with those reported for the (*R*)-isomer.

4.6. General procedure for the preparation of amines 6c–e, 11a–h and 22c,d

The method adopted for the synthesis of 2-(3-methoxyphenoxy)propan-1-amine (**6d**) is described. To a stirred solution of **14d** (1.80 g, 5.8 mmol) in MeOH (67 mL), glacial AcOH (11.6 mmol) and $N_2H_4{\cdot}H_2O$ (23.2 mmol) were added and the mixture was kept under reflux for 4 h. The solid residue was filtered off. After evaporation of the filtrate, the residue was taken up with EtOAc and extracted with 2 N HCl; then the aqueous phase was made alkaline and extracted twice with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum. The final product was a slightly yellowish oil (0.90 g, 86%): IR (neat): 3375 (NH_2) cm^{-1}; ^{1}H NMR δ 1.26 (d, 3H, J = 5.8 Hz, CH_3CH), 2.11 (br s, 2H, NH_2), 2.88 (d, 2H, J = 5.8 Hz, CH_2), 3.77 (s, 3H, CH_3O), 4.35 (apparent sextet, 1H, CH), 6.40–6.55 (m, 3H, Ar), 7.10–7.20 (m, 1H, Ar); ^{13}C NMR δ 17.4 (1C), 47.6 (1C), 55.5 (1C), 75.6 (1C), 102.6 (1C), 106.6 (1C), 108.2 (1C), 130.2 (1C), 159.4 (1C), 161.1 (1C); MS (70 eV) m/z (%) 181 (M^+, 17), 58 (100).

4.6.1. (−)-(*R*)-2-(3-Methoxyphenoxy)propan-1-amine [(−)-(*R*)-6d]

Prepared as reported above for **6d** starting from (*R*)-**14d**. Yield: 95%; slightly yellowish oil; $[\alpha]_D^{20}$ = −44 (c 1, $CHCl_3$); IR (neat): 3376 (NH_2) cm^{-1}; ^{1}H NMR δ 1.26 (d, 3H, J = 6.0 Hz, CH_3CH), 1.73 (br s, 2H, exch D_2O, NH_2), 2.88 (br s, 2H, CH_2), 3.77 (s, 3H, CH_3O), 4.35 (apparent sextet, 1H, CH), 6.44–6.55 (m, 3H, Ar), 7.16 (apparent t, 1H, Ar); ^{13}C NMR δ 17.4 (1C), 47.7 (1C), 55.5 (1C), 75.8 (1C), 102.6 (1C), 106.6 (1C), 108.2 (1C), 130.2 (1C), 159.5 (1C), 161.1 (1C); MS (70 eV) m/z (%) 181 (M^+, 26), 58 (100).

4.6.2. (+)-(*S*)-2-(3-Methoxyphenoxy)propan-1-amine [(+)-(*S*)-6d]

Prepared as reported above for (*RS*)-**6d** starting from (+)-(*S*)-**14d**. Yield: 73%; slightly yellowish oil; $[\alpha]_D^{20}$ = +45 (c 1, $CHCl_3$). Spectroscopic and spectrometric data were in agreement with those reported for the (*R*)-isomer.

4.6.3. 2-Phenoxypropan-1-amine (6c)

Prepared as reported above for **6d** starting from **14c**. Yield: 82%; IR (neat): 3375 (NH_2) cm^{-1}; ^{1}H NMR δ 1.27 (d, 3H, J = 6.0 Hz, CH_3), 1.69 (br s, 2H, NH_2), 2.90 (br s, 2H, CH_2), 4.36 (apparent sextet, 1H, CH), 6.88–6.99 (m, 3H, Ar), 7.23−7.34 (m, 2H, Ar); ^{13}C NMR δ 17.4 (1C), 47.7 (1C), 75.5 (1C), 116.3 (2C), 121.1 (1C), 129.8 (2C), 158.2 (1C); MS (70 eV) m/z (%) 151 (M^+, 10), 58 (100).

4.6.4. 2-[(3-Methoxyphenyl)thio]propan-1-amine (6e)

Prepared as reported above for **6d** starting from **14e**. Yield: 29%; slightly yellowish oil; IR (neat): 3299 (NH_2) cm^{-1}; ^{1}H NMR δ 1.29 (d, 3H, J = 6.9 Hz, CH_3CH), 1.95 (br s, 2H, NH_2), 2.70–2.85 (m, 2H, CH_2), 3.79 (s, 3H, CH_3O), 4.88–5.05 (m, 1H, CH), 6.72–6.84 (m, 1H, Ar), 6.86–7.05 (m, 2H, Ar), 7.13–7.25 (m, 1H, Ar); ^{13}C NMR δ 19.0 (1C), 47.3 (1C), 55.5 (2C), 112.9 (1C), 117.7 (1C), 124.5 (1C), 129.9 (1C), 135.9 (1C), 159.9 (1C); MS (70 eV) m/z (%) 197 (M^+, 43), 168 (100).

4.6.5. (−)-(*R*)-2-[(3-Methoxyphenyl)thio]propan-1-amine [(−)-(*R*)-6e]

Prepared as reported above for **6d** starting from (*R*)-**14e**. Yield: 68%; slightly yellowish oil; $[\alpha]_D^{20}$ = −2.0 (c 1, $CHCl_3$); IR (neat): 3376 (NH_2) cm^{-1}; ^{1}H NMR δ 1.30 (d, 3H, J = 6.9 Hz, CH_3CH), 1.98 (br t, 2H, J = 3.4 Hz, NH_2), 2.72–2.85 (m, 2H, CH_2), 3.79 (s, 3H, CH_3O), 4.97 (tq, seven lines, 1H, J = 6.3 Hz, CH), 6.74–6.84 (m, 1H, Ar), 6.90–7.05 (m, 2H, Ar), 7.15–7.25 (m, 1H, Ar); ^{13}C NMR δ 19.0 (1C), 47.1 (1C), 55.5 (2C), 113.0 (1C), 117.8 (1C), 124.6 (1C), 129.9 (1C), 135.8 (1C), 160.0 (1C); MS (70 eV) m/z (%) 197 (M^+, 36), 168 (100).

4.6.6. (+)-(*S*)-2-[(3-Methoxyphenyl)thio]propan-1-amine [(+)-(*S*)-6e]

Prepared as reported above for **6d** starting from (*S*)-**14e**. Yield: 63%; slightly yellowish oil; $[\alpha]_D^{20}$ = +4.4 (*c* 0.5, $CHCl_3$). Spectroscopic and spectrometric data were in agreement with those reported for the (*R*)-isomer.

4.6.7. 2-(4-Methoxyphenoxy)ethanamine (11a)

Prepared as reported above for **6d** starting from **10a**. Yield: 89%; slightly yellowish oil. Spectroscopic data were in agreement with the literature.[49]

4.6.8. 2-(2-Methoxyphenoxy)ethanamine (11b)

Prepared as reported above for **6d** starting from **10b**. Yield: 86%; slightly yellowish oil. Spectroscopic data were in agreement with the literature.[50]

4.6.9. 2-Phenoxyethanamine (11c)

Prepared as reported above for **6d** starting from **10c**. Yield: 60%; slightly yellowish oil; IR (neat): 3373 (NH_2) cm^{-1}; ^1H NMR δ 1.77 (s, 2H, NH_2), 3.07 (t, 2H, *J* = 5.0 Hz, CH_2N), 3.98 (t, 2H, *J* = 5.1 Hz, CH_2O), 6.84–7.0 (m, 3H, Ar), 7.22–7.34 (m, 2H, Ar); ^{13}C NMR δ 41.7 (1C), 70.2 (1C), 114.7 (2C), 121.1 (1C) 129.7 (2C), 159.1 (1C); MS (70 eV) *m*/*z* (%) 137 (M^+, 54), 44 (100).

4.6.10. 2-(3-Methoxyphenoxy)ethanamine (11d)

Prepared as reported above for **6d** starting from **10d**. Yield: 69%; slightly yellowish oil; IR (neat): 3370 (NH_2) cm^{-1}; ^1H NMR δ 1.68 (br s, 2H, NH_2), 3.08 (t, 2H, *J* = 5.1 Hz, CH_2N), 3.79 (s, 3H, CH_3O), 3.97 (t, 2H, *J* = 5.1 Hz, CH_2O), 6.48 (apparent t, 1H, Ar), 6.50 (d, 1H, *J* = 2.5 Hz, Ar), 6.52 (d, 1H, *J* = 2.5 Hz, Ar), 7.18 (apparent t, 1H, Ar); ^{13}C NMR δ 41.8 (1C), 55.5 (1C), 70.4 (1C), 101.3 (1C) 106.7 (1C), 107.0 (1C), 130.1 (1), 160.4 (1), 161.1 (1); MS (70 eV) *m*/*z* (%) 167 (M^+, 16), 124 (100).

4.6.11. 2-[(3-Methoxyphenyl)thio]ethanamine (11e)

Prepared as reported above for **6d** starting from **10e**. Yield: 51%; slightly yellowish oil; IR (neat): 3359 (NH_2) cm^{-1}; ^1H NMR δ 2.05 (br s, 2H, NH_2), 2.88–2.96 (m, 2H, CH_2N), 2.98–3.06 (m, 2H, CH_2O), 3.79 (s, 3H, CH_3), 6.72 (ddd, 1H, *J* = 8.3, 2.5, 0.8 Hz, Ar), 6.90 (apparent t, 1H, Ar) 6.93 (dt, 1H, *J* = 8.1, 1.2 Hz, Ar), 7.19 (apparent t, 1H, Ar); ^{13}C NMR δ 38.1 (1C), 41.2 (1C), 55.5 (1C), 112.1 (1C), 115.4 (1C), 122.0 (1C), 130.0 (1C), 137.3 (1C), 160.1 (1C); MS (70 eV) *m*/*z* (%) 183 (M^+, 33), 154 (100).

4.6.12. 2-(Phenylthio)ethanamine (11f)

Prepared as reported above **6d** starting from **10f**. Yield: 85%: slightly yellowish oil; IR (neat): 3357, 3285 (NH_2) cm^{-1}; ^1H NMR δ 1.67 (br s, 2H, NH_2), 2.86–2.96 (m, 2H, CH_2N), 2.98–3.05 (m, 2H, CH_2O), 7.19 (tt, 1H, *J* = 7.3, 1.7 Hz, Ar), 7.24–7.32 (m, 2H, Ar), 7.32–7.40 (m, 2H, Ar); ^{13}C NMR δ 38.3 (1C), 41.1 (1C), 126.5 (1C), 129.2 (2C) 130.0 (2C), 135.9 (1C); MS (70 eV) *m*/*z* (%) 153 (M^+, 23), 124 (100).

4.6.13. 2-[(4-Methoxyphenyl)thio]ethanamine (11g)

Prepared as reported above for **6d** starting from **10g**. Yield: 79%: slightly yellowish oil; IR (neat): 3362, 3294 (NH_2) cm^{-1}; ^1H NMR δ 1.58 (br s, exch D_2O, 2H, NH_2), 2.74–2.94 (m, 4H, CH_2CH_2), 3.78 (s, 3H, CH_3), 6.80–6.88 (m, 2H, Ar), 7.32–7.40 (m, 2H, Ar); ^{13}C NMR δ 40.4 (1C), 41.1 (1C), 55.5 (1C), 114.9 (2C), 125.9 (1C) 133.9 (2C), 159.3 (1C); MS (70 eV) *m*/*z* (%) 183 (M^+, 40), 154 (100).

4.6.14. 2-[(2-Methoxyphenyl)thio]ethanamine (11h)

Prepared as reported above for **6d** starting from **10h**. Yield: 76%: slightly yellowish oil; IR (neat): 3358 (NH_2) cm^{-1}; ^1H NMR δ 1.76 (br s, exch D_2O, 2H, NH_2), 2.80–2.90 (m, 2H, CH_2N), 2.92–3.02 (m, 2H, CH_2O), 3.88 (s, 3H, CH_3), 6.85 (d, *J* = 8.3 Hz, 1H, Ar), 6.91 (apparent dt, 1H, Ar), 7.21 (apparent dt, 1H, Ar), 7.32 (dd, 1H, *J* = 7.4, 1.5 Hz, Ar); ^{13}C NMR 37.2 (1C), 41.2 (1C), 56.0 (1C), 111.0 (1C) 121.3 (1C), 123.7 (1C), 128.0 (1C), 131.2 (1C), 158.3 (1C); MS (70 eV) *m*/*z* (%) 183 (M^+, 32), 154 (100).

4.6.15. 1-Phenoxypropan-2-amine (22c)

Prepared as reported above for **6d** starting from **21c**. Yield: 56%; slightly yellowish oil. Spectroscopic and spectrometric data were in agreement with those reported in the literature for (*R*)- and (*S*)-isomers.[38]

4.6.16. 1-(3-Methoxyphenoxy)propan-2-amine (22d)

Prepared as reported above for **6d** starting from **21d**. Yield: 94%; slightly yellowish oil: IR (neat): 3361 (NH) cm^{-1}; ^1H NMR δ 1.16 (d, 3H, *J* = 6.3 Hz, CH_3CH), 1.96 (br s, 2H, NH_2), 3.26–3.40 (br s, 1H, C*H*), 3.60–3.70 (m, 1H, C*H*H), 3.78 (s, 3H, CH_3O), 3.85 (dd, 1H, *J* = 8.8, 4.1 Hz, CH*H*), 6.43–6.56 (m, 3H, Ar), 7.17 (apparent t, 1H, Ar); ^{13}C NMR δ 20.0 (1C), 46.5 (1C), 55.5 (1C), 74.7 (1C), 101.2 (1C), 106.6 (1C), 106.9 (1C), 130.1 (1C), 160.4 (1C), 161.1 (1C); MS (70 eV) *m*/*z* (%) 181 (M^+, 3), 44 (100).

4.6.17. (−)-(*R*)-1-(3-Methoxyphenoxy)propan-2-amine [(−)-(*R*)-22d]

Prepared as reported above for **6d** starting from (*R*)-**21d**. Yield: 93%; slightly yellowish oil: $[\alpha]_D^{20}$ = −14.9 (*c* 2, $CHCl_3$); IR (neat): 3364 (NH) cm^{-1}; ^1H NMR δ 1.16 (d, 3H, *J* = 6.6 Hz, CH_3CH), 1.95 (br s, 2H, NH_2), 3.33 (br s, 1H, C*H*), 3.60–3.70 (m, 1H, C*H*H), 3.78 (s, 3H, CH_3O), 3.85 (dd, 1H, *J* = 9.1, 4.1 Hz, CH*H*), 6.44–6.56 (m, 3H, Ar), 7.16 (apparent t, 1H, Ar); ^{13}C NMR δ 20.0 (1C), 46.5 (1C), 55.5 (1C), 74.7 (1C), 101.2 (1C), 106.7 (1C), 106.9 (1C), 130.1 (1C), 160.4 (1C), 161.1 (1C); MS (70 eV) *m*/*z* (%) 181 (M^+, 4), 44 (100).

4.6.18. (+)-(*S*)-1-(3-Methoxyphenoxy)propan-2-amine [(+)-(*S*)-22d]

Prepared as reported above for **6d** starting from (−)-(*S*)-**21d**. Yield: 91%; slightly yellowish oil; $[\alpha]_D^{20}$ = +16.2 (*c* 5, $CHCl_3$). Spectroscopic and spectrometric data were in agreement with those found for the (*R*)-isomer.

4.7. General procedure for the preparation of acetamides 7a–e, 12a–h and 23c–d

The method adopted for the synthesis of *N*-[2-(4-methoxyphenoxy)propyl]acetamide (**7a**) is described. To a stirring solution of **6a** (0.43 g, 2.37 mmol) and Et_3N (0.66 mL, 4.75 mmol) in dry THF (16 mL) under N_2 atmosphere, acetic anhydride (0.48 g, 4.75 mmol) was added dropwise in an ice-water bath and the stirring was continued for 5 h. The reaction mixture was concentrated under vacuum. The residue was taken up with EtOAc and washed with 2 N HCl, a saturated solution of $NaHCO_3$ and then brine. The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (EtOAc) to give 0.16 g (30%) of **7a** as a yellow solid: mp 44–46 °C; IR (KBr): 3266 (NH), 1639 (C=O); ^1H NMR δ 1.23 (d, 3H, *J* = 6.0 Hz, CH_3CH), 1.98 (s, 3H, CH_3CO), 3.24 (ddd, 1H, *J* = 14.0, 7.4, 4.8 Hz, C*H*H), 3.68 (ddd, 1H, *J* = 14.0, 6.9, 3.3 Hz, CH*H*), 3.76 (s, 3H, CH_3O), 4.30–4.42 (m, 1H, C*H*), 5.94 (br s, 1H, N*H*), 6.76–6.90 (m, 4H, Ar); ^{13}C NMR δ 17.4 (1C), 23.5 (1C), 44.7 (1C), 55.9 (1C), 74.1 (1C), 115.0 (2C), 117.7 (2C), 151.6 (1C), 154.5 (1C), 170.5 (1C); MS (70 eV) *m*/*z* (%) 223 (M^+, 7), 100 (100).

4.7.1. *N*-[2-(2-Methoxyphenoxy)propyl]acetamide (7b)

Prepared as reported above for **7a** starting from **6b**. Yield: 82%; slightly yellowish oil; IR (neat): 3303 (NH), 1658 (C=O) cm^{-1}; ^1H

NMR δ 1.32 (d, 3H, J = 6.3 Hz, CH_3CH), 2.01 (s, 3H, CH_3CO), 3.23–3.35 (m, 1H, CHH), 3.64 (ddd, 1H, J = 14.0, 6.5, 2.9 Hz, CHH), 3.88 (s, 3H, CH_3O), 4.44–4.72 (m, 1H, CH), 6.57 (br s, 1H, NH), 6.82–7.06 (m, 4H, Ar); ^{13}C NMR δ 18.0 (1C), 23.5 (1C), 44.8 (1C), 56.1 (1C), 74.2 (1C), 112.4 (1C), 119.3 (1C), 121.5 (1C), 123.4 (1C), 147.1 (1C), 151.0 (1C), 170.7 (1C); MS (70 eV) m/z (%) 223 (M^+, 1), 100 (100).

4.7.2. *N*-(2-Phenoxypropyl)acetamide (7c)

Prepared as reported above for **7a** starting from **6c**. Yield: 92%; slightly yellowish oil; IR (neat): 3296 (NH), 1657 (C=O) cm^{-1}; ^{1}H NMR δ 1.27 (d, 3H, J = 6.0 Hz, CH_3CH), 1.98 (s, 3H, CH_3CO), 3.22–3.34 (m, 1H, CHH), 3.65–3.77 (m, 1H, CHH), 4.44–4.56 (m, 1H, CH), 5.92 (br s, 1H, NH), 6.87–7.00 (m, 3H, Ar), 7.24–7.34 (m, 2H, Ar); ^{13}C NMR δ 17.4 (1C), 23.5 (1C), 44.7 (1C), 72.9 (1C), 116.1 (2C), 121.4 (1C), 129.9 (2C), 157.7 (1C), 170.5 (1C); MS (70 eV) m/z (%) 193 (M^+, 2), 100 (100).

4.7.3. *N*-[2-(3-Methoxyphenoxy)propyl]acetamide (7d)

Prepared as reported above for **7a** starting from **6d**. Yield: 92%; slightly yellowish oil; IR (neat): 3296 (NH), 1655 (C=O) cm^{-1}; ^{1}H NMR δ 1.27 (d, 3H, J = 6.0 Hz, CH_3CH), 1.97 (s, 3H, CH_3CO), 3.22–3.33 (m, 1H, CHH), 3.64–3.74 (m, 1H, CHH), 3.78 (s, 3H, CH_3O), 4.42–4.54 (m, 1H, CH), 5.90 (br s, 1H, NH), 6.42–6.55 (m, 3H, Ar), 7.17 (apparent t, 1H, Ar); ^{13}C NMR δ 17.4 (1C), 23.5 (1C), 44.7 (1C), 55.5 (1C), 73.0 (1C), 102.6 (1C), 106.9 (1C), 108.1 (1C), 130.3 (1C), 159.0 (1C), 161.2 (1C), 170.5 (1C); MS (70 eV) m/z (%) 223 (M^+, 9), 100 (100).

4.7.4. (−)-(*R*)-*N*-[2-(3-Methoxyphenoxy)propyl]acetamide [(−)-(*R*)-7d]

Prepared as reported above for **7a** starting from (*R*)-**6d**. Yield: 49%; slightly yellowish oil; $[\alpha]_D^{20}$ = −84 (c 2, $CHCl_3$), 96% ee (chiral HPLC, Chiralpak IA, t_R 31.5 min, flow 1 mL/min, λ 280 nm, eluent 87:13:0.1 hexane/THF/TFA); IR (neat): 3295 (NH), 1652, 1602 (C=O) cm^{-1}; ^{1}H NMR δ 1.27 (d, 3H, J = 6.0 Hz, CH_3CH), 1.98 (s, 3H, CH_3CO), 3.22–3.34 (m, 1H, CHH), 3.69 (ddd, 1H, J = 13.8, 6.9, 3.3 Hz, CHH), 3.78 (s, 3H, CH_3O), 4.42–4.54 (m, 1H, CH), 6.00 (br s, 1H, NH), 6.42–6.55 (m, 3H, Ar), 7.17 (apparent t, 1H, Ar); ^{13}C NMR δ 17.4 (1C), 23.5 (1C), 44.7 (1C), 55.5 (1C), 73.0 (1C), 102.6 (1C), 106.9 (1C), 108.1 (1C), 130.3 (1C), 158.9 (1C), 161.2 (1C), 170.7 (1C); MS (70 eV) m/z (%) 223 (M^+, 8), 100 (100).

4.7.5. (+)-(*S*)-*N*-[2-(3-Methoxyphenoxy)propyl]acetamide [(+)-(*S*)-7d]

Prepared as reported above for **7a** starting from (*S*)-**6d**. Yield: 89%; slightly yellowish oil; $[\alpha]_D^{20}$ = +83 (c 1, $CHCl_3$), 96% ee (chiral HPLC, Chiralpak IA, t_R 35.5 min, flow 1 mL/min, λ 280 nm, eluent 87:13:0.1 hexane/THF/TFA). Spectroscopic and spectrometric data were in agreement with those reported for the (*R*)-isomer.

4.7.6. *N*-{2-[(3-Methoxyphenyl)thio]propyl}acetamide (7e)

Prepared as reported above for **7a** starting from **6e**. Yield: 90%; slightly yellowish oil; IR (neat): 3293 (NH), 1657 (C=O) cm^{-1}; ^{1}H NMR δ 1.29 (d, 3H, J = 6.6 Hz, CH_3CH), 1.94 (s, 3H, CH_3CO), 3.20–3.33 (m, 1H, CHH), 3.34–3.52 (m, 2H, CHH + CH), 3.80 (s, 3H, CH_3O), 5.86 (br s, 1H, NH), 6.79 (dd, 1H, J = 8.3 Hz, 2.5 Hz, Ar), 6.94–7.04 (m, 2H, Ar), 7.21 (apparent t, 1H, Ar); ^{13}C NMR δ 19.0 (1C), 23.4 (1C), 43.4 (1C), 44.7 (1C), 55.5 (1C), 113.2 (1C), 117.5 (1C), 124.3 (1C), 130.1 (1C), 135.3 (1C), 160.1 (1C), 170.4 (1C); MS (70 eV) m/z (%) 239 (M^+, 15), 180 (100).

4.7.7. (+)-(*R*)-*N*-{2-[(3-Methoxyphenyl)thio]propyl}acetamide [(+)-(*R*)-7e]

Prepared as reported above for **7a** starting from (−)-(*R*)-**6e**. Yield: 57%; slightly yellowish oil; $[\alpha]_D^{20}$ = +8.2 (c 2, $CHCl_3$); 80% ee (chiral HPLC, Chiralpak IB, t_R 50.3, flow 0.6 mL/min, λ 210 nm, eluent 95:5 hexane/*i*-PrOH); IR (neat): 3297 (NH), 1657 (C=O) cm^{-1}; ^{1}H NMR δ 1.29 (d, 3H, J = 6.9 Hz, CH_3CH), 1.94 (s, 3H, CH_3CO), 3.22–3.33 (m, 1H, CHH), 3.35–3.52 (m, 2H, CHH + CH), 3.80 (s, 3H, CH_3O), 5.85 (br s, 1H, NH), 6.75–6.82 (m, 1H, Ar), 6.95–7.02 (m, 1H, Ar), 7.22 (apparent t, 1H, Ar); ^{13}C NMR δ 19.0 (1C), 22.2 (1C), 43.4 (1C), 44.7 (1C), 55.5 (1C), 113.3 (1C), 117.5 (1C), 124.3 (1C), 130.1 (1C), 135.3 (1C), 160.1 (1C), 170.4 (1C); MS (70 eV) m/z (%) 239 (M^+, 2), 180 (100).

4.7.8. (−)-(*S*)-*N*-{2-[(3-Methoxyphenyl)thio]propyl}acetamide [(−)-(*S*)-7e]

Prepared as reported above for **7a** starting from (−)-(*S*)-**6e**. Yield: 98%; slightly yellowish oil; $[\alpha]_D^{20}$ = −19.0 (c 0.5, $CHCl_3$); 96% ee (chiral HPLC, Chiralpak IA, t_R 23.1, flow 1.0 mL/min, λ 210 nm, eluent 95:5 hexane/*i*-PrOH). Spectroscopic and spectrometric data were in agreement with those reported for the (*R*)-isomer.

4.7.9. *N*-[2-(4-Methoxyphenoxy)ethyl]acetamide (12a)

Prepared as reported above for **7a** starting from **11a**. Yield: 85%; white crystals: mp 100–101 °C (EtOAc/hexane); IR (KBr): 3291 (NH), 1646 (C=O) cm^{-1}; ^{1}H NMR δ 2.0 (s, 3H, CH_3C), 3.63 (apparent q, 2H, CH_2N), 3.76 (s, 3H, CH_3O), 3.98 (t, 2H, J = 4.9 Hz, CH_2O), 5.98 (br s, 1H, NH), 6.83 (s, 4H, Ar); ^{13}C NMR δ 23.5 (1C), 39.4 (1C), 56.0 (1C), 67.6 (1C), 115.0 (2C), 115.6 (2C), 152.8 (1C), 154.4 (1C), 170.4 (1C); MS (70 eV) m/z (%) 209 (M^+, 2), 86 (100). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.80; H, 7.24; N, 6.32.

4.7.10. *N*-[2-(2-Methoxyphenoxy)ethyl]acetamide (12b)

Prepared as reported above for **7a** starting from **11b**. Yield: 40%; white crystals: mp 62–63 °C (EtOAc/hexane); IR (KBr): 3541 (NH), 1660 (C=O) cm^{-1}; ^{1}H NMR δ 2.00 (s, 3H, CH_3C), 3.65 (apparent q, 2H, CH_2N), 3.87 (s, 3H, CH_3O), 4.09 (t, 2H, J = 5.1 Hz, CH_2O), 6.29 (br s, 1H, NH), 6.88–7.02 (m, 4H, Ar); ^{13}C NMR δ 23.5 (1C), 39.2 (1C), 56.0 (1C), 69.0 (1C), 112.1 (1C), 115.0 (1C), 121.4 (1C), 122.3 (1C), 148.0 (1C), 149.8 (1C), 170.5 (1C); MS (70 eV) m/z (%) 150 (M^+−59, 1), 86 (100). Anal. Calcd for $C_{11}H_{15}NO_3{\cdot}0.25H_2O$: C, 61.81; H, 7.31; N, 6.55. Found: C, 61.88; H, 7.02; N, 6.37.

4.7.11. *N*-(2-Phenoxyethyl)acetamide (12c)

Prepared as reported above for **7a** starting from **11c**. Yield: 62%; slightly yellowish crystals: mp 89–90 °C (EtOAc/hexane); IR (KBr): 3316 (NH), 1654 (C=O) cm^{-1}; ^{1}H NMR δ 2.01 (s, 3H, CH_3), 3.65 (apparent q, 2H, CH_2N), 4.02 (t, J = 5.1 Hz, 2H, CH_2O), 6.24 (br s, 1H, NH), 6.88 (d, 2H, J = 8.5 Hz, Ar), 6.96 (apparent t, 1H, Ar), 7.28 (apparent t, 2H, Ar); ^{13}C NMR δ 23.4 (1C), 39.3 (1C), 66.8 (1C), 114.6 (2C), 121.4 (1C), 129.8 (2C), 158.6 (1C), 170.7 (1C); MS (70 eV) m/z (%) 179 (M^+, 1), 86 (100). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.16; H, 7.33; N, 7.79.

4.7.12. *N*-[2-(3-Methoxyphenoxy)ethyl]acetamide (12d)

Prepared as reported above for **7a** starting from **11d**. Yield: 85%; slightly yellowish oil; ^{13}C NMR δ 23.5 (1C), 39.3 (1C), 55.5 (1C), 67.0 (1C), 101.2 (1C), 106.8 (1C), 106.9 (1C), 130.3 (1C), 159.9 (1C), 161.1 (1C), 170.5 (1C). Other spectroscopic data were in agreement with the literature.[51]

4.7.13. *N*-{2-[(3-Methoxyphenyl)thio]ethyl}acetamide (12e)

Prepared as reported above for **7a** starting from **11e**. Yield: 56%; slightly yellowish solid: mp 35–36 °C (toluene/*i*-Pr$_2$O); IR (KBr): 3255 (NH), 1639 (C=O) cm^{-1}; ^{1}H NMR δ 1.93 (s, 3H, CH_3C), 3.05 (t, 2H, J = 6.3 Hz, CH_2S), 3.45 (apparent q, 2H, CH_2N), 3.79 (s, 3H, CH_3O), 6.0 (br s, 1H, NH), 6.68–6.78 (m, 1H, Ar), 6.87–6.98 (m, 2H, Ar) 7.20 (apparent t, 1H, Ar); ^{13}C NMR δ 23.4 (1C), 33.5 (1C), 39.0 (1C), 55.5 (1C), 112.4 (1C), 115.1 (1C), 121.8 (1C), 130.2

(1C), 136.6 (1C), 160.2 (1C), 170.5 (1C); MS (70 eV) *m*/*z* (%) 225 (M^+, 20), 166 (100). Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.22. Found: C, 58.42; H, 6.80; N, 6.08.

4.7.14. *N*-[2-(Phenylthio)ethyl]acetamide (12f)

Prepared as reported above for **7a** starting from **11f**. Yield: 84%. Spectroscopic data were in agreement with the literature.[52]

4.7.15. *N*-{2-[(4-Methoxyphenyl)thio]ethyl}acetamide (12g)

Prepared as reported above for **7a** starting from **11g**. Yield: 81%; slightly yellowish crystals: mp 106–107 °C (EtOAc); IR (KBr): 3260 (NH), 1640 (C=O) cm^{-1}; ^1H NMR δ 1.94 (s, 3H, CH_3C), 2.93 (t, 2H, *J* = 6.3 Hz, CH_2S), 3.38 (apparent q, 2H, CH_2N), 3.78 (s, 3H, CH_3O), 5.97 (br s, 1H, N*H*), 6.80–6.90 (m, 2H, Ar), 7.32–7.42 (m, 2H, Ar); ^{13}C NMR δ 23.4 (1C), 35.8 (1C), 38.8 (1C), 55.6 (1C), 115.0 (2C), 125.1 (1C), 133.9 (2C), 159.6 (1C), 170.4 (1C); MS (70 eV) *m*/*z* (%) 225 (M^+, 33), 166 (100). Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.65; H, 6.71; N, 6.22. Found: C, 58.65; H, 6.87; N, 5.87.

4.7.16. *N*-{2-[(2-Methoxyphenyl)thio]ethyl}acetamide (12h)

Prepared as reported above for **7a** starting from **11h**. Yield: 80%; slightly yellowish oil; IR (neat): 3288 (NH), 1651 (C=O) cm^{-1}; ^1H NMR δ 1.94 (s, 3H, CH_3C), 3.01 (t, 2H, *J* = 6.2 Hz, CH_2S), 3.42 (apparent q, 2H, CH_2N), 3.90 (s, 3H, CH_3O), 6.01 (br s, 1H, N*H*), 6.88 (dd, 1H, *J* = 8.3, 0.8 Hz, Ar), 6.93 (apparent dt, 1H, Ar), 7.24 (apparent dt, 1H, Ar), 7.37 (dd, 1H, *J* = 7.7, 1.7 Hz, Ar); ^{13}C NMR δ 23.4 (1C), 33.1 (1C), 38.7 (1C), 56.1 (1C), 111.2 (1C), 121.5 (1C), 122.8 (1C), 128.6 (1C), 131.9 (1C), 158.4 (1C), 170.2 (1C); MS (70 eV) *m*/*z* (%) 225 (M^+, 24), 166 (100).

4.7.17. *N*-(1-Methyl-2-phenoxyethyl)acetamide (23c)

Prepared as reported above for **7a** starting from **22c**. Yield: 93%. Spectroscopic and spectrometric data were in agreement with those reported in the literature for (*R*)- and (*S*)-isomers.[38]

4.7.18. *N*-[2-(3-Methoxyphenoxy)-1-methylethyl]acetamide (23d)

Prepared as reported above for **7a** starting from **22d**. Yield: 28%; slightly yellowish oil; IR (neat): 3283 (NH), 1652, 1603 (C=O) cm^{-1}; ^1H NMR δ 1.29 (d, 3H, *J* = 6.9 Hz, CH_3CH), 1.98 (s, 3H, CH_3CO), 3.78 (s, 3H, CH_3O), 3.89 (dd, 1H, *J* = 9.1, 3.6 Hz, C*H*H), 3.94 (dd, 1H, *J* = 9.4, 4.1 Hz, CH*H*), 4.28–4.43 (m, 1H, C*H*), 5.85 (br d, 1H, N*H*), 6.40–6.58 (m, 3H, Ar), 7.17 (apparent t, 1H, Ar); ^{13}C NMR δ 17.8 (1C), 23.7 (1C), 44.8 (1C), 55.5 (1C), 70.8 (1C), 101.2 (1C), 106.8 (1C), 106.9 (1C), 130.2 (1C), 160.1 (1C), 161.1 (1C), 169.8 (1C); MS (70 eV) *m*/*z* (%) 223 (M^+, 3), 100 (100).

4.7.19. (+)-(*R*)-*N*-[2-(3-Methoxyphenoxy)-1-methylethyl]acetamide [(+)-(*R*)-23d]

Prepared as reported above for **7a** starting from (*R*)-**22d**. Yield: 83%; white crystals: mp 62–63 °C (EtOAc/hexane); $[\alpha]_D^{20}$ = +88 (*c* 2, $CHCl_3$); 98% ee (chiral HPLC, Chiralpak IA, t_R 16.3, flow 1.0 mL/min, λ 210 nm, eluent 95:5 hexane/*i*PrOH); IR (neat): 3274 (NH), 1645 (C=O) cm^{-1}; ^1H NMR δ 1.29 (d, 3H, *J* = 6.9 Hz, CH_3CH), 1.99 (s, 3H, CH_3CO), 3.79 (s, 3H, CH_3O), 3.89 (dd, 1H, *J* = 9.0, 3.6 Hz, C*H*H), 3.95 (dd, 1H, *J* = 9.3, 4.2 Hz, CH*H*), 4.30–4.40 (m, 1H, C*H*), 5.78 (br d, 1H, *J* = 6.9 Hz, N*H*), 6.43–6.57 (m, 3H, Ar), 7.18 (apparent t, 1H, Ar); MS (70 eV) *m*/*z* (%) 223 (M^+, 4), 100 (100). ^{13}C NMR spectrum was identical to the one reported for the racemate. Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.19; H, 7.85; N, 6.33.

4.7.20. (−)-(*S*)-*N*-[2-(3-Methoxyphenoxy)-1-methylethyl]acetamide [(−)-(*S*)-23d]

Prepared as reported above for **7a** starting from (*S*)-**22d**. Yield: 89%; white crystals: mp 62–63 °C (EtOAc/hexane); $[\alpha]_D^{20}$ = −72 (*c* 2, $CHCl_3$); 98% ee (chiral HPLC, Chiralpak IA, t_R 51.6, flow 0.5 mL/min, λ 230 nm, eluent 95:5 hexane/*i*PrOH). Spectroscopic and spectrometric data were in agreement with those found for the (*R*)-isomer. Anal. Calcd for $C_{12}H_{17}NO_3{\cdot}0.17C_6H_8$: C, 65.99; H, 7.81; N, 5.92. Found: C, 66.07; H, 8.22; N, 6.20.

4.8. General procedure for the synthesis of acetamides (23e,f)

The method adopted for the synthesis of (−)-(*S*)-*N*-[1-methyl-2-(phenylthio)ethyl]acetamide [(−)-(*S*)-**23f**] is described. A solution of **1f** (1.02 mL, 1.09 g, 9.93 mmol), (+)-(*S*)-**19** (0.77 mL, 0.746 g, 9.93 mmol), AcOH (0.57 mL, 9.93 mmol) and 2 N HCl (0.36 mL, 9.93 mmol) and two little pieces of zinc in benzene (1.6 mL) was heated under reflux in a flask fitted with a Dean–Stark apparatus for 6 h. All volatile matter were then evaporated under vacuum and the solid residue (1.70 g) was purified by flash column chromatography (EtOAc) to give 1.64 g (79%) of a slightly yellowish oil: $[\alpha]_D^{20}$ = −17.4 (*c* 1.3, $CHCl_3$): 99% ee (chiral GC, t_R 9.51 min, flow 1.3 mL/min, *T* 180 °C); IR (neat): 3279 (NH), 1647 (C=O) cm^{-1}; ^1H NMR δ 1.23 (d, 3H, *J* = 6.9 Hz, CH_3CH), 1.85 (s, 3H, CH_3CO), 3.04 (dd, 1H, *J* = 13.5, 6.1 Hz, C*H*H), 3.12 (dd, 1H, *J* = 13.6, 5.1 Hz, CH*H*), 4.23 (dtq, seven lines, 1H, *J* = 6.9 Hz, C*H*), 5.51 (br s, 1H, N*H*), 7.13–7.22 (m, 1H, Ar), 7.24–7.33 (m, 2H, Ar), 7.37–7.43 (m, 2H, Ar); ^{13}C NMR δ 19.8 (1C), 23.5 (1C), 40.1 (1C), 45.2 (1C), 126.5 (1C), 129.3 (1C), 129.6 (1C), 136.4 (1C), 169.7 (1C); MS (70 eV) *m*/*z* (%) 209 (M^+, 8), 150 (100).

4.8.1. *N*-[1-Methyl-2-(phenylthio)ethyl]acetamide (23f)

Prepared as reported above for (*S*)-**23f** starting from **19**. Yield: 68%; white crystals: mp 91–92 °C (CH_2Cl_2/petroleum ether); IR (neat): 3258 (NH), 1634 (C=O) cm^{-1}; ^1H NMR δ 1.23 (d, 3H, *J* = 6.6 Hz, CH_3CH), 1.85 (s, 3H, CH_3CO), 3.04 (dd, 1H, *J* = 13.5, 6.1 Hz, C*H*H), 3.12 (dd, 1H, *J* = 13.5, 5.0 Hz, CH*H*), 4.23 (dtq, seven lines, 1H, *J* = 6.5 Hz, C*H*), 5.58 (br s, 1H, N*H*), 7.13–7.22 (m, 1H, Ar), 7.24–7.33 (m, 2H, Ar), 7.35–7.44 (m, 2H, Ar); ^{13}C NMR δ 19.8 (1C), 23.5 (1C), 40.0 (1C), 45.2 (1C), 126.5 (1C), 129.3 (1C), 129.6 (1C), 136.4 (1C), 169.7 (1C); MS (70 eV) *m*/*z* (%) 209 (M^+, 8), 150 (100). Anal. Calcd for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69. Found: C, 62.73; H, 7.13; N, 6.73.

4.8.2. (+)-(*R*)-*N*-[1-Methyl-2-(phenylthio)ethyl]acetamide [(+)-(*R*)-23f]

Prepared as reported above for (*S*)-**23f** starting from (*R*)-**19**. Yield: 66%; slightly yellowish oil; $[\alpha]_D^{20}$ = +12.1 (*c* 1.2, $CHCl_3$); 99% (chiral GC, t_R 9.82 min, flow 1.3 mL/min, *T* 180 °C). Spectroscopic and spectrometric data were in agreement with those found for the (*S*)-isomer.

4.8.3. *N*-{2-[(3-Methoxyphenyl)thio]-1-methylethyl}acetamide (23e)

Prepared as reported above for (*S*)-**23f** starting from **1e** and **19**. Yield: 11%; slightly yellowish oil; IR (neat): 3281 (NH), 1645 (C=O) cm^{-1}; ^1H NMR δ 1.24 (d, 3H, *J* = 6.6 Hz, CH_3CH), 1.87 (s, 3H, CH_3CO), 3.03 (dd, 1H, *J* = 13.6, 6.2 Hz, C*H*H), 3.14 (dd, 1H, *J* = 13.7, 5.0 Hz, CH*H*), 4.23 (tq, seven lines, 1H, *J* = 6.5 Hz, C*H*), 5.50 (br d, 1H, *J* = 4.1 Hz, N*H*), 6.65–6.78 (m, 1H, Ar), 6.92–7.02 (m, 2H, Ar), 7.19 (apparent t, 1H, Ar); ^{13}C NMR δ 19.8 (1C), 23.5 (1C), 39.7 (1C), 45.2 (1C), 55.5 (1C), 112.3 (1C), 114.6 (1C), 121.5 (1C), 130.1 (1C), 137.7 (1C), 160.2 (1C), 169.8 (1C); MS (70 eV) *m*/*z* (%) 239 (M^+, 12), 180 (100).

4.8.4. (+)-(*R*)-*N*-{2-[(3-Methoxyphenyl)thio]-1-methylethyl}acetamide [(+)-(*R*)-23e]

Prepared as reported above for (*S*)-**23f** starting from **1e** and (*R*)-**19**. Yield: 7%; slightly yellowish oil; $[\alpha]_D^{20}$ = +3.9 (*c* 1.4, $CHCl_3$); >99% (chiral GC, t_R 33.8 min, flow 1.4 mL/min, *T* 170 °C); IR (neat): 3281 (NH), 1650 (C=O) cm^{-1}; ^1H NMR δ 1.23 (d, 3H, *J* = 6.6 Hz, CH_3CH), 1.87 (s, 3H, CH_3CO), 3.01 (dd, 1H, *J* = 13.6, 6.2 Hz, C*H*H), 3.13 (dd, 1H, *J* = 13.6, 5.1 Hz, CH*H*), 3.79 (s, 3H, CH_3O), 4.23 (tq, seven lines, 1H, *J* = 6.5 Hz, C*H*), 5.66 (br d, 1H, *J* = 6.0 Hz, N*H*), 6.64–6.74 (m, 1H,

Ar), 6.93–7.0 (m, 2H, Ar), 7.18 (apparent t, 1H, Ar); ^{13}C NMR δ 19.7 (1C), 23.5 (1C), 39.7 (1C), 45.2 (1C), 55.6 (1C), 112.2 (1C), 114.6 (1C), 121.4 (1C), 130.1 (1C), 137.7 (1C), 160.2 (1C), 169.8 (1C); MS (70 eV) *m*/*z* (%) 239 (M^+, 14), 180 (100).

4.8.5. (−)-(*S*)-*N*-{2-[(3-Methoxyphenyl)thio]-1-methylethyl}acetamide [(−)-(*S*)-23e]

Prepared as reported above for (*S*)-**23f** starting from **1e** and (*S*)-**19**. Yield: 22%; slightly yellowish oil; $[\alpha]_D^{20} = -8.1$ (*c* 4.1, $CHCl_3$); >99% ee (chiral GC, t_R 32.7 min, flow 1.4 mL/min, *T* 170 °C). Spectroscopic and spectrometric data were in agreement with those found for the (*R*)-isomer.

4.9. General procedure for the preparation of phthalimidoalkyl aryl ethers (10a–d, 14c–e and 21c,d)

The method adopted for the synthesis of 2-(2-phenoxyethyl)-1*H*-isoindole-1,3(2*H*)-dione (**10c**) is described. A solution of diethyl azodicarboxylate (DEAD, 2.73 g, 15.7 mmol) in dry THF (60 mL) was added dropwise to a solution of **8** (2.0 g, 10.5 mmol), **1c** (1.48 g, 15.7 mmol) and triphenylphosphine (4.12 g, 15.7 mmol) in dry THF (40 mL) under N_2 atmosphere at room temperature. The reaction mixture was stirred overnight and then was concentrated in vacuo. Et_2O was added to the residue and the solid filtered off. The filtrate was evaporated and the residue was purified by flash chromatography (petroleum ether/EtOAc 8:2) to give 1.66 g of **10c** as a white solid (59%): mp 130–132 °C; IR (KBr): 1771, 1716 (C=O) cm^{-1}; ^{1}H NMR δ 4.11 (t, 2H, *J* = 5.8 Hz, CH_2N), 4.22 (t, 2H, *J* = 5.6 Hz, CH_2O), 6.85–6.97 (m, 3H, ArO), 7.18–7.30 (m, 2H, ArO), 7.67–7.78 (m, 2H, Ar), 7.82–7.90 (m, 2H, Ar); ^{13}C NMR δ 37.6 (1C), 64.8 (1C), 114.8 (2C), 121.3 (1C), 123.6 (2C), 129.7 (2C), 132.3 (2C), 134.3 (2C), 158.5 (1C), 168.4 (2C); MS (70 eV) *m*/*z* (%) 267 (M^+, 17), 174 (100). Anal. Calcd for $C_{16}H_{13}NO_3 \cdot 0.33H_2O$: C, 70.32; H, 5.04; N, 5.13. Found: C, 70.18; H, 4.85; N, 5.22.

4.9.1. 2-[2-(4-Methoxyphenoxy)ethyl]-1*H*-isoindole-1,3(2*H*)-dione (10a)

Prepared as reported above for **10c** starting from **1a**. Yield: 44%; white solid: mp 135–136 °C; IR (KBr): 1770, 1716 (C=O) cm^{-1}; ^{1}H NMR δ 3.73 (s, 3H, CH_3O), 4.05–4.12 (m, 2H, CH_2N), 4.14–4.22 (m, 2H, CH_2O), 6.74–6.86 (m, 4H, ArO), 7.67–7.76 (m, 2H, Ar), 7.82–7.90 (m, 2H, Ar); ^{13}C NMR δ 37.7 (1C), 55.9 (1C), 65.7 (1C), 114.9 (2C), 116.0 (2C), 123.5 (2C), 132.3 (2C), 134.2 (2C), 152.7 (1C), 154.4 (1C), 168.4 (2C); MS (70 eV) *m*/*z* (%) 297 (M^+, 12), 174 (100).

4.9.2. 2-[2-(2-Methoxyphenoxy)ethyl]-1*H*-isoindole-1,3(2*H*)-dione (10b)

Prepared as reported above for **10c** starting from **1b**. Yield: 40%; white solid: mp 107–109 °C; IR (KBr): 1772, 1713 (C=O) cm^{-1}; ^{1}H NMR δ 3.74 (s, 3H, CH_3O), 4.08–4.18 (m, 2H, CH_2N), 4.24–4.32 (m, 2H, CH_2O), 6.81–6.98 (m, 4H, ArO), 7.68–7.76 (m, 2H, Ar), 7.83–7.90 (m, 2H, Ar); ^{13}C NMR δ 37.5 (1C), 56.1 (1C), 66.4 (1C), 112.5 (1C), 115.2 (1C), 121.1 (1C), 122.3 (1C), 123.5 (2C), 132.4 (2C), 134.2 (2C), 148.1 (1C), 150.2 (1C), 168.4 (2C); MS (70 eV) *m*/*z* (%) 297 (M^+, 9), 174 (100).

4.9.3. 2-[2-(3-Methoxyphenoxy)ethyl]-1*H*-isoindole-1,3(2*H*)-dione (10d)

Prepared as reported above for **10c** starting from **1d**. Yield: 42%; white solid: mp 113–114 °C; IR (KBr): 1765, 1708 (C=O) cm^{-1}; ^{1}H NMR δ 3.75 (s, 3H, CH_3O), 4.05–4.14 (m, 2H, CH_2N), 4.18–4.25 (m, 2H, CH_2O), 6.40–6.52 (m, 3H, ArO), 7.13 (apparent t, 1H, ArO), 7.68–7.76 (m, 2H, Ar), 7.82–7.90 (m, 2H, Ar); ^{13}C NMR δ 37.5 (1C), 55.5 (1C), 65.0 (1C), 101.4 (1C), 106.9 (1C), 107.2 (1C), 123.6 (2C), 130.1 (1C), 132.3 (2C), 134.2 (2C), 159.8 (1C), 161.1 (1C), 168.3 (2C); MS (70 eV) *m*/*z* (%) 297 (M^+, 15), 174 (100).

4.9.4. 2-[2-Phenoxypropyl]-1*H*-isoindole-1,3(2*H*)-dione (14c)

Prepared as reported above for **10c** starting from phthalimide and **13c**. Yield: 22%; white crystals: mp 91–92 °C (EtOAc/hexane); IR (KBr): 1774, 1721 (C=O) cm^{-1}; ^{1}H NMR δ 1.37 (d, 3H, *J* = 6.0 Hz, CH_3), 3.77 (dd, 1H, *J* = 13.8, 5.2 Hz, CHH), 4.04 (dd, 1H, *J* = 13.8, 7.4 Hz, CH*H*), 4.72–4.86 (m, 1H, C*H*), 6.82–6.96 (m, 3H, ArO), 7.16–7.25 (m, 2H, ArO), 7.66–7.74 (m, 2H, Ar), 7.78–7.86 (m, 2H, Ar); ^{13}C NMR δ 18.2 (1C), 43.0 (1C), 71.1 (1C), 116.0 (2C), 121.2 (1C), 123.5 (2C), 129.7 (2C), 132.2 (2C), 134.2 (2C), 157.8 (1C), 168.5 (2C); MS (70 eV) *m*/*z* (%) 281 (M^+, 9), 188 (100).

4.9.5. 2-[2-(3-Methoxyphenoxy)propyl]-1*H*-isoindole-1,3(2*H*)-dione (14d)

Prepared as reported above for **10c** starting from phthalimide and **13d**. Yield: 91%; white solid: mp 96–97 °C; IR (KBr): 1774, 1713 (C=O) cm^{-1}; ^{1}H NMR δ 1.37 (d, *J* = 6.0 Hz, 3H, CH_3CH), 3.70–3.80 (m overlapping s at 3.74, 1H, C*H*H), 3.74 (s overlapping m at 3.70–3.80, 3H, CH_3O), 4.03 (dd, 1H, *J* = 13.8, 7.4 Hz, CH*H*), 4.70–4.83 (m, 1H, C*H*), 6.38–6.45 (m, 1H, ArO), 6.46–6.56 (m, 2H, ArO), 7.09 (apparent t, 1H, ArO), 7.64–7.74 (m, 2H, Ar), 7.78–7.86 (m, 2H, Ar); ^{13}C NMR δ 18.2 (1C), 43.0 (1C), 55.5 (1C), 71.1 (1C), 102.2 (1C), 107.1 (1C), 108.0 (1C), 123.5 (2C), 130.1 (1C), 132.1 (2C), 134.2 (2C), 160.0 (1C), 161.0 (1C), 168.5 (2C); MS (70 eV) *m*/*z* (%) 311 (M^+, 28), 188 (100).

4.9.6. (−)-(*R*)-2-[2-(3-Methoxyphenoxy)propyl]-1*H*-isoindole-1,3(2*H*)-dione [(−)-(*R*)-14d]

Prepared as reported above for **10c** starting from phthalimide and (*R*)-**13d**. Yield: 52%; white solid: mp 98–99 °C; $[\alpha]_D^{20} = -57$ (*c* 2, $CHCl_3$); IR (KBr): 1774, 1705 (C=O) cm^{-1}; ^{1}H NMR δ 1.42 (d, 3H, *J* = 6.0 Hz, CH_3CH), 3.76–3.85 (m overlapping s at 3.79, 1H, C*H*H), 3.79 (s overlapping m at 3.76–3.85, 3H, CH_3O), 4.08 (dd, 1H, *J* = 14.0, 7.4 Hz, CH*H*), 4.81 (apparent sextet, 1H, C*H*), 6.42–6.50 (m, 1H, ArO), 6.52–6.60 (m, 2H, ArO), 7.14 (apparent t, 1H, ArO), 7.70–7.78 (m, 2H, Ar), 7.82–7.92 (m, 2H, Ar); ^{13}C NMR δ 18.2 (1C), 42.9 (1C), 55.5 (1C), 71.1 (1C), 102.2 (1C), 107.1 (1C), 108.0 (1C), 123.5 (2C), 130.1 (1C), 132.1 (2C), 134.2 (2C), 159.0 (1C), 161.0 (1C), 168.5 (2C); MS (70 eV) *m*/*z* (%) 311 (M^+, 25), 188 (100).

4.9.7. (+)-(*S*)-2-[2-(3-Methoxyphenoxy)propyl]-1*H*-isoindole-1,3(2*H*)-dione [(+)-(*S*)-14d]

Prepared as reported above for **10c** starting from phthalimide and (*S*)-**13d**. Yield: 61%; white solid: mp 84–86 °C; $[\alpha]_D^{20} = +52$ (*c* 2, $CHCl_3$). Spectroscopic and spectrometric data were in agreement with those reported for the (*R*)-isomer.

4.9.8. 2-{2-[(3-Methoxyphenyl)thio]propyl}-1*H*-isoindole-1,3(2*H*)-dione (14e)

Prepared as reported above for **10c** starting from phthalimide and **13e**. Yield: 62%; white solid: mp 56–58 °C; IR (KBr): 1772, 1713 (C=O) cm^{-1}; ^{1}H NMR δ 1.33 (d, 3H, *J* = 6.6 Hz, CH_3CH), 3.70–3.96 (m overlapping s at 3.76, 2H, CH_2), 3.76 (s overlapping m at 3.70–3.80, 3H, CH_3O), 4.90–5.05 (m, 1H, C*H*), 6.52–6.60 (m, 1H, ArO), 6.92–7.00 (m, 2H, ArO), 7.02–7.10 (m, 1H, ArO), 7.63–7.71 (m, 2H, Ar), 7.74–7.82 (m, 2H, Ar); ^{13}C NMR δ 22.2 (1C), 40.7 (1C), 44.3 (1C), 55.5 (1C), 113.0 (1C), 116.2 (1C), 123.4 (1C), 123.6 (1C), 123.8 (1C), 129.9 (1C), 132.0 (2C), 134.1 (2C), 135.5 (1C), 159.8 (1C), 168.5 (2C); MS (70 eV) *m*/*z* (%) 327 (M^+, 100).

4.9.9. (+)-(*R*)-2-{2-[(3-Methoxyphenyl)thio]propyl}-1*H*-isoindole-1,3(2*H*)-dione [(+)-(*R*)-14e]

Prepared as reported above for **10c** starting from phthalimide and (*R*)-**13e**. Yield: 85%; slightly yellowish solid: mp 66–68 °C (EtOAc/petroleum ether); $[\alpha]_D^{20} = +62$ (*c* 2, $CHCl_3$); MS (70 eV) *m*/*z* (%) 327 (M^+, 100).

4.9.10. (−)-(*S*)-2-{2-[(3-Methoxyphenyl)thio]propyl}-1*H*-isoindole-1,3(2*H*)-dione [(−)-(*S*)-14e]

Prepared as reported above for **10c** starting from phthalimide and (*S*)-**13e**. Yield: 52%; white solid: mp 62–64 °C (EtOAc/hexane); $[\alpha]_D^{20} = -65$ (*c* 2.4, $CHCl_3$); IR (KBr): 1773, 1714 (C=O) cm^{-1}; ^1H NMR δ 1.34 (d, *J* = 6.6 Hz, 3H, CH_3CH), 3.72–3.95 (m overlapping s at 3.77, 3H, $CH + CH_2$), 3.77 (s overlapping m at 3.72–3.95, 3H, CH_3O), 6.54–6.60 (m, 1H, ArO), 6.95–7.01 (m, 2H, ArO), 7.02–7.11 (m, 1H, ArO), 7.65–7.72 (m, 2H, Ar), 7.73–7.80 (m, 2H, Ar); ^{13}C NMR δ 18.7 (1C), 40.7 (1C), 44.3 (1C), 55.4 (1C), 113.0 (1C), 116.2 (1C), 123.4 (2C), 123.6 (1C), 129.9 (1C), 132.0 (2C), 134.1 (2C), 135.5 (1C), 159.8 (1C), 168.5 (2C).

4.9.11. 2-(1-Methyl-2-phenoxyethyl)-1*H*-isoindole-1,3(2*H*)-dione (21c)

Prepared as reported above for **10c** starting from **1c** and (*RS*)-**20** using diisopropyl azodicarboxylate (DIAD) instead of DEAD. Yield: 44%; slightly yellowish oil; IR (neat): 1775, 1705 (C=O) cm^{-1}; ^1H NMR δ 1.56 (d, 3H, *J* = 7.1 Hz, CH_3CH), 4.16 (dd, 1H, *J* = 9.5, 5.6 Hz, CHH), 4.53 (apparent t, 1H, CHH), 4.73–4.88 (m, 1H, CH), 6.80–6.94 (m, 3H, ArO), 7.16–7.28 (m, 2H, ArO), 7.65–7.74 (m, 2H, Ar), 7.76–7.87 (m, 2H, Ar); ^{13}C NMR δ 15.4 (1C), 46.7 (1C), 68.4 (1C), 115.0 (2C), 121.3 (1C), 123.4 (2C), 129.7 (2C), 129.8 (2C), 134.2 (2C), 158.6 (1C), 168.6 (2C); MS (70 eV) *m*/*z* (%) 281 (M^+, 13), 188 (100).

4.9.12. 2-[2-(3-Methoxyphenoxy)-1-methylethyl]-1*H*-isoindole-1,3(2*H*)-dione (21d)

Prepared as reported above for **10c** starting from **1d** and **20**. Yield: 47%; slightly yellowish oil; IR (neat): 1774, 1709 (C=O) cm^{-1}; ^1H NMR δ 1.55 (d, 3H, *J* = 7.1 Hz, CH_3CH), 3.73 (s, 3H, CH_3O), 4.07–4.19 (m, 1H, CHH), 4.51 (apparent t, 1H, CHH), 4.73–4.86 (m, 1H, CH), 6.36–6.51 (m, 3H, ArO), 7.12 (apparent t, 1H, ArO), 7.66–7.75 (m, 2H, Ar), 7.78–7.86 (m, 2H, Ar); ^{13}C NMR δ 15.4 (1C), 46.7 (1C), 55.5 (1C), 68.5 (1C), 101.4 (1C), 107.0 (1C), 107.1 (1C), 123.4 (2C), 130.0 (1C), 132.2 (2C), 134.2 (2C), 159.8 (1C), 161.0 (1C), 168.6 (2C); MS (70 eV) *m*/*z* (%) 311 (M^+, 25), 188 (100).

4.9.13. (+)-(*R*)-2-[2-(3-Methoxyphenoxy)-1-methylethyl]-1*H*-isoindole-1,3(2*H*)-dione [(+)-(*R*)-21d]

Prepared as reported above for **21c** starting from **1d** and (*R*)-**20**. Yield: 64%; slightly yellowish oil; $[\alpha]_D^{20} = +14.9$ (*c* 2, $CHCl_3$); IR (neat): 1774, 1713 (C=O) cm^{-1}; ^1H NMR δ 1.55 (d, 3H, *J* = 6.9 Hz, CH_3CH), 3.74 (s, 3H, CH_3O), 4.07–4.20 (m, 1H, CHH), 4.51 (apparent t, 1H, CHH), 4.72–4.86 (m, 1H, CH), 6.37–6.50 (m, 3H, ArO), 7.11 (apparent t, 1H, ArO), 7.66–7.75 (m, 2H, Ar), 7.78–7.87 (m, 2H, Ar); ^{13}C NMR δ 15.4 (1C), 46.7 (1C), 55.5 (1C), 68.5 (1C), 101.4 (1C), 107.0 (1C), 107.1 (1C), 123.4 (1C), 123.6 (1C), 130.0 (1C), 132.2 (2C), 134.2 (1C), 134.3 (1C), 159.8 (1C), 161.0 (1C), 168.6 (2C); MS (70 eV) *m*/*z* (%) 311 (M^+, 18), 188 (100).

4.9.14. (−)-(*S*)-2-[2-(3-Methoxyphenoxy)-1-methylethyl]-1*H*-isoindole-1,3(2*H*)-dione [(−)-(*S*)-21d]

Prepared as reported above for **21c** starting from **1d** and (*S*)-**20**. Yield: 90%; slightly yellowish oil; $[\alpha]_D^{20} = -16.7$ (*c* 4, $CHCl_3$). Spectroscopic and spectrometric data were in agreement with those reported for the (*R*)-isomer.

4.10. General procedure for the preparation of phthalimidoalkyl aryl thioethers (10e–h)

The method adopted for the synthesis of 2-[2-(phenylthio)ethyl]-1*H*-isoindole-1,3(2*H*)-dione (**10f**) is described. K_2CO_3 (0.54 g, 3.9 mmol) was added to a solution of 2-(2-bromoethyl)-1*H*-isoindole-1,3(2*H*)-dione (**9**) (1.0 g, 3.9 mmol) in dry DMF (80 mL) under N_2 atmosphere. The reaction mixture was heated at 100 °C and then a solution of benzenethiol (**1f**) (0.48 g, 4.3 mmol) in 40 mL of dry DMF was added dropwise during a period of 3 h. The mixture was stirred at this temperature for 17 h. After evaporation of the solvent, the residue was taken up with EtOAc, washed with 0.5 N NaOH, then with a saturated solution of NaCl. The organic phase was dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by crystallization (EtOAc/hexane) to give 0.97 g (87%) of **10f** as a slightly yellowish solid: mp 55–56 °C; IR (KBr): 1769, 1713 (C=O) cm^{-1}; ^1H NMR δ 3.18–3.28 (m, 2H, CH_2N), 3.88–3.98 (t, 2H, *J* = 7.0 Hz, CH_2O), 7.12 (tt, *J* = 7.4, 1.6 Hz, 1H, ArO), 7.20–7.28 (m, 2H, ArO), 7.38–7.44 (m, 2H, ArO), 7.66–7.74 (m, 2H, Ar), 7.76–7.84 (m, 2H, Ar); ^{13}C NMR δ 31.9 (1C), 37.8 (1C), 123.5 (2C), 126.6 (1C), 129.2 (2C), 130.0 (2C), 132.2 (2C), 134.2 (2C), 135.1 (1C), 168.3 (2C); MS (70 eV) *m*/*z* (%) 283 (M^+, 42), 136 (100).

4.10.1. 2-{2-[(3-Methoxyphenyl)thio]ethyl}-1*H*-isoindole-1,3(2*H*)-dione (10e)

Prepared as reported above for **10f** starting from **1e**. Yield: 76%; slightly yellowish solid: mp 95–96 °C; IR (KBr): 1763, 1710 (C=O) cm^{-1}; ^1H NMR δ 3.23 (t, 2H, *J* = 7.0 Hz, CH_2S), 3.80 (s, 3H, CH_3), 3.95 (t, 2H, *J* = 7.0 Hz, CH_2N), 6.59–6.67 (m, 1H, ArO), 6.93–7.01 (m, 2H, ArO), 7.13 (apparent t, 1H, ArO), 7.66–7.74 (m, 2H, Ar), 7.76–7.85 (m, 2H, Ar); ^{13}C NMR δ 31.6 (1C), 37.9 (1C), 55.5 (1C), 112.7 (1C), 114.7 (1C), 121.9 (1C), 123.5 (2C), 130.1 (1C), 132.2 (2C), 134.2 (2C), 136.4 (1C), 160.1 (1C), 168.3 (2C); MS (70 eV) *m*/*z* (%) 313 (M^+, 94), 166 (100).

4.10.2. 2-{2-[(4-Methoxyphenyl)thio]ethyl}-1*H*-isoindole-1,3(2*H*)-dione (10g)

Prepared as reported above for **10f** starting from **1g**. Yield: 63%; slightly yellowish solid: mp 98–100 °C; IR (KBr): 1768, 1716 (C=O) cm^{-1}; ^1H NMR δ 3.13 (t, 2H, *J* = 6.7 Hz, CH_2S), 3.74 (s, 3H, CH_3), 3.88 (t, 2H, *J* = 6.9 Hz, CH_2N), 6.74–6.82 (m, 2H, ArO), 7.36–7.44 (m, 2H, Ar), 7.65–7.74 (m, 2H, Ar), 7.75–7.85 (m, 2H, Ar); ^{13}C NMR δ 33.8 (1C), 38.0 (1C), 55.5 (1C), 114.9 (2C), 123.4 (2C), 125.5 (1C), 132.3 (2C), 133.7 (2C), 134.1 (2C), 159.4 (1C), 168.3 (2C); MS (70 eV) *m*/*z* (%) 313 (M^+, 97), 166 (100).

4.10.3. 2-{2-[(2-Methoxyphenyl)thio]ethyl}-1*H*-isoindole-1,3(2*H*)-dione (10h)

Prepared as reported above for **10f** starting from **1h**. Yield: 47%; slightly yellowish solid: mp 91–92 °C; IR (KBr): 1771, 1705 (C=O) cm^{-1}; ^1H NMR δ 3.17–3.25 (m, 2H, CH_2S), 3.85–3.95 (m overlapping s at 3.87, 2H, CH_2N), 3.87 (s, overlapping m at 3.85–3.95, 3H, CH_3), 6.80 (dd, 1H, *J* = 8.2, 1.1 Hz, Ar), 6.87 (dt, 1H, *J* = 7.7, 1.3 Hz, Ar), 7.14 (ddd, 1H, *J* = 8.2, 7.4, 1.6 Hz, Ar), 7.43 (dd, 1H, *J* = 7.7, 1.6 Hz, Ar), 7.65–7.73 (m, 2H, Ar), 7.75–7.84 (m, 2H, Ar); ^{13}C NMR δ 30.2 (1C), 37.9 (1C), 55.9 (1C), 111.0 (1C), 121.3 (1C), 122.7 (1C), 123.4 (2C), 128.2 (1C), 131.4 (1C), 132.3 (2C), 134.1 (2C), 158.2 (1C), 168.2 (2C); MS (70 eV) *m*/*z* (%) 313 (M^+, 66), 166 (100).

4.11. General procedure for the preparation of cyclopropanecarboxamides (15d,e)

The method adopted for the synthesis of *N*-[2-(3-methoxyphenoxy)propyl]cyclopropane carboxamide (**15d**) is described. To a stirring solution of **6d** (0.50 g, 2.76 mmol) and Et_3N (0.11 mL, 0.83 mmol) in dry toluene (5 mL) under N_2 atmosphere, a solution of cyclopropanecarbonyl chloride (0.29 g, 2.76 mmol) was added dropwise. The reaction mixture was refluxed for 3 h, then the residue was taken up with EtOAc and washed twice with 2 N NaOH, twice with 2 N HCl and twice with a saturated aqueous NaCl solution. The combined organic layers were dried (Na_2SO_4) and concentrated to give a yellow oil (78%) which was purified by

column chromatography on silica gel (EtOAc) to give 0.60 g (87%) of **15d** as a slightly yellowish oil: IR (neat): 3299 (NH), 1646, 1602 (C=O) cm^{-1}; ^1H NMR δ 0.65–0.78 (m, 2H, C*H*HC*H*H), 0.90–1.02 (m, 2H, CH*H*CH*H*), 1.22–1.38 (m overlapping d at 1.28, 1H, C*H*CO), 1.28 (d overlapping m at 1.22–1.38, 3H, J = 6.3 Hz, CH_3CH), 3.24–3.36 (m, 1H, C*H*HN), 3.68–3.82 (m overlapping s at 3.79, 1H, CH*H*N), 3.79 (s overlapping m at 3.68–3.82, 3H, CH_3O), 4.43–4.55 (m, 1H, C*H*CH$_3$), 6.03 (br s, 1H, N*H*), 6.46–6.56 (m, 3H, Ar), 7.18 (apparent t, 1H, Ar); ^{13}C NMR δ 7.4 (2C), 15.0 (1C), 17.4 (1C), 44.8 (1C), 55.5 (1C), 73.3 (1C), 102.7 (1C), 107.0 (1C), 108.2 (1C), 130.3 (1C), 159.1 (1C), 161.2 (1C), 173.9 (1C); MS (70 eV) m/z (%) 249 (M^+, 6), 126 (100).

4.11.1. (−)-(*R*)-*N*-[2-(3-Methoxyphenoxy)propyl]cyclopropanecarboxamide [(−)-(*R*)-15d]

Prepared as reported above for **15d** starting from (*R*)-**6d**. Yield: 82%; slightly yellowish oil; $[\alpha]_D^{20}$ = −80 (c 2, $CHCl_3$), 95% ee (chiral HPLC, Chiralpak IA, t_R 31.3, flow 0.5 mL/min, λ 230 nm, eluent 95:5 hexane/EtOH); IR (neat): 3301 (NH), 1646, 1602 (C=O) cm^{-1}; ^1H NMR δ 0.65–0.77 (m, 2H, C*H*HC*H*H), 0.90–1.02 (m, 2H, CH*H*CH*H*), 1.25–1.40 (m overlapping d at 1.27, 1H, C*H*CO), 1.27 (d overlapping m at 1.25–1.40, 3H, J = 6.3 Hz, CH_3CH), 3.30 (ddd, 1H, J = 14.0, 7.5, 4.8 Hz, C*H*HN), 3.72 (ddd, 1H, J = 13.9, 7.1, 3.5 Hz, CH*H*N), 3.78 (s, 3H, CH_3O), 4.43–4.53 (m, 1H, C*H*CH$_3$), 6.06 (br s, 1H, N*H*), 6.46–6.55 (m, 3H, Ar), 7.18 (apparent t, 1H, Ar); ^{13}C NMR δ 7.5 (2C), 15.0 (1C), 17.4 (1C), 44.7 (1C), 55.5 (1C), 73.2 (1C), 102.6 (1C), 106.9 (1C), 108.2 (1C), 130.3 (1C), 159.0 (1C), 161.2 (1C), 174.0 (1C); MS (70 eV) m/z (%) 249 (M^+, 6), 126 (100).

4.11.2. (+)-(*S*)-*N*-[2-(3-Methoxyphenoxy)propyl]cyclopropanecarboxamide [(+)-(*S*)-15d]

Prepared as reported above for **15d** starting from (*S*)-**6d**. Yield: 58%; slightly yellowish oil; $[\alpha]_D^{20}$ = +88 (c 2, $CHCl_3$), 95% ee (chiral HPLC, Chiralpak IA, t_R 28.0, flow 0.5 mL/min, λ 230 nm, eluent 95:5 hexane/EtOH). Spectroscopic and spectrometric data were in agreement with those reported for the (*R*)-isomer.

4.11.3. *N*-{2-[(3-Methoxyphenyl)thio]propyl}cyclopropanecarboxamide (15e)

Prepared as reported above for **15d** starting from **6e**. Yield: 80%; slightly yellowish oil; IR (neat): 3298 (NH), 1646 (C=O) cm^{-1}; ^1H NMR δ 0.65–0.80 (m, 2H, C*H*HC*H*H), 0.90–1.10 (m, 2H, CH*H*CH*H*), 1.22–1.35 (m overlapping d at 1.29, 1H, C*H*CO), 1.29 (d overlapping m at 1.22–1.35, 3H, J = 6.9 Hz, CH_3CH), 3.25–3.56 (m, 3H, CH_2CH), 3.80 (s, 3H, CH_3O), 6.00 (br s, 1H, N*H*), 6.75–6.85 (m, 1H, Ar), 6.95–7.05 (m, 2H, Ar), 7.22 (apparent t, 1H, Ar); ^{13}C NMR δ 7.4 (2C), 15.0 (1C), 19.0 (1C), 43.7 (1C), 44.8 (1C), 55.5 (1C), 113.3 (1C), 117.6 (1C), 124.4 (1C), 130.1 (1C), 135.3 (1C), 160.1 (1C), 173.8 (1C); MS (70 eV) m/z (%) 265 (M^+, 17), 180 (100).

4.11.4. (−)-(*R*)-*N*-{2-[(3-Methoxyphenyl)thio]propyl}cyclopropanecarboxamide [(−)-(*R*)-15e]

Prepared as reported above for **15d** starting from (*R*)-**6e**. Yield: 90%; slightly yellowish oil; $[\alpha]_D^{20}$ = −11.2 (c 0.5, $CHCl_3$); 97% ee (chiral HPLC, Chiralpak IA, t_R 21.5, flow 0.4 mL/min, λ 210 nm, eluent 50:50 CH_3CN/H_2O); IR (neat): 3299 (NH), 1645 (C=O) cm^{-1}; ^1H NMR δ 0.63–0.80 (m, 2H, C*H*HC*H*H), 0.85–1.05 (m, 2H, CH*H*CH*H*), 1.20–1.35 (m overlapping d at 1.29, 1H, C*H*CO), 1.29 (d overlapping m at 1.22–1.35, 3H, J = 6.9 Hz, CH_3CH), 3.20–3.58 (m, 3H, CH_2CH), 3.80 (s, 3H, CH_3O), 5.99 (br s, 1H, N*H*), 6.79 (dd, 1H, J = 8.3, 2.2 Hz, Ar), 6.97 (d, 1H, J = 2.2 Hz, Ar), 7.00 (d, 1H, J = 8.0 Hz, Ar), 7.22 (apparent t, 1H, Ar); ^{13}C NMR δ 7.4 (2C), 14.9 (1C), 19.0 (1C), 43.7 (1C), 44.8 (1C), 55.5 (1C), 113.3 (1C), 117.6 (1C), 124.4 (1C), 130.1 (1C), 135.3 (1C), 160.1 (1C), 173.8 (1C); MS (70 eV) m/z (%) 265 (M^+, 17), 180 (100).

4.11.5. (+)-(*S*)-*N*-{2-[(3-Methoxyphenyl)thio]propyl}cyclopropanecarboxamide [(+)-(*S*)-15e]

Prepared as reported above for **14d** starting from (*S*)-**6e**. Yield: 95%; slightly yellowish oil; $[\alpha]_D^{20}$ = +16.0 (c 0.5, $CHCl_3$), 96% ee (chiral HPLC, Chiralpak IA, t_R 20.1, flow 0.4 mL/min, λ 210 nm, eluent 50:50 CH_3CN/H_2O). Spectroscopic and spectrometric data were in agreement with those reported for the (*R*)-isomer.

4.11.6. *N*-[2-(3-Methoxyphenoxy)propyl]butanamide (16d)

Prepared as reported above for **7a** starting from butyric anhydride and **6d**. There was a little difference in the procedure. In fact, butyric acid in excess was taken away by extracting with 2 N NaOH aqueous solution. Yield: 83%; slightly yellowish oil; IR (neat): 3301 (NH), 1649 (C=O) cm^{-1}; ^1H NMR δ 0.91 (t, 3H, J = 7.4 Hz, CH_3CH$_2$), 1.27 (d, 3H, J = 6.3 Hz, CH_3CH), 1.63 (sextet, 2H, J = 7.4 Hz, CH_2CH$_3$), 2.14 (t, 2H, J = 7.4 Hz, CH_2CO), 3.21–3.35 (m, 1H, C*H*HNH), 3.63–3.75 (m overlapping s at 3.78, 1H, CH*H*NH), 3.78 (s overlapping m at 3.63–3.75, 3H, CH_3O), 4.42–4.54 (m, 1H, C*H*), 5.85 (br s, 1H, N*H*), 6.45–6.58 (m, 3H, Ar), 7.17 (apparent t, 1H, Ar); ^{13}C NMR δ 13.9 (1C), 17.4 (1C), 19.3 (1C), 38.9 (1C), 44.5 (1C), 55.5 (1C), 73.2 (1C), 102.6 (1C), 106.9 (1C), 108.2 (1C), 130.3 (1C), 159.0 (1C), 161.2 (1C), 173.4 (1C); MS (70 eV) m/z (%) 251 (M^+, 5), 128 (100).

4.11.7. (−)-(*R*)-*N*-[2-(3-Methoxyphenoxy)propyl]butanamide [(−)-(*R*)-16d]

Prepared as reported above for **16d** starting from butyric anhydride and (*R*)-**6d**. Yield: 80%; slightly yellowish oil; $[\alpha]_D^{20}$ = −71 (c 1, $CHCl_3$); 96% ee (chiral HPLC, Chiralpak IA, t_R 59.9, flow 0.4 mL/min, λ 210 nm, eluent 30:70 CH_3CN/H_2O); IR (neat): 3318 (NH), 1602 (C=O) cm^{-1}; ^1H NMR δ 0.92 (t, 3H, J = 7.3 Hz, CH_3CH$_2$), 1.27 (d, 3H, J = 6.0 Hz, CH_3CH), 1.64 (sextet, 2H, J = 7.4 Hz, CH_2CH$_3$), 2.15 (t, 2H, J = 7.5 Hz, CH_2CO), 3.29 (ddd, 1H, J = 13.9, 7.4, 5.1 Hz, C*H*HNH), 3.69 (ddd, 1H, J = 14.0, 7.1, 3.5 Hz, CH*H*NH), 3.78 (s, 3H, CH_3O), 4.42–4.55 (m, 1H, C*H*), 5.85 (br s, 1H, N*H*), 6.43–6.60 (m, 3H, Ar), 7.17 (apparent t, 1H, Ar); ^{13}C NMR δ 14.0 (1C), 17.4 (1C), 19.3 (1C), 38.9 (1C), 44.5 (1C), 55.5 (1C), 73.1 (1C), 102.6 (1C), 106.9 (1C), 108.1 (1C), 130.3 (1C), 159.0 (1C), 161.2 (1C), 173.4 (1C); MS (70 eV) m/z (%) 251 (M^+, 5), 128 (100).

4.11.8. (+)-(*S*)-*N*-[2-(3-Methoxyphenoxy)propyl]butanamide [(+)-(*S*)-16d]

Prepared as reported above for **16d** starting from butyric anhydride and (*S*)-**6d**. Yield: 69%; slightly yellowish oil; $[\alpha]_D^{20}$ = +54 (c 2, $CHCl_3$); 94% ee (chiral HPLC, Chiralpak IA, t_R 57.86, flow 0.4 mL/min, λ 210 nm, eluent 30:70 CH_3CN/H_2O). Spectroscopic and spectrometric data were in agreement with those reported for the (*R*)-isomer.

4.11.9. *N*-{2-[(3-Methoxyphenyl)thio]propyl}butanamide (16e)

Prepared as reported above for **16d** starting from butyric anhydride and **6e**. Yield: 75%; slightly yellowish oil; IR (neat): 3294 (NH), 1646 (C=O) cm^{-1}; ^1H NMR δ 0.93 (t, 3H, J = 7.4 Hz, CH_3CH$_2$), 1.29 (d, 3H, J = 6.6 Hz, CH_3CH), 1.63 (sextet, 2H, J = 7.4 Hz, CH_2CH$_3$), 2.12 (t, 2H, J = 7.4 Hz, CH_2CO), 3.24–3.52 (m, 3H, CH_2CH), 3.80 (s, 3H, CH_3O), 5.83 (br s, 1H, N*H*), 6.76–6.84 (m, 1H, Ar), 6.93–7.04 (m, 2H, Ar), 7.22 (apparent t, 1H, Ar); ^{13}C NMR δ 14.0 (1C), 19.0 (1C), 19.3 (1C), 38.9 (1C), 43.5 (1C), 44.4 (1C), 55.5 (1C), 113.2 (1C), 117.6 (1C), 124.3 (1C), 130.1 (1C), 135.2 (1C), 160.1 (1C), 173.3 (1C); MS (70 eV) m/z (%) 267 (M^+, 11), 180 (100).

4.11.10. (−)-(*R*)-*N*-{2-[(3-Methoxyphenyl)thio]propyl}butanamide [(−)-(*R*)-16e]

Prepared as reported above for **16d** starting from butyric anhydride and (*R*)-**6e**. Yield: 98%; slightly yellowish oil; $[\alpha]_D^{20}$ = −16.2 (c 0.5, $CHCl_3$); 97% ee (chiral HPLC, Chiralpak IA, t_R 133.6, flow 0.4 mL/

min, λ 210 nm, eluent 30:70 CH_3CN/H_2O); IR (neat): 3296 (NH), 1646 (C=O) cm^{-1}; ^1H NMR δ 0.93 (t, 3H, J = 7.4 Hz, CH_3CH_2), 1.29 (d, 3H, J = 6.6 Hz, CH_3CH), 1.63 (sextet, 2H, J = 7.4 Hz, CH_2CH_3), 2.12 (t, 2H, J = 7.4 Hz, CH_2CO), 3.22–3.52 (m, 3H, CH_2CH), 3.80 (s, 3H, CH_3O), 5.83 (br s, 1H, NH), 6.75–6.84 (m, 1H, Ar), 6.92–7.04 (m, 2H, Ar), 7.22 (apparent t, 1H, Ar); ^{13}C NMR δ 14.0 (1C), 19.0 (1C), 19.3 (1C), 38.9 (1C), 43.6 (1C), 44.5 (1C), 55.5 (1C), 113.3 (1C), 117.6 (1C), 124.4 (1C), 130.1 (1C), 135.3 (1C), 160.1 (1C), 173.3 (1C); MS (70 eV) m/z (%) 267 (M^+, 13), 180 (100).

4.11.11. (+)-(*S*)-*N*-{2-[(3-Methoxyphenyl)thio]propyl}butanamide [(+)-(*S*)-16e]

Prepared as reported above for **16d** starting from butyric anhydride and (*S*)-**6e**. Yield: 98%; slightly yellowish oil; $[\alpha]_D^{20}$ = +16.9 (c 0.5, $CHCl_3$); 96% ee (chiral HPLC, Chiralpak IA, t_R 120.8, flow 0.4 mL/min, λ 210 nm, eluent 30:70 CH_3CN/H_2O). Spectroscopic and spectrometric data were in agreement with those reported for the (*R*)-isomer.

4.11.12. (+)-(*R*)-Methyl 2-(3-methoxyphenoxy)propanoate [(+)-(*R*)-18d]

Prepared as reported above for **10c** starting from **1d** and (*S*)-**17**. Yield: 80%; slightly yellowish oil; $[\alpha]_D^{20}$ = +22.3 (c 2, $CHCl_3$); IR (neat): 1759, 1738 (C=O) cm^{-1}; ^1H NMR δ 1.60 (d, 3H, J = 6.9 Hz, CH_3CH), 3.74 (s, 3H, CH_3OCO), 3.76 (s, 3H, CH_3O), 4.75 (q, 1H, J = 6.8 Hz, CH), 6.39–6.48 (m, 2H, Ar), 6.49–6.56 (m, 1H, Ar), 7.15 (apparent t, 1H, Ar); ^{13}C NMR δ 18.8 (1C), 52.5 (1C), 55.5 (1C), 72.7 (1C), 101.9 (1C), 107.0 (1C), 107.6 (1C), 130.2 (1C), 159.0 (1C), 161.1 (1C), 172.9 (1C); MS (70 eV) m/z (%) 210 (M^+, 58), 151 (100).

4.11.13. (−)-(*S*)-Methyl 2-(3-methoxyphenoxy)propanoate [(−)-(*S*)-18d]

Prepared as reported above for **10c** starting from **1d** and (*R*)-**17**. Yield: 86%; slightly yellowish oil; $[\alpha]_D^{20}$ = −19.9 (c 2, $CHCl_3$). Spectroscopic and spectrometric data were in agreement with those reported for the (*R*)-isomer.

4.11.14. (+)-(*R*)-Methyl 2-[(3-methoxyphenyl)thio]propanoate [(+)-(*R*)-18e]

Prepared as reported above for **10c** starting from **1e** and (*S*)-**17**. Yield: 42%; slightly yellowish oil; $[\alpha]_D^{20}$ = +132 (c 1, $CHCl_3$); IR (neat): 1737 (C=O) cm^{-1}; ^1H NMR δ 1.49 (d, 3H, J = 7.1 Hz, CH_3CH), 3.69 (s, 3H, CH_3OCO), 3.80 (s overlapping m at 3.75–3.85, 3H, CH_3O), 3.75–3.85 (m overlapping s at 3.80, 1H, CH), 6.78–6.86 (m, 1H, Ar), 6.95–7.05 (m, 2H, Ar), 7.22 (apparent t, 1H, Ar); ^{13}C NMR δ 17.8 (1C), 45.3 (1C), 52.6 (1C), 55.5 (1C), 114.1 (1C), 117.9 (1C), 125.0 (1C), 130.0 (1C), 134.7 (1C), 159.9 (1C), 173.4 (1C); MS (70 eV) m/z (%) 226 (M^+, 80), 167 (100).

4.11.15. (−)-(*S*)-Methyl 2-[(3-methoxyphenyl)thio]propanoate [(−)-(*S*)-18e]

Prepared as reported above for **10c** starting from **1e** and (*R*)-**17**. Yield: 30%; slightly yellowish oil; $[\alpha]_D^{20}$ = −104 (c 1, $CHCl_3$). Spectroscopic and spectrometric data were in agreement with those reported for the (*R*)-isomer.

4.12. MLT receptor binding assay

Binding affinities of compounds were determined using 2-[^{125}I]iodomelatonin as the labelled ligand in competition experiments on cloned human MT_1 and MT_2 receptors expressed in NIH3T3 rat fibroblast cells. The characterization of NIH3T3-MT_1 and -MT_2 cells was already described in detail.[53,54] Membranes were incubated for 90 min at 37 °C in binding buffer (Tris/HCl 50 mM, pH 7.4). The final membrane concentration was 5–10 μg of protein per tube. The membrane protein level was determined in accordance with a previously reported method.[55] 2-[^{125}I]Iodomelatonin (100 pM) and different concentrations of MLT and/or the new compounds were incubated with the receptor preparation for 90 min at 37 °C. IC_{50} values were determined by nonlinear fitting strategies with the program PRISM (GraphPad SoftWare Inc., San Diego, CA). The pK_i values were calculated from the IC_{50} values in accordance with the Cheng–Prusoff equation.[56] The pK_i values are the mean of at least three independent determinations performed in duplicate. To define the functional activity of the new compounds at MT_1 and MT_2 receptor subtypes, [^{35}S]GTPγS binding assays in NIH3T3 cells expressing human-cloned MT_1 or MT_2 receptors were performed. The amount of bound [^{35}S]GTPγS is proportional to the level of the analogue-induced G-protein activation and is related to the intrinsic activity of the compound under study. The detailed description and validation of this method were reported elsewhere,[53,57] membranes (15–25 μg of protein, final incubation volume 100 μL) were incubated at 30 °C for 30 min in the presence and in the absence of MLT analogues in an assay buffer consisting of [^{35}S]GTPγS (0.3–0.5 nM), GDP (50 μM), NaCl (100 mM), and $MgCl_2$ (3 mM). Nonspecific binding was defined using [^{35}S]GTPγS (10 μM). In cell lines expressing human MT_1 or MT_2 receptors, MLT produced a concentration-dependent stimulation of basal [^{35}S]GTPγS binding with a maximal stimulation, above basal levels, of 370% and 250% in MT_1 and MT_2 receptors, respectively. Basal stimulation is the amount of [^{35}S]GTPγS specifically bound in the absence of compounds, and it was taken as 100%. The maximal G-protein activation was measured in each experiment by using MLT (100 nM). Compounds were added at three different concentrations (one concentration was equivalent to 100 nM MLT, a second one was 10 times smaller, and a third one was 10 times larger), and the percent stimulation above basal was determined. The equivalent concentration was estimated on the basis of the ratio of the affinity of the test compound over that of MLT. It was assumed that at the equivalent concentration the test compound occupies the same number of receptors as 100 nM MLT. All of the measurements were performed in triplicate. The relative intrinsic activity (IAr) values were obtained by dividing the maximum ligand-induced stimulation of [^{35}S]GTPγS binding by that of MLT, as measured in the same experiment. By convention, the natural ligand MLT has an efficacy (E_{max}) of 100%. Full agonists stimulate [^{35}S]GTPγS binding with a maximum efficacy close to that of MLT itself. If E_{max} is between 30% and 70% that of MLT (0.3 < IAr < 0.7), the compound is considered a partial agonist, whereas if E_{max} is lower than 30% (IAr <0.3), the compound is considered an antagonist.[58]

Acknowledgements

This work was accomplished thanks to the financial support of the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR). The authors thank Professors Franco Fraschini, Nicola Tangari, and Vincenzo Tortorella for their valuable suggestions and helpful inputs in the early stages of the project.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2010.06.100. These data include MOL files and InChiKeys of the most important compounds described in this article.

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