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Short communication

Synthesis, pharmacology and molecular modeling of *N*-substituted 2-phenyl-indoles and benzimidazoles as potent $GABA_A$ agonists

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Abstract

Among the known non-benzodiazepine hypnotic drugs, Zolpidem (**1a**), Indiplon (**2a**) and Zaleplon (**2b**) have shown high affinity and selectivity for the α_1 subunit of the GABA-A receptor. Our group has performed pharmacophoric and ADMET-prediction studies to evaluate a virtual library of new molecules based on privileged structures. Among these, we have synthesized a library of *N*-substituted indoles and a library of *N*-substituted benzimidazoles. Afterwards, in vitro screening and in vivo spontaneous motor activity in mice has revealed molecules with good in vitro affinities for the α_1 receptor and potent in vivo induction of sedation.

Keywords: Zolpidem; Zaleplon; Indiplon; Non-benzodiazepinic; GABA-A receptor; Indoles; Benzimidazoles; ADME; Volsurf; Catalyst; Combinatorial chemistry

1. Introduction

The benzodiazepine (BZ) classes of drugs are used clinically for their anxiolytic, hypnotic, muscle-relaxant and anticonvulsant actions. They act allosterically to influence central γ-aminobutyric acid (GABA)-mediated neurotransmission [1].

GABA-A receptors are pentameric assemblies of a large range of subunits (α1-6, β1-3, γ1-3, δ, ε, π and θ), of which the α subunit is of particular importance in determining the pharmacology of the BZ binding site [2]. The major BZ-sensitive GABA-A receptor subtypes in the brain are α1βxγ2, α2βxγ2, α3βxγ2, and α5βxγ2 and their distribution in the brain shows distinct regional variations.

Ligands at the BZ site are categorized as agonists, inverse agonists, or antagonists. Agonists act by increasing the frequency of channel opening to give a net hyperpolarization of the neuron and a decreased excitability. BZ inverse agonists have the opposite effect and decrease the frequency of channel openings, resulting in a depolarization and an increased neuronal excitability. Between the two efficacy extremes, there is a continuum of partial agonists and partial inverse agonists. Antagonists without efficacy do not alter chloride flow and are functionally silent.

As the effect of BZs is limited to modulate the activity of an endogenous transmitter, they have quite low acute toxicity. Nevertheless, there is considerable clinical concern about undesirable side-effects such as sedation, amnesia and, in particular, the ability to induce both physical and psychological dependence [3]. Another problem, particularly with respect to the use of BZs as anticonvulsant, is the quite rapid development of tolerance [4].

It is clear that improved ligands, in terms of activity, profile and side effects should be interesting. Among the known non-benzodiazepine ligands, the *N,N*-dialkyl-2-phenylacetamidoimidazo[1,2-*a*]pyridines Zolpidem (**1a**) and Alpidem (**1b**) and the pyrazolo[1,5-*a*]pyrimidines Indiplon (**2a**) and Zaleplon (**2b**) (Scheme 1) showed both high affinity and selectivity toward the corresponding receptors [5].

An examination of the structure-activity relationships (SAR) of affinity and efficacy of these and other compounds [6] at the BZ receptor has assisted in development of several pharmacophoric models for ligand–receptor interaction. These models are characterized by a number of points of lipophilic and hydrogen-bonding ligand–receptor interaction [7], and in some

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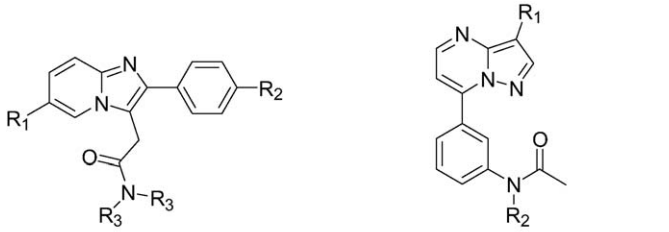
cases [8] areas of steric hindrance have also been defined. According to these models, Fig. 1 shows the hydrophobic and H–acceptor interactions in Zolpidem.

According to this model, we took Zolpidem (**1a**) as stating point. We followed a strategy based on scaffold hopping [9], and we proposed to replace the central core imidazo[1,2-*a*]pyridine by using indoles and benzimidazoles. These scaffolds have been reported as privileged structures [10]. We proposed to use a similar distribution of the different substituents, related to the models. Fig. 2 shows such distribution of the substituents of one of the molecules of the library (**14f**), according to the pharmacophore described above.

There are precedents in the literature about the indole scaffold concerning hypnotic activity [11,12]. More concretely, 2-[5-chloro-2-(4-chloro-phenyl)-1*H*-indol-3-yl]-*N*-heptyl-*N*-pentyl-acetamide (**3a**) and 2-[2-(4-fluoro-phenyl)-1*H*-indol-3-yl]-*N*-heptyl-*N*-pentyl-acetamide (**3b**) (Scheme 2) have been reported.

These compounds have low affinity for the α1 subunit of the GABAA receptor; however, they show induction of sedation in vivo, as showed in Table 1. The reason for this apparent contradiction is due to these indoles stimulate the synthesis of neurosteroids who interact with GABAA receptor and who are the direct responsible for this activity in vivo.

In this context, we carried out a previous selection of the molecules to synthesize. The first step of the selection process was the construction, using the CombiChem module of Accord for Excel [13], of a virtual library of 500 compounds by varying R substituents. All the compounds were filtered by Lipinski4s rule of 5 [14] implemented in Accord for Excel. Compounds verifying such rules were submitted to Volsurf [15] in order to calculate predicted ADME BBB-property (Blood-Brain Barrier). The selection criteria BBB > 0.30 was used. Afterwards, the last step of the selection process consisted in running under catalyst [16] the pharmacophore described in the literature for Zolpidem (**1a**) [10–15]. Thus, over 20 compounds were selected to be synthesized which are summarized in Tables 2 and 3 together with their MW, logP (KOWWIN), num-



1a Zolpidem R^1=R^2=R^3=Me
1b Alpidem R^1=R^2=Cl, R^3=Pr
2a Indiplon R^1=thienyl-CO, R^2=Me
2b Zaleplon R^1=CN, R^2=Et

Scheme 1. Structures of Zolpidem, Alpidem, Indiplon and Zaleplon.

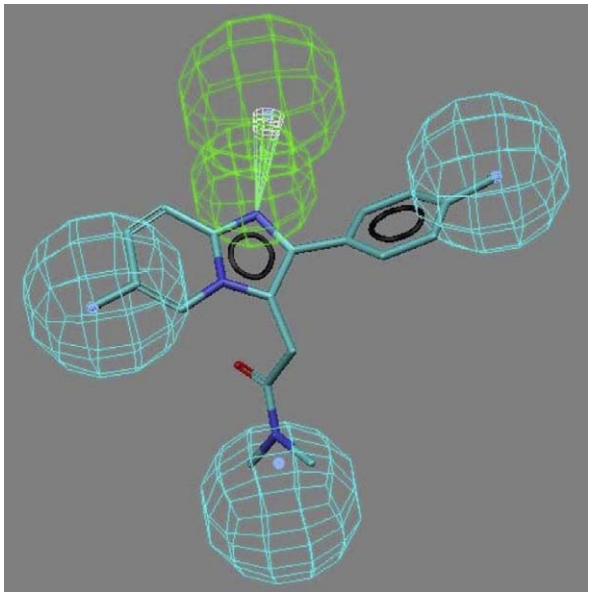


Fig. 1. Pharmacophoric model for Zolpidem (**1a**).

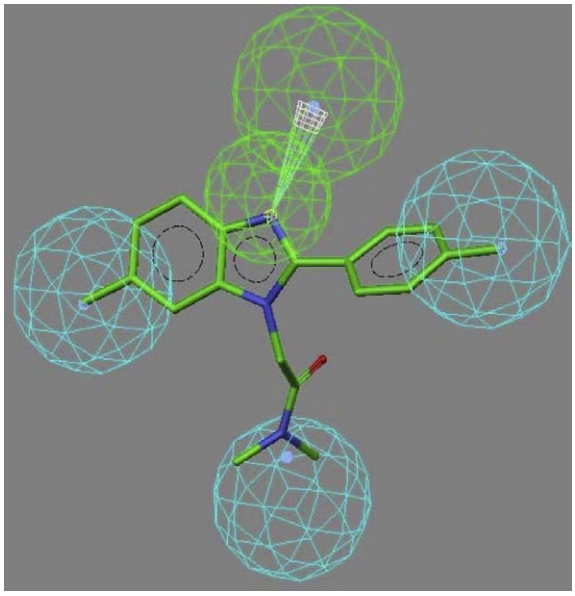
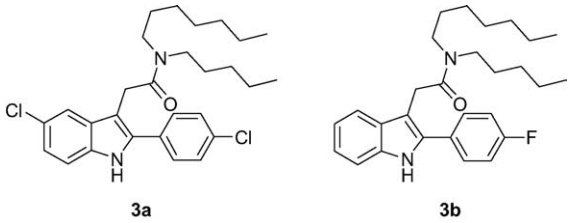


Fig. 2. Pharmacophoric model for benzimidazole **14d**.



Scheme 2. Indole structures reported (**3a**–**b**).

Table 1
In vitro (binding α1) and in vivo (spontaneous motor activity, SMA) inhibitions of indoles **3a** and **3b** compared with the standard molecules Zolpidem (**1a**) and Zaleplon (**2b**)

Compound	In vitro binding α_1 inh (%)		In vivo SMA inhibition (%)
	10^{-5} M	10^{-7} M	
1a	99.4	73.6	90.8
2b	97.2	23.4	47.2
3a	7.0	19.9	60.2
3b	0.0	0.0	57.7

Table 2
Structure of *N*-substituted indoles synthesized (**10a**–**r**) together with their ClogP (KOWWIN), number of HBA (HBD is 0) and BBB calculated values (standard dataset and method, Volsurf [15]), together with experimental in vitro inhibitory activity and in vivo spontaneous motor activity inhibition

	R-group table			Yield	LCMS		Predicted ADME[13, 15] Lipinski rule of 5			In vitro Binding α_1 inhibition (%)		In vivo SMA
Compound	R1	R2	R3	(%)	Purity (%)	M + 1	ClogP	HBA	BBB[15]	10^{-5}M	10^{-7}M	Inhibition (%)
10a	H	H	Methyl/methyl	30	95	279	3.67	3	0.88	4.5	0	–
10b	Me	F	Ethyl/ethyl	36	91	339	5.4	3	1.08	0	0	–
10c	Me	F	Propyl/propyl	29	90	367	6.38	3	1.07	0	0	–
10d	Me	F	Butyl/butyl	37	91	395	7.36	3	0.96	0	0	–
10e	Me	F	Pyrrolidine	6	100	337	5.29	3	0.92	0.4	0	–
10f	Me	F	Morpholine	7	99	353	4.03	4	0.45	17.1	1.6	–
10g	Me	F	Thiomorpholine	28	84	369	4.88	3	0.98	0	0	–
10h	Me	H	Ethyl/ethyl	21	91	321	5.2	3	1.07	43	3.9	–
10i	Me	H	Propyl/propyl	14	96	349	6.18	3	1.08	0	0	–
10j	Me	H	Butyl/butyl	25	94	391	7.71	3	0.97	0	0	–
10k	Me	H	Pyrrolidine	35	85	319	5.09	3	1.06	39.2	18.3	–
10l	Me	H	Morpholine	14	85	335	3.83	4	0.61	0	0	–
10m	Me	H	Thiomorpholine	16	84	351	4.68	3	0.95	0	0	–
10n	Me	Me	Ethyl/ethyl	37	98	335	5.75	3	1.09	39.7	14.2	–
10p	Me	Me	Propyl/propyl	25	97	363	6.73	3	1.08	73.6	37.2	92
10q	Me	Me	Butyl/butyl	22	98	377	7.16	3	0.96	65	31.5	–
10r	Me	Me	Morpholine	11	98	349	4.38	4	0.57	0.2	0	–

Table 3
Structure of *N*-substituted benzimidazoles synthesized (**14a**–**f**) together with their ClogP (KOWWIN), number of HBA (HBD is 0) and BBB calculated values (standard dataset and method, Volsurf [15]), together with experimental in vitro inhibitory activity and in vivo spontaneous motor activity inhibition

	R-group table			Yield	LCMS		Predicted ADME[13, 15] Lipinski rule of 5			In vitro Binding α_1 Inhibition (%)		In vivo SMA
Compound	R1	R2	R3	(%)	Purity (%)	M + 1	ClogP	HBA	BBB	10^{-5}M	10^{-7}M	Inhibition (%)
14a	Cl	CF_3	Ethyl/ethyl	36	92	411	5.44	4	0.63	10.7	0	–
14b	Cl	CF_3	Morpholine	21	94	425	4.07	5	0.35	0	0	–
14c	Me	Me	Ethyl/ethyl	24	91	336	4.93	4	0.83	0	0	–
14d	Me	Me	Methyl/methyl	35	100	308	3.94	4	0.89	90.6	8.3	86
14e	MeO	Br	Propyl/propyl	8	91	445	5.78	5	0.45	0	0	–
14f	MeO	Br	Pyrrolidine	22	98	415	4.69	5	0.75	47.1	0	–

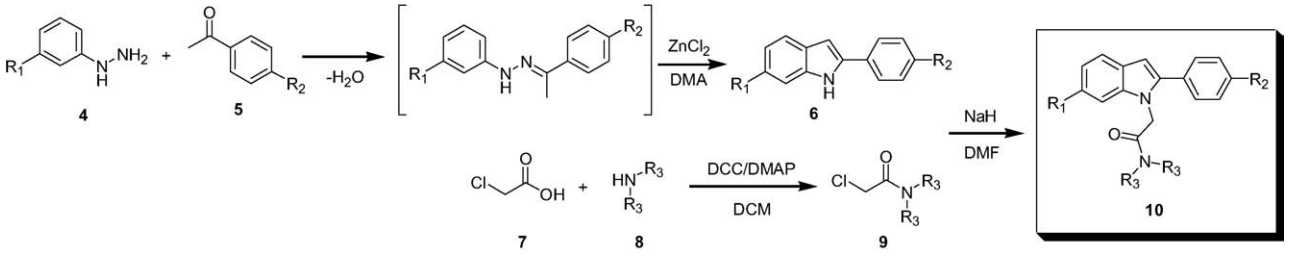
ber of H-bond acceptors and donors and BBB calculated values.

2. Chemistry

From the chemical point of view, on the one hand, the synthetic pathway for the indoles (**10**) consists in a three-step convergent strategy, as showed in Scheme 3. The indole scaffold (**6**) can be obtained by the Fischer rearrangement [17] between a phenylhydrazine (**4**) and a phenone (**5**). The second step of the synthesis is an acylation between the indole (**6**) and a chloroacetamide (**9**), obtained by coupling between chloroacetic acid (**7**) and the corresponding amine (**8**). This three-step convergent strategy yields the desired product (**10**).

On the other hand, the synthetic pathway for the benzimidazoles (**14**) is similar to the indoles (**10**), as showed in Scheme 4. The first step consists in a coupling between an aromatic 1,2-diamine (**11**) and an aldehyde (**12**), yielding the benzimidazole scaffold (**13**). The aforementioned coupling of the chloroacetic acid (**7**) and an amine (**8**) allows one to obtain the corresponding chloroacetamide (**9**) which is condensed with the benzimidazole (**13**) to yield the desired compound (**14**).

The yield of the two final couplings described above is, in general, low. The reason for these low yields is the low reac-



Scheme 3. Synthetic Pathway for the indoles **10a**–**r**.

tivity of chloroacetamides (**9**). A preparative LCMS purification of the crudes was performed in order to obtain the desired products.

3. Pharmacology

Male Sprague–Dawley rats were used to obtain membranes containing α_1-$GABA_A$ receptor (from cerebellum). The affinity of compounds **10a**–**r** and **14a**–**f** for α_1-$GABA_A$ receptors was determined by competitive tests using radiolabeled flumazenil as ligand using 96-well microtiter plate format. Membranes containing the study receptors were incubated with radiolabeled flumazenil (at a final concentration of 1 nM) and ascending concentrations of test compounds. Percentage of specific binding for every concentration of test compound was determined using a scintillation counter.

The in vivo effects of these compounds were assessed by a predictive sedation-hypnosis test in mice. Groups of 5–8 male CD1 mice, weighing 22–26 g at the time of test, were used. The test compounds were administered in single equimolecular intraperitoneal doses, suspended in 0.25% agar with 10 μl of Tween in a volume of 10 ml/kg. Control animals received the vehicle alone. Using a Smart System (Panlab, S.L., Spain) the traveled distance in cm is recorded for each mouse at 5-min intervals during a period of 30 min after dosing. The inhibition percentage traveled distance of treated animals versus control animals (the first 5 min were discarded) was calculated.

4. Results and discussion

The activity results for these two libraries are summarized in Tables 2 and 3. Results include in vitro activities as well as in vivo data for the most active indole (**10p**) and benzimidazole (**14d**).

For the indole scaffold, the SAR data reveals that, in general, when R1/R2 are Me/F or H/H, the molecules are not active. The molecules with higher affinity for the receptor are those that have aliphatic chains as R3 substituents. This SAR can be extrapolated to the SAR of Zolpidem (**1a**) or Alpidem (**1b**). For instance, in Zolpidem R1/R2 are Me/Me, and for Alpidem R3 are propyl/propyl.

For benzimidazole scaffold, although there are fewer compounds and in consequence the SAR is less consistent, we can see that the most active molecule is **14d** where R1/R2 are Me/Me and R3 are Me/Me.

If we compare the affinity of Zolpidem (**1a**) with the affinity of **10p** and **14d**, and after we compare the in vivo activities, we can conclude that **10p** and **14d** have the same in vivo activity as Zolpidem, although their affinity is not so high. This fact can be explained with better pharmacokinetic parameters of **10p** and **14d** versus Zolpidem, or a better intrinsic activity for the receptor.

In conclusion, we report that we have discovered two new families of molecules with good in vitro affinities for the α_1 receptor and potent in vivo induction of sedation.

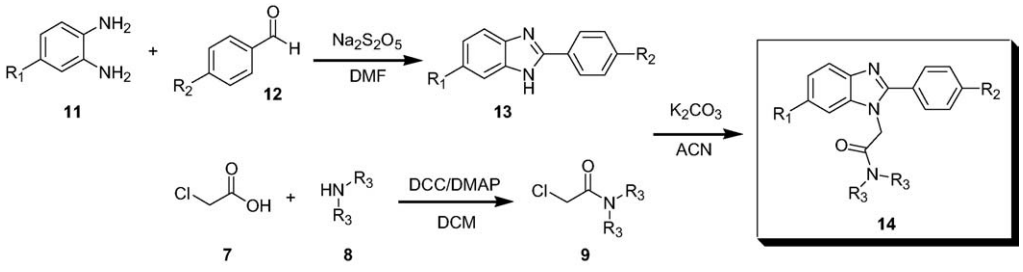
5. Experimental protocols

5.1. Chemistry

All melting points were determined with a Büchi 530 capillary apparatus and are uncorrected. Infrared spectra were recorded in a Nicolet Magna 560 FTIR spectrophotometer. ^1H and ^{13}C NMR spectra were determined in a Varian Gemini-300 operating in a field strength of 300 and 75.5 MHz, respectively. Chemical shifts are given in parts per million (δ) values downfield from Me_4Si as internal standard and coupling constants (*J*) in Hz. Standard and peak multiplicities are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quadruplet; br, broad signal; m, multiplet. ESI (+) and (–) mass spectra were recorded on a Agilent HP1100 mass spectrometer coupled to a HPLC using the following conditions: Column: X-Terra RP18, 3.5 μm, 4.6 × 50 mm (Waters); Injected volume: 2 μl; Eluent: A: acetonitrile/B: ammonium formate 10 mM pH = 9.20; Gradient: A from 20% to 60% in 6 min, then maintaining at 60% for 3 min; Flow-rate: 1 ml/min; Temperature: 30 °C; Detection: 240 nm.

5.1.1. General procedure for preparation of 2-chloro-N,N-disubstituted-acetamide derivatives (9)

To a solution of 2 eq of chloroacetic acid (**7**) in DCM is added a solution of 1 eq of dicyclohexylcarbodiimide (DCC) in DCM. The solution is stirred at room temperature for 30 min. To the resulting suspension are added a solution of 1 eq of the corresponding amine (**8**) and 0.5 eq of DMAP in DCM, and the resulting crude is stirred overnight at room temperature. The urea is filtered off, and the solution is washed with water, 6 N HCl, 6 N NaOH and finally again with water. The organic layer is dried over $MgSO_4$, filtered off and the solvent is removed in vacuo. The residue thus obtained is the desired chloroacetamide (**9**).



Scheme 4. Synthetic Pathway for the benzimidazoles **14a**–**f**.

5.1.2. General procedure for preparation of 1H-indole derivatives (6)

To 1 eq of the hydrazine (**4**) is added 1 eq of the phenone (**5**), and the resulting mixture is stirred at 100 °C for 30 min. The water is removed in vacuo, and a solution of 5 eq of $ZnCl_2$ in DMA is added. The mixture is stirred at 170 °C for 12 h. After this period, the crude is allowed to cool and is extracted with DCM/water. The organic layer is dried over $MgSO_4$, filtered off and the solvent is removed in vacuo, to obtain the desired 1*H*-indole (**6**).

5.1.3. General procedure for preparation of 1H-benzimidazole derivatives (13)

To a solution of 1 eq of the aldehyde (**12**) in DMF are added 1 eq of the amine (**11**) and 4 eq of $Na_2S_2O_5$, and the resulting mixture is stirred at 120 °C for 12 h. After this period, the crude is allowed to cool and is solved in ethyl acetate. To the resulting solution is added water, and the solid thus obtained is filtered off and washed with water, to obtain the desired 1*H*-benzimidazole (**13**).

5.1.4. General procedure for preparation of N,N-disubstituted-indol-1-yl-acetamide derivatives (10)

1.2 eq of NaH are added to DMF under argon. To this mixture, 1 eq of the indole (**6**) is added and the mixture is stirred under argon at room temperature for 2 h. The crude is cooled to 0 °C and 3 eq of chloroacetamide (**9**) are added very slowly. The mixture is stirred at room temperature for 12 h. After this period, methanol is added to the crude and the solvent is removed in vacuo. The residue is extracted with DCM/water. The organic layer is dried over $MgSO_4$, filtered off and the solvent is removed in vacuo, to obtain the desired product (**10**).

^{1}H NMR **10a**: ($CDCl_3$, ppm) δ 7.63–6.59 (m, Ar, 10H), 4.85 (s, CH_2, 2H), 2.99 (s, Me, 3H), 2.93 (s, Me, 3H). ^{1}H NMR **10b**: (DMSO, ppm) δ 7.91–6.47 (m, Ar, 8H), 4.95 (s, CH_2, 2H), 3.29 (m CH_2, 4H), 2.47 (s, Me, 3H), 1.04 (m, Me, 6H). ^{1}H NMR **10c**: (DMSO, ppm) δ 7.49–6.54 (m, Ar, 8H), 4.95 (s, CH_2, 2H), 3.22 (m, CH_2, 4H), 2.38 (s, Me, 3H), 1.44 (m, CH_2, 4H), 0.77 (m, Me, 6H). ^{1}H NMR **10d**: (DMSO, ppm) δ 7.50–6.46 (m, Ar, 8H), 4.95 (s, CH_2, 2H), 3.22 (m, CH_2, 4H), 2.07 (s, Me, 3H), 1.40 (m, CH_2, 4H), 1.21 (m, CH_2, 4H), 0.85 (m, Me, 6H). ^{1}H NMR **10e**: (DMSO, ppm) δ 7.55–6.47 (m, Ar, 8H), 4.88 (s, CH_2, 2H), 3.47 (m, CH_2, 2H), 3.29 (m, CH_2, 2H), 2.07 (s, Me, 3H), 1.89 (m, CH_2, 2H), 1.57 (m, CH_2, 2H). ^{1}H NMR **10f**: ($CDCl_3$, ppm) δ 7.52–6.63 (m, Ar, 8H), 4.86 (s, CH_2, 2H), 3.70–3.42 (m, morpholine, 8H), 2.61 (s, Me, 3H). ^{1}H NMR **10g**: ($CDCl_3$, ppm) δ 7.52–6.65 (m, Ar, 8H), 5.01 (s, CH_2, 2H), 3.80–3.50 (m, thiomorpholine, 8H), 2.53 (s, Me, 3H). ^{1}H NMR **10 h**: (DMSO, ppm) δ 7.83–6.48 (m, Ar, 9H), 4.92 (s, CH_2, 2H), 3.29 (m, CH_2, 4H), 2.39 (s, Me, 3H), 1.02 (m, Me, 6H). ^{1}H NMR **10i**: (DMSO, ppm) δ 7.44–6.48 (m, Ar, 9H), 4.94 (s, CH_2, 2H), 3.24 (m, CH_2, 4H), 2.39 (s, Me, 3H), 1.47 (m, CH_2, 4H), 0.80 (m, Me, 6H). ^{1}H NMR **10j**: (DMSO, ppm) δ 7.45–6.47 (m, Ar, 9H), 4.96 (s, CH_2, 2H), 3.25 (m, CH_2, 4H), 2.40 (s, Me, 3H), 1.40 (m, CH_2, 4H), 1.20 (m, 4H, CH_2), 0.84 (m, Me, 6H). ^{1}H NMR **10l**: (DMSO, ppm) δ 7.43–6.49 (m, Ar, 9H), 4.99 (s, CH_2, 2H), 3.56–3.40 (m, morpholine, 8H), 2.41 (s, Me, 3H). ^{1}H NMR **10m**: (DMSO, ppm) δ 7.81–6.81 (m, Ar, 9H), 5.00 (s, CH_2, 2H), 3.70 (m, thiomorpholine, 4H), 2.50 (m, thiomorpholine, 4H), 2.40 (s, Me, 3H). ^{1}H NMR **10n**: (DMSO, ppm) δ 7.76–6.44 (m, Ar, 8H), 4.90 (s, CH_2, 2H), 3.33 (m, CH2, 4H), 2.40 (s, Me, 3H), 2.34 (s, Me, 3H), 1.04 (m, Me, 6H). ^{1}H NMR **10p**: (DMSO, ppm) δ 7.43–6.43 (m, Ar, 8H), 4.92 (s, CH_2, 2H), 3.24 (m, CH_2, 4H), 2.39 (s, Me, 3H), 2.34 (s, Me, 3H), 1.47 (m, CH_2, 4H), 0.81 (m, Me, 6H). ^{1}H NMR **10q**: (DMSO, ppm) δ 7.43–6.42 (m, Ar, 8H), 4.90 (s, CH_2, 2H), 3.25 (m, CH_2, 4H), 2.39 (s, Me, 3H), 2.34 (s, Me, 3H), 1.42 (m, CH_2, 4H), 1.22 (m, CH_2, 4H), 0.85 (m, Me, 6H). ^{1}H NMR **10r**: (DMSO, ppm) δ 7.43–6.44 (m, Ar, 8H), 4.97 (s, CH_2, 2H), 3.57 (m, morpholine, 8H), 2.40 (s, Me, 3H), 2.35 (s, Me, 3H).

5.1.5. General procedure for preparation of N,N-disubstituted-benzoimidazol-1-yl-acetamide derivatives (14)

To a suspension of 2.2 eq of potassium carbonate in acetonitrile are added 1.2 eq of chloroacetamide (**9**) and 1 eq of benzimidazole (**13**). The mixture is stirred at reflux for 12 h. The crude is allowed to cool and it is filtered off. The solvent is removed in vacuo, to obtain the desired product (**14**).

^{1}H NMR **14a**: (DMSO, ppm) δ 7.90–7.27 (m, Ar, 7H), 5.29 (s, CH_2, 2H), 3.24 (m, CH_2, 4H), 0.92 (m, Me, 6H). ^{1}H NMR **14b**: (DMSO, ppm) δ 7.96–7.27 (m, Ar, 7H), 5.35 (s, CH_2, 2H), 3.62–3.44 (m, morpholine, 8H). ^{1}H NMR **14c**: (DMSO, ppm) δ 7.51–7.02 (m, Ar, 7H), 5.09 (s, CH_2, 2H), 3.32 (m, CH_2, 4H), 2.41 (s, Me, 3H), 2.36 (s, Me, 3H), 1.02 (m, Me, 6H). ^{1}H NMR **14d**: ($CDCl_3$, ppm) δ 7.69–7.01 (m, Ar, 7H), 4.89 (s, CH_2, 2H), 3.03 (m, Me, 6H), 2.49 (s, Me, 3H), 2.42 (s, Me, 3H). ^{1}H NMR **14e**: (DMSO, ppm) δ 7.72–6.84 (m, Ar, 7H), 5.18 (s, CH_2, 2H), 3.79 (s, MeO, 3H), 3.20 (m, CH_2, 4H), 1.56 (m, CH_2, 4H), 1.40 (m, CH_2, 4H), 0.80 (m, Me, 6H). ^{1}H NMR **14f**: (DMSO, ppm) δ 7.73–6.83 (m, Ar, 7H), 5.08 (s, CH_2, 2H), 3.79 (s, MeO, 3H), 3.53 (m, pyrrol, 4H), 1.84 (m, pyrrol, 4H).

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