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5-Aryl-imidazo[2,1-*c*][1,4]benzodiazepine derivatives as tricyclic constrained analogues of diazepam and Ro5-4864. Synthesis and binding properties at peripheral and central benzodiazepine receptors

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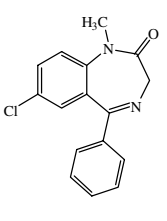
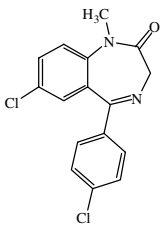
Four series of 5-aryl-imidazo[2,1-*c*][1,4]benzodiazepine derivatives **1a–f**, **2a–f**, **3a–f**, and **4a–f** were synthesized and tested for their affinity at both the peripheral and central benzodiazepine receptors. Among the four series, only N-10 and C-11 sites were changed, mainly [N(CH_3)−CO], [N=CH], [NH−CO], [NH−CH_2], and in each series the halogen site was varied at the positions C-7, C-2′, and C-4′. In particular, 10-methyl-benzodiazepinones **1a** and **1b** were designed as tricyclic constrained analogues of diazepam and Ro5-4864. All the tested compounds did not show significant binding activity at central benzodiazepine receptors, but relatively good PBzR binding affinities were found for 10-methyl-benzodiazepinone **1c** and benzodiazepines **2b**, **c**. Benzodiazepinones **3a–f** were prepared by cyclization with 1,1′-carbonyldiimidazole of the corresponding 2-(aryl-imidazol-1-yl-methyl)-arylamines, obtained from the suitable (2-amino-aryl)-aryl-methanols with 1,1'-carbonyldiimidazole in different conditions. *N*-Alkylation of **3a–f** to **1a–f** was achieved using dimethylformamide-dimethylacetal. Reduction of **3a–f** to **4a–f** was accomplished with lithium aluminum hydride or borane and oxidation of **4a–f** to **2a–f** was performed with manganese (IV) oxide.

1. Introduction

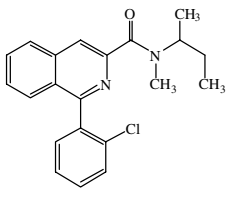
Benzodiazepines (Bz) are clinically used as muscle relaxants, anticonvulsants, anxiolytics, and sedative-hypnotics. These effects are mediated primarily via the central benzodiazepine receptors (CBzR) located in the central nervous system. Benzodiazepines also bind to other receptors, mainly located in peripheral tissues and glial cells in the brain, called peripheral benzodiazepine receptors (PBzR) (Gavish et al. 1999). The PBzR appears to be a heteromeric complex of at least three different subunits, including a 18 kDa subunit, a voltage-dependent anion channel (VDAC) with a molecular mass of 32 kDa, and an adenine nucleotide carrier (ANC) with a molecular mass of 30 kDa (Okubo et al. 2004). Although the receptor was first identified as a binding site for the benzodiazepine diazepam in peripheral organ systems, the benzodiazepine Ro5-4864 and the isoquinoline carboxamide PK11195 are the archetypal pharmacological tools for characterizing the receptor and its function (Casellas et al. 2002).



Diazepam



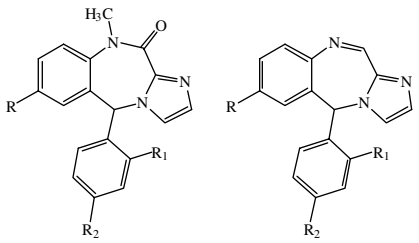
Ro5-4864



PK11195

Isoquinoline carboxamides interact specifically with the 18 kDa subunit, whereas the 30 and 32 kDa subunits are labeled by the benzodiazepine ligands (McEnery et al. 1992). Other studies appointed that the 18 kDa peripheral benzodiazepine receptor can be labeled by benzodiazepines, such as Ro5-4864, and isoquinoline carboxamides such as PK11195 and that their binding domains are overlapping but not identical (Farges et al. 1993). However, the binding of benzodiazepine and isoquinoline carboxamide ligands is mutually competitive at low nanomolar concentrations.

Consistent with its localization in the mitochondrial permeability transition pore (MPTP), PBzR is involved in the regulation of apoptosis, but also in the regulation of cell proliferation, cell differentiation, steroidogenesis, calcium flow, cellular respiration, cellular immunity, malignancy. The use of specific PBzR ligands that modulate PBzR activity may have potential therapeutic applications and might be of significant clinical benefit in the management of a large spectrum of different disorders including cancer and auto-immune, infectious and neurodegenerative diseases (Galiegue et al. 2003).



1a-f **2a-f**

	a	b	c	d	e	f
R	Cl	Cl	Cl	H	H	H
R_1	H	H	Cl	H	H	Cl
R_2	H	Cl	H	H	Cl	H

Although structural requirements for imidazo[1,5-*a*][1,4]-benzodiazepines (e.g., midazolam) binding to $GABA_A$ receptors have been well studied (Kucken et al. 2003), imidazo[2,1-*c*][1,4]benzodiazepines do not exhibit considerable binding affinity for central benzodiazepine receptors (Castellano et al. 2001).

In search of new classes of compounds acting selectively at the PBzR, we herein report the synthesis and the affinity data at both the PBzR and the CBzR of a series of imidazo[2,1-*c*][1,4]benzodiazepinones derivatives (**1a–f**) designed as tricyclic constrained analogues of diazepam (cfr. **1a**), Ro5-4864 (cfr. **1b**), and related compounds. Imidazo[2,1-*c*][1,4]benzodiazepines **2a–f** were also prepared and tested for comparison with their corresponding carboxamido analogs.

2. Investigations and results

2.1. Chemistry

Starting from 5-aryl-10,11-dihydro-5*H*-imidazo[2,1-*c*][1,4]-benzodiazepin-11-ones **3a–f**, we obtained the 10-methyl derivatives **1a–f** by alkylation with dimethylformamide-dimethylacetal in toluene and the 5-aryl-10,11-dihydro-5*H*-imidazo[2,1-*c*][1,4]benzodiazepines **4a–f** by reduction with lithium aluminum hydride or borane (Scheme). Oxidation of compounds **4a–f** with manganese (IV) oxide furnished the 5-aryl-5*H*-imidazo[2,1-*c*][1,4]benzodiazepines **2a–f**. Cyclization of derivatives **5a–f** to **3a–f** was performed utilizing 1,1′-carbonyldiimidazole at reflux in 1,2-dichlorobenzene and imidazole derivatives **5a–f** were obtained with the same reagent in CH_2Cl_2 at room temperature starting from **6a–f**. Compounds **6a–f** were prepared by reduction of aminobenzophenones **7a–f** commercially available (**7a**, **c**, **d** Fluka), or prepared (**7b**, **e**, **f**) following the method of Cortes et al. (2001). As we obtained compound **7f** in low yield (<5%) we prepared benzhydrol **6f** (46% yield) directly from aniline and 2-chlorobenzaldehyde in the presence of phenyldichloroborane according to the method described by Toyoda et al. (1980).

2.2. Binding studies

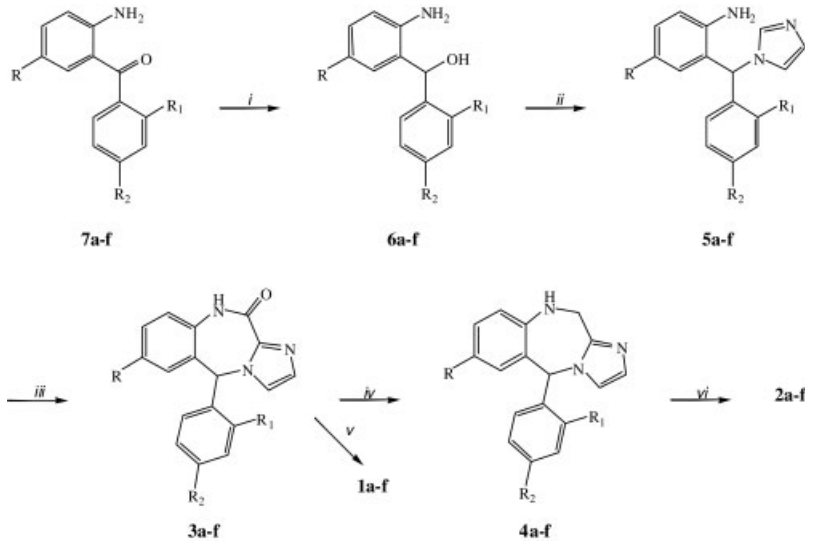
All the synthesized compounds were evaluated as racemic mixture for their *in vitro* binding affinity at PBzR by means of a binding assay using [^{3}H]PK11195 (1 nM final concentration) as radioligand and rat adrenal cortex as receptor source (Yamagishi and Kawaguchi 1998). Binding affinity at CBzR was determined using [^{3}H]flumazenil (2.5 nM final concentration) and, respectively, rat cerebral cortex (Lipartiti et al. 1995). Binding data, reported in the Table, are expressed as percentage of inhibition of specific radioligand binding at 10 μM compound concentration and as IC_{50} (μM) only when the value is major than 60%.

3. Discussion

From the data shown in the Table, it appears that all tested derivatives did not display any CBzR affinity, because they inhibited the binding of [^{3}H]flumazenil at rat brain membranes to an extent varying from 0% to 30% at a fixed 10 μM concentration. Among the synthesized 5-aryl-imidazo[2,1-*c*][1,4]benzodiazepine derivatives, compounds **1c** and **2b**, **c** emerged as new appreciable (IC_{50} = 1.36, 0.93, 5.20 μM respectively) and selective PBzR ligands.

In the carboxamido derivatives **1** and **3** the presence of the methyl group on the nitrogen at the 10-position strongly

Scheme



i) N_aBH_4, MeOH, r.t.; ii) 1,1′-carbonyldiimidazole, dichloromethane, r.t.; iii) 1,1′-carbonyldiimidazole,1,2-dichlorobenzene, reflux; iv) $LiAlH_4$, THF, r.t. or BH_3, THF, reflux; v) dimethylformamide-dimethylacetal, toluene, reflux; vi) manganese (IV) oxide, benzene, reflux.

Table: PBzR and CBzR binding affinities of previously described compounds 1a–f – 4a–f

Compd.	PBzR[a]	PBzR[b]	CBzR[c]	Compd.	PBzR[a]	CBzR[c]
1a	39 ± 5		7 ± 6	**3a**	18 ± 7	9 ± 6
1b	58 ± 3		2 ± 9	**3b**	9 ± 3	0 ± 11
1c	89 ± 1	1.36 ± 0.12	19 ± 4	**3c**	26 ± 5	30 ± 8
1d	0 ± 8		17 ± 3	**3d**	5 ± 2	11 ± 2
1e	21 ± 7		17 ± 10	**3e**	6 ± 0	29 ± 6
1f	43 ± 1		12 ± 1	**3f**	0 ± 2	16 ± 2
2a	45 ± 6		5 ± 3	**4a**	41 ± 5	3 ± 1
2b	90 ± 1	0.93 ± 0.24	0 ± 13	**4b**	27 ± 6	0 ± 8
2c	66 ± 3	5.20 ± 1.21	15 ± 4	**4c**	14 ± 8	8 ± 2
2d	8 ± 6		2 ± 4	**4d**	6 ± 10	6 ± 2
2e	51 ± 2		9 ± 10	**4e**	1 ± 8	27 ± 8
2f	13 ± 2		27 ± 3	**4f**	0 ± 2	14 ± 2

Each value is the mean ± SEM of three determinations
[a] Inhibition of [^{3}H]PK 11195 binding expressed as percentage of inhibition at 10 μM concentration
[b] Inhibition of [^{3}H]PK 11195 binding expressed as IC_{50} (μM) [diazepam $IC_{50} = 2.94 \pm 0.59$ μM, Ro5-4864 $IC_{50} = 49.8 \pm 4.8$ nM, PK 11195 $IC_{50} = 15.8 \pm 6.3$ nM]
[c] Inhibition of [^{3}H]flumazenil binding expressed as percentage of inhibition at 10 μM concentration [diazepam $IC_{50} = 30.8 \pm 6.4$ nM]

affects the affinity. The introduction of a chloro substituent at the phenyl group of the benzodiazepine nucleus determined a significant improvement of the binding affinity (e.g., **1a**–**c** in comparison with **1d**–**f**). It seems to hypothesize that the halogen substituent could interact with the L3 lipophilic region of the convergent pharmacophore models developed by different groups for PBR ligands (Campagna et al. 2004 and 2003; Anzini et al. 2001; Cinone et al. 2000; Campiani et al. 1996), made up of three lipophilic pockets (L1, L3, and L4) and a H-bond donor group (HB2). In the series **1a**–**f**, also the introduction of a chloro substituent on the pendant phenyl ring at the 5-position, which could interact with the L1 lipophilic region, determined an improvement in activity. This effect was more evident for the *ortho* position (**1c**, $IC_{50} = 1.36$ μM), similar to that present in PK11195, than for the *para* position (**1b**), concordant to that present in Ro5-4864. When the chloro substituent on the pendant phenyl ring was absent, like in the structure of diazepam, the affinity for the PBzR decreased. These results are consistent with data establishing that affinity of PK11195 is higher than the affinity of Ro5-4864, the latter being superior to that of diazepam. In compounds **2a**–**f** and **4a**–**f**, which lacked the carbonyl group at C-11, the promising affinity for PBzR is strictly associated with the presence of the double bond at the 10-11-position. 7-Chloro-5-(4-chloro-phenyl)-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine **2b** was the most effective ($IC_{50} = 0.93$ μM) of all tested derivatives, although the importance of the carbonyl group in the interaction of PBzR ligands with their receptors has been emphasized in the pharmacophore models developed. In particular, the amide carbonyl group of ligands such as PK11195 should be involved in hydrogen bonding acceptor interaction with Ser 41 of the receptor protein (Trapani et al. 2005). Hydrogen-bonding acceptor capability of the imidazole nitrogen (N-1 in **2b**) was hypothesized to play the same role of the carbonyl oxygen in forming interactions with the hydrogen-bonding donor site HB2.

In conclusion, the introduction of diazepam and Ro5-4864 structure in an imidazobenzodiazepine system does not improve the affinity for the PBzR. This seems to be not associated with the sterically demanding imidazole ring but it is most likely due to the different spatial arrangement of pharmacophoric groups in the new derivatives. In fact compound **1c** ($IC_{50} = 1.36$ μM), bearing a chloro substituent in 2′ position, and compounds **2b** ($IC_{50} = 0.93$ μM) and **2c** ($IC_{50} = 5.20$ μM), in which the imidazole nitrogen isosterically replaces the carbonyl group, have an affinity in the diazepam range ($IC_{50} = 2.94$ μM). Moreover, the affinity of compounds **2b** and **2c** prompts us to design new derivatives. It has been speculated that the introduction of a flexible lipophilic chain in position 2 or 3 of the tricyclic ring system might enhance the affinity for PBzR by interacting with the lipophilic pocket L4 of the receptor. If the results will be consistent with this hypothesis, the resolution of the racemates might be important.

4. Experimental

4.1. Chemistry

Melting points were taken on a Büchi 530 apparatus and are uncorrected. Elemental analyses were performed for C, H, N and experimental results agreed to within ±0.40% of the theoretical values. Mass spectra data were determined on a V6-Micromass 7070 H spectrometer and the parent peaks were consistent with the molecular weights. The ^{1}H NMR spectra were recorded on a Varian 200 MHz instrument, using $CDCl_3$ as solvent unless indicated. Chemical shifts are expressed in δ (ppm) and the coupling constants J in Hz. The following abbreviations were used: s, singlet; br s, broad singlet; d, doublet; t, triplet; m, multiplet; dd, double doublet. Exchange with deuterium oxide was used to identify OH and NH protons. Column chromatography was performed using Merck aluminum oxide 90 (0.063–0.200 mm) and Merck silica gel 60 (0.015–0.040 mm).

4.1.1. General procedure for preparation of the 5-aryl-10-methyl-11-oxo-10,11-dihydro-5H-imidazo[2,1-c][1,4]benzodiazepines **1a**–**f**

A solution of the suitable 5-aryl-10,11-dihydro-11-oxo-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**3a**–**f**) (1.2 mmol) in toluene (50 ml) was heated at reflux with a Dean-Stark apparatus for 1 h, then dimethylformamide-dimethylacetal (1.4 g, 12.0 mmol) was added in a single portion. The mixture was heated at reflux for 5 h. Upon cooling, the solvent was evaporated and the crude product purified by alumina column chromatography, using chloroform as eluent. After evaporation of the solvent, the solid was crystallized from benzene-ligroin.

4.1.1.1. 7-Chloro-10-methyl-11-oxo-5-phenyl-10,11-dihydro-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**1a**)

87% yield, m.p. >290 °C. ^{1}H NMR ($CDCl_3$): 3.02 (s, 3 H, CH_3), 6.22 (s, 1 H, CH), 6.75 (s, 2 H), 7.15–7.55 (m, 8 H).
$C_{18}H_{14}ClN_3O$ (323.8)

4.1.1.2. 7-Chloro-10-methyl-11-oxo-5-(4-chloro-phenyl)-10,11-dihydro-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**1b**)

89% yield, m.p. 262–263 °C. ^{1}H NMR ($CDCl_3$): 3.12 (s, 3 H, CH_3), 6.22 (s, 1 H, CH), 6.72 (d, 2 H, J = 8.42), 7.23–7.52 (m, 7 H).
$C_{18}H_{13}Cl_2N_3O$ (358.2)

4.1.1.3. 7-Chloro-10-methyl-11-oxo-5-(2-chloro-phenyl)-10,11-dihydro-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**1c**)

83% yield, m.p. 225 °C. ^{1}H NMR ($CDCl_3$): 3.22 (s, 3 H, CH_3), 6.53 (s, 1 H, CH), 6.84 (d, 1 H, J = 8.06), 7.16–7.46 (m, 7 H), 7.67 (d, J = 2.56, 1 H).
$C_{18}H_{13}Cl_2N_3O$ (358.2)

4.1.1.4. 10-Methyl-11-oxo-5-phenyl-10,11-dihydro-5*H*-imidazo[2,1-*c*][1,4]-benzodiazepine (**1d**)

84% yield, m.p. 205 °C. ^{1}H NMR ($CDCl_3$): 3.05 (s, 3 H, CH_3), 6.30 (s, 1 H, CH), 6.67–6.78 (m, 2 H), 7.15–7.50 (m, 9 H).
$C_{18}H_{15}N_3O$ (289.3)

4.1.1.5. 10-Methyl-11-oxo-5-(4-chloro-phenyl)-10,11-dihydro-5*H*-imidazo-[2,1-*c*][1,4]benzodiazepine (**1e**)

87% yield, m.p. 258 °C. ^{1}H NMR ($CDCl_3$): 3.13 (s, 3 H, CH_3), 6.28 (s, 1 H, CH), 6.72 (d, 2 H, J = 8.42), 7.23–7.52 (m, 8 H).
$C_{18}H_{14}ClN_3O$ (323.8)

4.1.1.6. 10-Methyl-11-oxo-5-(2-chloro-phenyl)-10,11-dihydro-5*H*-imidazo-[2,1-*c*][1,4]benzodiazepine (**1f**)

59% yield, m.p. 251–253 °C. ^{1}H NMR ($CDCl_3$): 3.29 (s, 3 H, CH_3), 6.65 (s, 1 H, CH), 6.86 (d, 1 H, J = 7.4), 7.15–7.51 (m, 8 H), 7.69 (m, 1 H).
$C_{18}H_{14}ClN_3O$ (323.8)

4.1.2. General procedure for preparation of the 5-aryl-5H-imidazo[2,1-c][1,4]benzodiazepines **2a–f**

A mixture of 85% manganese (IV) oxide activated (2.0 g) in benzene (30 ml) was heated at reflux with a Dean-Stark apparatus for 1 h, then a solution of the suitable 5-aryl-10,11-dihydro-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**5a–e**) (1.5 mmol) in benzene (20 ml) was added in a single portion. The mixture was heated at reflux for 3 h. Upon cooling, the solid was filtered and the solvent evaporated under reduced pressure to give a residue which was purified by alumina column chromatography, using chloroform as eluent.

4.1.2.1. 7-Chloro-5-phenyl-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**2a**)

51% yield, m.p. (crystallization solvent) 216–218 °C (benzene-ligroin). ^{1}H NMR ($CDCl_3$): 6.28 (s, 1 H, CH), 6.53–6.56 (m, 2 H), 7.10–7.55 (m, 8 H), 8.33 (s, 1 H, CH=).
$C_{17}H_{12}ClN_3$ (293.8)

4.1.2.2. 7-Chloro-5-(4-chloro-phenyl)-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**2b**)

54% yield, m.p. (crystallization solvent) 233–234 °C (benzene-ligroin). ^{1}H NMR ($CDCl_3$): 6.28 (s, 1 H, CH), 6.50 (d, J = 8.4, 2 H), 7.07–7.70 (m, 7 H), 8.37 (s, 1 H, CH=).
$C_{17}H_{11}Cl_2N_3$ (328.2)

4.1.2.3. 7-Chloro-5-(2-chloro-phenyl)-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**2c**)

54% yield, m.p. (crystallization solvent) 74–77 °C (benzene-ligroin). ^{1}H NMR ($CDCl_3$): 6.80 (s, 1 H, CH), 7.00–7.60 (m, 9 H), 8.53 (s, 1 H, CH=).
$C_{17}H_{11}Cl_2N_3$ (328.2)

4.1.2.4. 5-Phenyl-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**2d**)

50% yield, m.p. (crystallization solvent) 150–152 °C (benzene-ligroin). ^{1}H NMR ($CDCl_3$): 6.32 (s, 1 H, CH), 6.50–6.62 (m, 2 H), 7.10–7.61 (m, 9 H), 8.36 (s, 1 H, CH=).
$C_{17}H_{13}N_3$ (259.3)

4.1.2.5. 5-(4-Chloro-phenyl)-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**2e**)

48% yield, m.p. (crystallization solvent) 120–121 °C (cyclohexane-ligroin). ^{1}H NMR ($CDCl_3$): 6.34 (s, 1 H, CH), 6.50 (d, J = 8.4, 2 H), 7.00–7.60 (m, 6 H), 8.40 (s, 1 H, CH=).
$C_{17}H_{12}ClN_3$ (293.8)

4.1.2.6. 5-(2-Chloro-phenyl)-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**2f**)

31% yield, m.p. (crystallization solvent) 153–154 °C (toluene-ligroin). ^{1}H NMR ($CDCl_3$): 6.90 (s, 1 H, CH), 7.08–7.53 (m, 9 H), 7.66 (m, 1 H), 8.59 (s, 1 H, CH=).
$C_{17}H_{12}ClN_3$ (293.8)

4.1.3. General procedure for preparation of the 5-aryl-11-oxo-10,11-dihydro-5H-imidazo[2,1-c][1,4]benzodiazepines **3a–f**

1,1′-Carbonyldiimidazole (2.43 g, 15 mmol) was added to a solution of the suitable 2-[aryl-imidazol-1-yl-methyl]-phenylamines (**5a–e**) (10 mmol) in 1,2-dichlorobenzene (20 ml). The mixture was heated at reflux under nitrogen for 3 h. Upon cooling, petroleum spirit was added. The solid obtained was collected, washed with diethyl ether and purified by alumina column chromatography (eluent mixture chloroform-ethanol 97 : 3). After evaporation of the solvent, the solid was crystallized from ethanol.

4.1.3.1. 7-Chloro-11-oxo-5-phenyl-10,11-dihydro-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**3a**)

50% yield, m.p. > 290. ^{1}H NMR (DMSO): 6.51–6.62 (m, 2 H), 6.95 (s, 1 H, CH), 7.16–7.76 (m, 8 H), 10.42 (s, 1 H, NH).
$C_{17}H_{12}ClN_3O$ (309.8)

4.1.3.2. 7-Chloro-11-oxo-5-(4-chloro-phenyl)-10,11-dihydro-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**3b**)

45% yield, m.p. > 280 °C. ^{1}H NMR (DMSO): 6.59 (d, J = 8.42, 2 H), 6.99 (s, 1 H, CH), 7.19–7.85 (m, 7 H), 10.50 (s, 1 H, NH).
$C_{17}H_{11}Cl_2N_3O$ (344.2)

4.1.3.3. 7-Chloro-11-oxo-5-(2-chloro-phenyl)-10,11-dihydro-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**3c**)

51% yield, m.p. > 290 °C. ^{1}H NMR (DMSO): 6.62–6.75 (m, 1 H), 7.12–7.85 (m, 9 H, CH e ArH), 10.6 (s, 1 H, NH).
$C_{17}H_{11}Cl_2N_3O$ (344.2)

4.1.3.4. 11-Oxo-5-phenyl-10,11-dihydro-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**3d**)

56% yield, m.p. > 290 °C. ^{1}H NMR (DMSO): 6.49–6.61 (m, 2 H), 6.91 (s, 1 H, CH), 7.12–7.70 (m, 9 H), 10.32 (s, 1 H, NH).
$C_{17}H_{13}N_3O$ (275.3)

4.1.3.5. 11-Oxo-5-(4-chloro-phenyl)-10,11-dihydro-5*H*-imidazo[2,1-*c*][1,4]-benzodiazepine (**3e**)

56% yield, m.p. > 290 °C. ^{1}H NMR (DMSO): 6.57 (d, J = 8.42, 2 H), 6.97 (s, 1 H, CH), 7.10–7.75 (m, 8 H), 10.42 (s, 1 H, NH).
$C_{17}H_{12}ClN_3O$ (309.8)

4.1.3.6. 11-oxo-5-(2-chloro-phenyl)-10,11-dihydro-5*H*-imidazo[2,1-*c*][1,4]-benzodiazepine (**3f**)

56% yield, m.p. > 290 °C dec. ^{1}H NMR ($CDCl_3$): 6.82 (s, 1 H), 7.17–7.43 (m, 9 H), 7.63 (m, 1 H), 8.97 (br s, 1 H, NH).
$C_{17}H_{12}ClN_3O$ (309.8)

4.1.4. General procedures for preparation of the 5-aryl-10,11-dihydro-5H-imidazo[2,1-c][1,4]benzodiazepines **4a–f**

Method A (**4a**, **c**, **d**): A solution of the suitable 5-aryl-10,11-dihydro-11-oxo-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**3a**, **c**, **d**) (4 mmol) in THF (20 ml) was added dropwise at room temperature to a stirred solution of $LiAlH_4$ (0.76 g, 20 mmol) in THF (100 ml) under nitrogen. The mixture was heated at reflux for 5 h. Upon cooling to 0 °C, the solution was treated dropwise with water (0.5 ml), 15% aqueous NaOH (0.8 ml), and finally with water (1.1 ml). The mixture was stirred for 1 h and then filtered. The solvent was evaporated under reduced pressure to give a crude product which was purified by alumina column chromatography, using chloroform as eluent. After evaporation of the solvent, the solid was crystallized from ethanol.
Method B (**4b**, **e**, **f**): A solution of the suitable 5-aryl-10,11-dihydro-11-oxo-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**3b**, **e**, **f**) (4 mmol) in THF (20 ml) was treated with borane (1 M in THF, 20 ml, 20 mmol) and then heated to reflux for 5 h. Upon cooling, the reaction mixture was treated with methanol (15 ml) and concentrated to an oil. The oil was dissolved in water (5 ml) and then treated with NaOH 1 N until pH ~13. The mixture was treated with HCl 3 N until pH ~1 and then again with NaOH 3 N until pH ~9. The reaction mixture was extracted with ethyl acetate (3 × 100 ml). The combined extracts were dried with sodium sulfate, evaporated to give a solid which was purified by alumina column chromatography, using chloroform as eluent. After evaporation of the solvent, the solid was crystallized from benzene-ligroin.

4.1.4.1. 7-Chloro-5-phenyl-10,11-dihydro-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**4a**)

62% yield, m.p. 190–192 °C. ^{1}H NMR ($CDCl_3$): 3.95–4.18 (m, 2 H, CH_2), 4.19–4.30 (m, 1 H, NH), 6.19 (s, 1 H, CH), 6.50–7.40 (m, 10 H).
$C_{17}H_{14}ClN_3$ (295.8)

4.1.4.2. 7-Chloro-5-(4-chloro-phenyl)-10,11-dihydro-5*H*-imidazo[2,1-*c*][1,4]-benzodiazepine (**4b**)

76% yield, m.p. 200–205 °C. ^{1}H NMR ($CDCl_3$): 4.02–4.35 (m, 2 H, CH_2), 4.35–4.45 (m, 1 H, NH), 6.13 (s, 1 H, CH), 6.68 (d, J = 9.52, 1 H), 6.82 (d, J = 8.42, 2 H), 7.05–7.34 (m, 6 H).
$C_{17}H_{13}Cl_2N_3$ (330.2)

4.1.4.3. 7-Chloro-5-(2-chloro-phenyl)-10,11-dihydro-5*H*-imidazo[2,1-*c*][1,4]-benzodiazepine (**4c**)

50% yield, m.p. 195–197 °C. ^{1}H NMR ($CDCl_3$): 4.29–4.52 (m, 2 H, CH_2), 4.53–4.73 (m, 1 H, NH), 6.51 (s, 1 H, CH), 6.74 (d, J = 8.42, 1 H), 6.99 (br s, 1 H), 7.07–7.50 (m, 7 H).
$C_{17}H_{13}Cl_2N_3$ (330.2)

4.1.4.4. 5-Phenyl-10,11-dihydro-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**4d**)

48% yield, m.p. 238 °C. ^{1}H NMR ($CDCl_3$): 4.05–4.20 (m, 2 H, CH_2), 4.22–4.36 (m, 1 H, NH), 6.22 (s, 1 H, CH), 6.70 (d, J = 8.06, 1 H), 6.78–6.98 (m, 3 H), 7.05 (s, 1 H), 7.12–7.38 (m, 6 H).
$C_{17}H_{15}N_3$ (261.3)

3.1.4.5. 5-(4-Chloro-phenyl)-10,11-dihydro-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**4e**)

80% yield, m.p. 175–178 °C. ^{1}H NMR ($CDCl_3$): 4.06–4.28 (m, 3 H, CH_2 e NH), 6.18 (s, 1 H, CH), 6.67–7.39 (m, 10 H).
$C_{17}H_{14}ClN_3$ (295.8)

4.1.4.6. 5-(2-Chloro-phenyl)-10,11-dihydro-5*H*-imidazo[2,1-*c*][1,4]benzodiazepine (**4f**)

33% yield, m.p. 204–205 °C. ^{1}H NMR ($CDCl_3$): 4.18 (br s, 1 H, NH), 4.30 (dd, $J_A = 15.2$ e $J_B = 4.8$, 1 H), 4.55 (dd, $J_A = 15.2$ e $J_B = 3.6$, 1 H), 6.59 (s, 1 H), 6.72–6.96 (m, 3 H), 7.15–7.50 (m, 7 H).
$C_{17}H_{14}ClN_3$ (295.8)

4.1.5. General procedure for preparation of the 2-[aryl-imidazol-1-yl-methyl]-arylamines **5a–f**

To a solution of the suitable alcohol **6a–f** (10 mmol) in dry dichloromethane (15 ml) was added 1,1′-carbonyldiimidazole (2.43 g, 15 mmol) at room temperature. After stirring under nitrogen at room temperature for 30 min, the mixture was extracted with HCl 0.5 N (4 × 30 ml). Organic phase was eliminated while aqueous solution was basified with NaOH 2 N and extracted with ethyl acetate (3 × 100 ml). The combined extracts were dried with sodium sulfate, evaporated to give a solid which was purified by silica gel column chromatography, using ethyl acetate as eluent.

4.1.5.1. 4-Chloro-2-(imidazol-1-yl-phenyl-methyl)-phenylamine (**5a**)

31% yield, m.p. (crystallization solvent) 173–175 °C (ethanol). ^{1}H NMR ($CDCl_3$): 3.56 (s, 2 H, NH_2), 6.51–6.58 (m, 2 H), 6.69 (d, J = 8.42, 1 H), 6.89 (s, 1 H, CH), 7.07–7.23 (m, 4 H), 7.36–7.54 (m, 4 H).
$C_{16}H_{14}ClN_3$ (283.8)

4.1.5.2. 4-Chloro-2-[(4-chloro-phenyl)-imidazol-1-yl-methyl]-phenylamine (**5b**)

39% yield, m.p. (crystallization solvent) 165 °C (benzene-ligroin). ^{1}H NMR ($CDCl_3$): 3.43 (s, 2 H, NH_2), 6.43 (s, 1 H, CH), 6.50 (d, J = 2.2, 1 H), 6.68 (d, J = 8.1, 1 H), 6.82 (s, 1 H), 7.01 (d, J = 8.42, 2 H), 7.11–7.19 (m, 2 H), 7.30–7.43 (m, 3 H).
$C_{16}H_{13}Cl_2N_3$ (318.2)

4.1.5.3. 4-Chloro-2-[(2-chloro-phenyl)-imidazol-1-yl-methyl]-phenylamine (**5c**)

59% yield, m.p. (crystallization solvent) 132–134 °C (benzene-ligroin). ^{1}H NMR ($CDCl_3$): 3.61 (s, 2 H, NH_2), 6.52 (m, 1 H), 6.72 (d, J = 8.42, 1 H), 6.83–6.88 (m, 3 H), 7.15–7.50 (m, 6 H).
$C_{16}H_{13}Cl_2N_3$ (318.2)

4.1.5.4. 2-(Imidazol-1-yl-phenyl-methyl)-phenylamine (**5d**)

42% yield, m.p. (crystallization solvent) 135–137 °C (ethanol). ^{1}H NMR ($CDCl_3$): 3.43 (s, 2 H, NH_2), 6.44–6.59 (m, 2 H), 6.63–6.79 (m, 2 H), 6.84 (s, 1 H, CH), 7.02–7.43 (m, 8 H).
$C_{16}H_{15}N_3$ (249.3)

4.1.5.5. 2-[(4-Chloro-phenyl)-imidazol-1-yl-methyl]-phenylamine (**5e**)

35% yield, m.p. (crystallization solvent) 170 °C (benzene-ligroin). ^{1}H NMR ($CDCl_3$): 3.47 (s, 2 H, NH_2), 6.50–6.64 (m, 2 H), 6.72–6.92 (m, 3 H), 7.00–7.50 (m, 7 H).
$C_{16}H_{14}ClN_3$ (283.8)

4.1.5.6. 2-[(2-Chloro-phenyl)-imidazol-1-yl-methyl]-phenylamine (**5f**)

31% yield, m.p. (crystallization solvent) 145–148 °C (toluene). ^{1}H NMR ($CDCl_3$): 3.50 (br s, 2 H, NH_2), 6.54 (m, 1 H), 6.72–6.88 (m, 5 H), 7.16–7.51 (m, 6 H).
$C_{16}H_{14}ClN_3$ (283.8)

4.1.6. General procedure for preparation of the (2-amino-aryl)-aryl-methanols **6a–f**

A cooled solution of opportune aminobenzophenone **7a-f** (30.0 mmol) in methanol (200 ml) was treated portionwise with an excess of sodium borohydride powder until the reaction was completed (TLC), then the solvent was removed under reduced pressure. The residue was taken up with water (200 ml) and extracted with chloroform. The organic phase was dried with sodium sulfate and the solvent was evaporated to give a solid which was recrystallized from ethanol (95–98% yield).

4.1.6.1. (2-Amino-5-chloro-phenyl)-phenyl-methanol (**6a**)

M.p. 100–102 °C [107–109 °C (Miki et al. 2002)]. ^{1}H NMR ($CDCl_3$): 2.50 (br s, 1 H, OH), 3.95 (br s, 2 H, NH_2), 5.80 (s, 1 H, CH), 6.60 (d, J = 8.3, 1 H), 7.00–7.15 (m, 2 H), 7.23–7.42 (m, 5 H).
$C_{13}H_{12}ClNO$ (233.7)

4.1.6.2. (2-Amino-5-chloro-phenyl)-(4-chloro-phenyl)-methanol (**6b**)

M.p. 126–127 °C [123.5–125 °C from benzene (Lednicer and Emmert 1971)]. ^{1}H NMR ($CDCl_3$): 2.54 (br s, 1 H, OH), 3.94 (br s, 2 H, NH_2), 5.75 (s, 1 H, CH), 6.59 (d, J = 8.4, 1 H), 6.98 (d, J = 2.6, 1 H), 7.05 (dd, $J_A = 8.4$ e $J_B = 2.6$, 1 H), 7.20–7.40 (m, 4 H).
$C_{13}H_{11}Cl_2NO$ (268.1)

4.1.6.3. (2-Amino-5-chloro-phenyl)-(2-chloro-phenyl)-methanol (**6c**)

M.p. 98–99 °C [101–102 °C from dichloromethane-petroleum ether (Toyoda et al. 1980)]. ^{1}H NMR ($CDCl_3$): 2.60 (br s, 1 H, OH), 4.10 (br s, 2 H, NH_2), 6.18 (s, 1 H, CH), 6.61 (d, J = 8.4, 1 H), 6.85 (d, J = 2.2, 1 H), 7.05 (dd, $J_A = 8.4$ e $J_B = 2.2$, 1 H), 7.20–7.45 (m, 4 H).
$C_{13}H_{11}Cl_2NO$ (268.1)

4.1.6.4. (2-Amino-phenyl)-phenyl-methanol (**6d**)

M.p. 105–107 °C [110–112 °C from aq. ethanol (Fleming et al. 1986)]. ^{1}H NMR ($CDCl_3$): 2.60 (br s, 1 H, OH), 3.95 (br s, 2 H, NH_2), 5.85 (s, 1 H, CH), 6.60–6.80 (m, 2 H), 6.95–7.20 (m, 2 H), 7.20–7.45 (m, 5 H).
$C_{13}H_{13}NO$ (199.3)

4.1.6.5. (2-Amino-phenyl)-(4-chloro-phenyl)-methanol (**6e**)

M.p. 99–100 °C [97–98.5 °C from diethyl ether-hexane (Lednicer and Emmert 1971)]. ^{1}H NMR ($CDCl_3$): 2.60 (br s, 1 H, OH), 4.00 (br s, 2 H, NH_2), 5.86 (s, 1 H, CH), 6.65–6.83 (m, 2 H), 6.99–7.50 (m, 6 H).
$C_{13}H_{12}ClNO$ (233.7)

4.1.6.6. (2-Amino-phenyl)-(2-chloro-phenyl)-methanol (**6f**)

M.p. 91–92 °C [91–92 °C from dichloromethane-petroleum ether (Toyoda et al. 1980)]. ^{1}H NMR ($CDCl_3$): 2.65 (d, J = 4.0, 1 H, OH), 4.16 (br s, 2 H, NH_2), 6.23 (d, J = 4.0, 1 H, CH), 6.67 (m, 2 H), 6.88 (m, 1 H), 7.15 (m, 1 H), 7.25–7.46 (m, 3 H), 7.56 (m, 1 H).
$C_{13}H_{12}ClNO$ (233.7)

4.1.7. General procedure for preparation of the (2-amino-aryl)-aryl-methanones **7b**, **e**, **f**

A stirred solution of 25.0 ml (34.2 g, 0.2 mol) of *o*- or *p*-chlorobenzoyl chloride was heated to 120 °C, then 0.04 mol of aniline or *p*-chloroaniline was added slowly. Once dissolution, 0.04 mol of zinc chloride was carefully added and the reaction mixture was heated at 220–230 °C for 3 h.
After cooling to 120 °C, the mixture was washed with water and the residual semisolid was dissolved with 500 ml of a mixture of sulfuric acid, acetic acid and water (2 : 1 : 1). The solution was heated at reflux for 17–24 h, after which the reaction mixture was poured into ice water (750 ml), extracted with dichloromethane (3 × 200 ml) and washed with 15% aqueous ammonium hydroxide solution (2 × 100 ml) and water at pH 7. The organic phase was dried over sodium sulfate, filtered and evaporated at reduced pressure to give a solid which was purified by crystallization (**7b**) or by silica gel column chromatography, using ethyl acetate-petroleum ether 1 : 9 as eluent (**7e**, **f**).

4.1.7.1. (2-Amino-5-chloro-phenyl)-(4-chloro-phenyl)-methanone (**7b**)

40% yield, m.p. (crystallization solvent) 114 °C (ethanol) [114.5–116.5 °C from diethyl ether-hexane (Lednicer and Emmert 1971)]. ^{1}H NMR ($CDCl_3$): 6.04 (br s, 2 H, NH_2), 6.68 (d, J = 8.4, 1 H), 7.24 (dd, $J_A = 8.4$ e $J_B = 2.6$, 1 H), 7.36 (d, J = 2.6, 1 H), 7.45 (d, J = 8.8, 2 H), 7.57 (d, J = 8.8, 2 H).
$C_{13}H_9Cl_2NO$ (266.1)

4.1.7.2. (2-Amino-phenyl)-(4-chloro-phenyl)-methanone (**7e**)

30% yield, m.p. (crystallization solvent) 98–100 °C (ethanol) [100–101 °C from ethanol-water (Hall et al. 1972)]. ^{1}H NMR ($CDCl_3$): 6.10 (br s, 2 H, NH_2), 6.58–6.82 (m, 2 H), 7.24–7.68 (m, 6 H).
$C_{13}H_{10}ClNO$ (231.7)

4.1.7.3. (2-Amino-phenyl)-(2-chloro-phenyl)-methanone (**7f**)

5% yield, m.p. (crystallization solvent) 58–60 °C (ethanol-water) [58–60 °C from ethanol-water (Sternbach et al. 1963)]. ^{1}H NMR ($CDCl_3$): 6.46 (br s, 2 H, NH_2), 6.57 (m, 1 H), 6.72 (m, 1 H), 7.17 (m, 1 H), 7.29–7.49 (m, 5 H).
$C_{13}H_{10}ClNO$ (231.7)

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