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SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME 2-IMIDAZOLINYLHYDRAZONE DERIVATIVES

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Abstract: A series of *N*-(imidazolidin-2-ylidene)hydrazones and *N*-(4,5-dihydro-1*H*-imidazol-2-yl)-*N*-methylhydrazones were prepared and examined for α_1-, α_2-adrenergic and imidazoline I_1, I_2 receptors binding affinities as well as cytotoxic activity against human tumor cell lines. Among the compounds tested, 2-naphthaldehyde *N*-(imidazolidin-2-ylidene)hydrazone (**3e**) exhibited a significant affinity for both α_2-adrenergic and imidazoline I_1 receptors (K_i = 94.3 nM and IC_{50} = 51.7 nM, respectively). Moreover, pyridine-2-carboxaldehyde *N*-(imidazolidin-2-ylidene)hydrazone (**3l**) showed the highest binding affinity to α_1-adrenoceptors (K_i = 24.6 nM), while quinoline-2-carboxaldehyde *N*-(imidazolidin-2-ylidene)hydrazone (**3m**) displayed the highest I_2 affinity with a K_i value of 26.7 nM and a high selectivity with respect to α_2-adrenergic and imidazoline I_1 receptors (K_i = 22470.0 nM and IC_{50} = 6145.0 nM, respectively).
None of the tested *N*-(4,5-dihydro-1*H*-imidazol-2-yl)-*N*-methylhydrazones **4p-u** displayed cytotoxic activity.

Keywords: 2-imidazolinylhydrazones; synthesis; structure; binding affinities at α_1-, α_2-adrenergic and imidazoline I_1, I_2 receptors

Imidazolines constitute an important class of therapeutic agents acting on a-adrenergic and/or imidazoline receptors (1). For example, α_2-agonists are useful for the treatment of hypertension, glaucoma, opiate- and alcohol withdrawal, muscle spasticity and behavior disorders. They are also used as anxiolytic, sedative and antinociceptive agents, while the potential therapeutic applications for α_2-antagonists include depression, Raynaud's disease and type II diabetes (2-4). Compounds possessing agonist activity at α_1-adrenoceptors may protect from abnormal heart rhythm and stress urinary incontinence. On the other hand, α_1-antagonists are effective agents in the management of arterial hypertension. It has been also demonstrated that blockade of α_1-adrenoceptors decreases the development of benign prostatic hyperplasia (5-6).

In the early 1980s, Bousquet and co-workers suggested the existence of binding sites specific for imdazoline-like compounds (7). Since then, the concept of imidazoline receptors (I_1, I_2 and I_3) has been developed and their role in the regulation of a large panel of biological functions has been investigated. For example, the centrally acting antihypertensive agents produce hypotensive effect by activating not only α_2-adrenoceptors but also imidazoline I_1 receptors within the central nervous system. Moreover, imidazoline I_1 receptors are also involved in the modulation of ocular pressure and in the secretion of renal sodium (8, 9). The second type of binding sites, I_2 receptors identified on both monoamine oxidase MAO-A and MAO-B isoforms as regulatory sites, are able to modulate MAO activity. Therefore, selective imidazoline I_2 receptors ligands with inhibitory activity against MAO may be valuable for the therapy of depression, Parkinson's and Alzheimer's diseases as well as Huntington's chorea (10). There is also evidence that selective imidazoline I_2 receptors compounds play a role in the modulation of opioid-induced analgesia (9). Finally, imidazoline I_3 receptors, which are involved in the control of K_{ATP}^+ channels located within pancreas, might be a target for the development of useful therapeutic agents for the treatment of type II diabetes (11).

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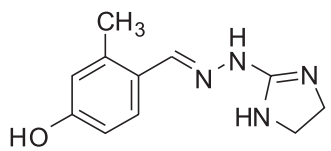
It is well known that hydrazones possess diverse biological properties and this structural motif is present in antimicrobial, anticonvulsant, analgesic, antiinflammatory, antitubercular or anticancer agents (12). The hydrazone functionality is also found in the structure of biologically active 2-imidazoline derivatives. For example, the hydrazone **CBS 1726** is an α_2-adrenergic agonist developed for glaucoma therapy (13), whereas **KUM 32** is a centrally acting hypotensive agent (14) (Figure 1). Furthermore, various 2-imidazolinylhydrazones have been described with anticancer activity (15-17). The most effective of them, *bisantrene*, shows topoisomerase II inhibition (18) (Figure 1).

As a part of our research program aiming at the synthesis of imidazoline derivatives with potential biological activities (19, 20), we attempted the synthesis of a series of 2-imidazoline analogues of type **A** containing hydrazone moiety (Figure 1). The compounds obtained were evaluated for their affinity at α-adrenergic (α_1 and α_2) and imidazoline (I_1 and I_2) receptors as well as cytotoxic activity against human tumor cell lines.

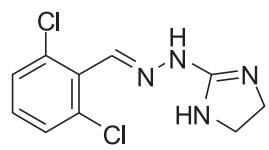
EXPERIMENTAL

Chemistry

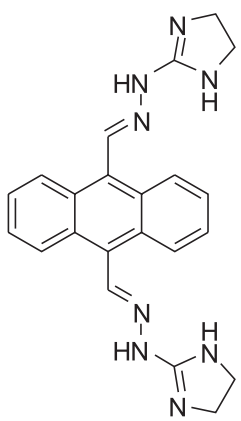
Melting points (m.p.) were determined on a Büchi SMP 20 apparatus and are uncorrected. The IR spectra were recorded on a 1600 FTIR Perkin Elmer spectrophotometer for potassium bromide pellets and frequencies are expressed in cm^{-1}. NMR spectra were recorded on a Varian Gemini 200 or Varian Unity 500 spectrometer using a residual solvent signal as the reference standard. The chemical shifts are given as δ-values and coupling constants (*J*) are in Hertz. Abbreviations are as follows: s, singlet; d, doublet; dd, doublet of doublets; m, multiplet; br, broad. Results of N elemental analysis for all compounds were within ± 0.4% of theoretical values. 2-Chloro-4,5-dihydroimidazole (**1**) was obtained according to the procedure described by Trani and Bellasio (21). The following hydrazones **2a** (22), **2d-e** (23), **2k** (24), **2l** (25) and **2m-o** (26) were prepared according to procedures described previously. The hydrazones **2b** (23), **2c** (27), **2f** (27), **2g** (28), **2h** (29), **2i** (30) and **2j** (31) were prepared



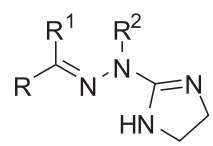
CBS 1276



KUM 32



Bisantrene



A

R = alkyl, aryl, heteroaryl

R1 = H, alkyl, aryl; R^2 = H, CH_3

Figure 1.

by refluxing the corresponding aldehyde/ketone (40 mmol) with 98% hydrazine hydrate (either 400 mmol, 19.4 mL for **2b-c** and **2f** or 200 mmol, 9.7 mL for **2g-j**) in anhydrous ethanol (30 mL) containing 3 to 5 drops of glacial acetic acid in the case of **2g-j**.

General procedure for synthesis of heteroaryl aldehyde/ketone *N*-methylhydrazones 2p-u

A solution of equimolar amounts (20 mmol) of the appropriate heteroaryl-2-carboxaldehyde/ketone and 98% methylhydrazine in acetonitrile (10 mL) was stirred under reflux for 1 h. Then, the solvent was evaporated under reduced pressure to give the corresponding crude product **2p-u**. The known compounds **2p** (32), **2s** (33), **2t** (34) and **2u** (35) were used in the next step without further purification. Hydrazone **2r** was purified by crystallization from *n*-heptane (3.0 g, 82%); m.p. 83-85°C; IR (KBr, cm^{-1}): 3265, 3150, 3070, 2990, 2935, 2875, 1600, 1555, 1525, 1500; ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 8.20-8.16 (2H, m, N=CH and CH quin.), 7.90-7.86 (3H, m, quin.), 7.69-7.66 (1H, m, quin.), 7.50-7.47 (2H, m, NH and CH quin.), 2.92 (3H, s, CH_3). Analysis: Calcd. for $C_{11}H_{11}N_3$: N, 22.59. Found: N, 22.37.

Dicyclopropylketone *N*-(imidazolidin-2-ylidene) hydrazone hydrochloride (3a) and free base 4a

A solution of 2-chloro-4,5-dihydroimidazole (**1**) (24 mmol) in CH_2Cl_2 (30 mL) was treated with equimolar amount of hydrazone **2a** (2.98 g, 24 mmol) and then was stirred at room temperature for 12 h. The insoluble material that precipitated was separated by filtration and the filtrate was evaporated to dryness. The crude product thus obtained was purified by crystallization from anhydrous ethanol to give hydrochloride **3a**.

Free base **4a** was obtained by treatment of an aqueous solution of **3a** (5 mmol) with 5% aqueous NaOH at 5°C.

Physical and analytical data for compounds **3a** and **4a** are presented in Tables 1 and 2.

General procedure for synthesis of aryl and heteroaryl aldehyde/ketone *N*-(imidazolidin-2-ylidene)hydrazone hydrochlorides 3b, 3d-f, 3j-n and free bases 4b, 4d-f, 4j-n

A solution of 2-chloro-4,5-dihydroimidazole (**1**) (24 mmol) in CH_2Cl_2 (30 mL) was treated with equimolar amount of the appropriate hydrazone **2b**, **2d-f**, **2j-n** (24 mmol) and then was stirred at room temperature for 12 h. The solid product that precipitated was filtered off, washed with CH_2Cl_2 and Et_2O, and purified by crystallization from suitable solvent. Physical and analytical data for compounds **3b**, **3d-f** and **3j-n** are presented in Tables 1 and 2.

Free bases **4b**, **4d-f** and **4j-n** were obtained by treatment of an aqueous solution or suspension of the corresponding hydrochlorides **3b**, **3d-f** and **3j-n** (5 mmol) with 5% aqueous NaOH at 5°C and crystallization of the resulting precipitate from suitable solvent. Physical and analytical data for compounds **4b**, **4d-f** and **4j-n** are presented in Tables 1 and 2.

4n: ^{13}C NMR (50 MHz, DMSO-d_6, δ ppm) : 165.5 (C-2, imidaz.), 157.7 (N=C), 150.0, 148.3, 135.6, 122.2, 120.0 (5C, pyr.), 42.5, 42.0 (C-4, C-5 imidaz.), 12.3 (CH_3).

General procedure for synthesis of aryl and heteroaryl aldehyde/ketone *N*-(imidazolidin-2-ylidene)hydrazone hydrochlorides 3c, 3g-i, 3o and free bases 4c, 4g-i, 4o

The reaction of **1** (24 mmol) with equimolar amount of the appropriate hydrazone **2c, 2g-i**, **2o** (24 mmol) was carried out according to the procedure described above for **3b**, **3d-f** and **3j-n**. Due to difficulties in purification of the corresponding hydrochlorides **3c**, **3g-i** or **3o** by crystallization, the crude products were converted into the corresponding free bases **4c**, **4g-i** and **4o** using the procedure described for **4b**, **4d-f** and **4j-n**. Physical and analytical data for compounds **4c, 4g-i** and **4o** are presented in Tables 1 and 2.

Then, to the solution or suspension of the appropriate free base **4c**, **4g-i**, **4o** (1 mmol) in anhydrous methanol (10 mL), HCl/MeOH solution (d = 12.2 g/100 mL, 1.2 mmol, 0.36 mL) was added dropwise. After stirring for 30 min at room temperature the solvent was evaporated to dryness under reduced pressure. The crude product thus obtained was purified by crystallization from suitable solvent. Physical and analytical data for compounds **3c, 3g-i** and **3o** are presented in Tables 1 and 2.

General procedure for synthesis of aryl and heteroaryl aldehyde/ketone *N*-(4,5-dihydro-1*H*-imidazol-2-yl)-*N*-methylhydrazone hydrochlorides 3p-u and free beses 4p-u

The reaction of **1** (24 mmol) in CH_2Cl_2 (30 mL) with an equimolar amount of the appropriate methylhydrazone **2p-u** (24 mmol) was carried out according to the procedure described for **3b**, **3d-f** and **3j-n** except the reaction time which was shortened to 2 h. The crude product thus obtained was purified by crystallization from suitable solvent. Physical and analytical data for compounds **3p-u** are presented in Tables 1 and 2.

Table 1. Physical and analytical data for compounds **3a-u** and **4a-u**

Compd. No.	M.P. (°C) solvent	Yield (%)	Formula Molecular weight	Analysis Calcd./Found %N	IR (KBr, λ cm^{-1})
3a	136-139 EtOH	45	$C_{10}H_{17}ClN_4$ 228.72	24.50 24.41	3320, 3140, 3005, 2915, 1655, 1615, 1410
3b	280-284 EtOH	47	$C_{10}H_{12}Cl_2N_4$ 259.14	21.62 21.43	3265, 3140, 3040, 2965, 1655, 1610, 1485
3c (KUM-32)	222-224[a] EtOH	35 293.59	$C_{10}H_{11}Cl_3N_4$	19.08 19.36	3295, 3145, 3085, 2959, 2905, 1655,1610, 1425, 1380
3d	230-232 EtOH	44	$C_{14}H_{15}ClN_4$ 274.76	20.39 20.12	3355, 3145, 2980, 1665, 1605, 1415, 1375, 1290, 1065
3e	255-257 *i*-PrOH	44	$C_{14}H_{15}ClN_4$ 274.76	20.39 20.02	3220, 3100, 2900, 1660, 1605, 1495, 1375
3f	296-299 MeOH	45	$C_{11}H_{14}Cl_2N_4$ 273.17	20.51 20.23	3255, 3145, 2920, 1665, 1620, 1485
3g	263-267 *i*-PrOH	41	$C_{16}H_{17}ClN_4$ 300.79	18.63 18.68	3260, 3120, 2970, 1650, 1615, 1490, 1455, 1380
3h	241-242 EtOH	64	$C_{17}H_{19}ClN_4$ 314.82	17.79 17.43	3265, 3120, 2970, 1660, 1610, 1485, 1375
3i	288-289 EtOH	58	$C_{16}H_{16}Cl_2N_4$ 335.25	16.71 17.00	3260, 3130, 2970, 1660, 1615, 1485, 1375
3j	260-262 EtOH	48	$C_{17}H_{19}ClN_4O$ 330.82	16.94 16.62	3135, 2965, 1660, 1610, 1505, 1245
3k	274-277 EtOH	34	$C_{18}H_{17}ClN_4$ 324.81	17.25 17.03	3215, 3145, 1640, 1600, 1480, 1325
3l	225-227 i-PrOH	45	$C_9H_{12}ClN_5$ 225.67	31.03 30.81	3070, 2954, 1660, 1615, 1585, 1475, 1365
3m	270-272 EtOH	62 275.73	$C_{13}H_{14}ClN_5$	25.40 25.46	3455, 3410, 3125, 2720, 1660, 1605, 1595, 1500, 1360
3n	264-267 EtOH	48	$C_{10}H_{14}ClN_5$ 239.70	29.21 29.43	3135, 2965, 1675, 1625, 1470, 1375
3o	242-244 EtOH	43	$C_{15}H_{16}ClN_5$ 301.78	23.20 23.01	3102, 2975, 1650, 1615, 1430, 1325
3p	275-277 EtOH	64	$C_{10}H_{14}ClN_5$ 239.70	29.21 29.20	3400, 3100, 2965, 1645, 1610, 1575
3r	265-266 EtOH	60	$C_{14}H_{16}ClN_5$ 289.74	24.17 23.83	3350, 3220, 3130, 3065, 3010, 1640, 1580, 1505
3s	308-310 MeOH	50	$C_9H_{13}ClN_4O$ 228.66	24.50 24.29	3200, 3090, 2925, 1645, 1610, 1580
3t	295-298 EtOH	50	$C_9H_{13}ClN_4S$ 244.72	22.89 23.01	3235, 3055, 2900, 1640, 1575, 1480
3u	229-231 *i*-PrOH	57	$C_{11}H_{16}ClN_5$ 253.71	27.60 27.90	3215, 3105, 2900, 1630, 1570, 1470

Table 1. continuation

Compd. No.	M.P. (°C) solvent	Yield (%)	Formula Molecular weight	Analysis Calcd./Found %N	IR (KBr, λ cm^{-1})
4a	121-123	45	$C_{10}H_{16}N_4$ 192.27	29.14 29.21	3435, 3185, 2995, 1640, 1495, 1395
4b	209-211[b] EtOH	75	$C_{10}H_{11}ClN_4$ 222.68	25.16 25.23	3525, 3455, 3170, 2945, 1635, 1580, 1485, 1390
4c	176-178[c] *i*-PrOH	54	$C_{10}H_{10}Cl_2N_4$ 257.13	21.79 22.08	3320, 3055, 2935, 1645, 1610, 1570, 1430, 1390
4d	159-162 *i*-PrOH	60	$C_{14}H_{14}N_4$ 238.30	23.51 23.42	3420, 3195, 2950, 1650, 1550, 1425
4e	209-212 MeOH	50	$C_{14}H_{14}N_4$ 238.30	23.51 23.58	3455, 3150, 2970, 1635, 1580, 1410
4f	213-215[d] DMF	55	$C_{11}H_{13}ClN_4$ 236.70	23.67 23.43	3450, 3160, 2950, 1630, 1570, 1480
4g	202-203	75	$C_{16}H_{16}N_4$ 264.34	21.20 21.20	3445, 3130, 2950, 1625, 1575, 1535, 1490, 1405
4h	182-185 MeCN	40	$C_{17}H_{18}N_4$ 278.36	20.13 20.21	3440, 3265, 3135, 2970, 1620, 1575, 1490, 1380
4i	178-179 MeCN	67	$C_{16}H_{15}ClN_4$ 298.78	18.75 18.78	3285, 3055, 2935, 1620, 1485, 1380
4j	193-196 DMF	56	$C_{17}H_{18}N_4O$ 294.36	19.03 19.05	3445, 3115, 2960, 1630, 1600, 1505, 1410
4k	218-221 MeOH	56	$C_{18}H_{16}N_4$ 288.36	19.43 19.46	3450, 3415, 3145, 1620, 1480, 1395, 1320
4l	221-223 EtOH	59	$C_9H_{11}N_5$ 189.22	37.01 37.12	3150, 2935, 1635, 1565, 1385
4m	241-242 EtOH	58	$C_{13}H_{13}N_5$ 239.27	29.27 29.66	3455, 3125, 2880, 1640, 1590, 1550, 1405
4n	209-210 EtOH	64	$C_{10}H_{13}N_5$ 203.24	34.46 34.40	3305, 3230, 3145, 2870, 1630, 1565, 1505, 1405
4o	189-191 MeCN	46	$C_{15}H_{15}N_5$ 266.39	26.29 26.32	3285, 1620, 1580, 1540, 1385
4p	165-166 MeCN	48	$C_{10}H_{13}N_5$ 203.24	34.46 34.18	3225, 2870, 1620, 1570, 1520
4r	142-144 MeCN	48	$C_{14}H_{15}N_5$ 253.31	27.64 26.96	3355, 3185, 2870, 1615, 1570, 1510, 1500
4s	87-90 Me_2CO	42	$C_9H_{12}N_4O$ 192.22	29.15 28.89	3300, 2840, 1615, 1585, 1510
4t	98-100 MeCN	45	$C_9H_{12}N_4S$ 208.28	26.90 26.72	3140, 2840, 1620, 1570, 1495, 1440
4u	123-125 MeCN	41	$C_{11}H_{15}N_5$ 213.27	32.22 32.23	3190, 2860, 1620, 1600, 1570, 1515

[a] Lit. m.p. 231-232°C (MeCN) (39). [b] Lit. m.p. 208-210°C (EtOH) (40). [c] Lit. m.p. 178-179°C (41). [d] Lit. m.p. 214°C (42).

Table 2. ^{1}H NMR spectral data for compounds **3a-u** and **4a-u**

Compd. No.	^{1}H NMR (DMSO-d_6, δ ppm)
3a	11.80 (s, 1H, $NH^{\oplus}$), 8.40 (brs, 1H, NH), 7.90 (brs, 1H, NH), 3.65 (s, 4H, 2 × CH_2, imidaz.), 2.07-2.02 (m, 1H, CH), 1.24-1.21 (m, 1H, CH), 1.20-0.95 (m, 4H, 2 × CH_2), 0.83-0.77 (m, 2H, CH_2), 0.68-0.61 (m, 2H, CH_2)[a]
3b	12.97 (s, 1H, $NH^{\oplus}$), 8.80 (brs, 2H, 2 × NH), 8.30 (s, 1H, N=CH), 7.87 (d, *J* = 8.3 Hz, 2H, ArH), 7.54 (d, *J* = 8.3 Hz, 2H, ArH), 3.72 (s, 4H, 2 × CH_2, imidaz.)[a]
3c (KUM-32)	3.31 (brs, 1H, $NH^{\oplus}$), 8.67 (brs, 2H, 2 × NH), 8.55 (s, 1H, N=CH), 7.59 (d, *J* = 7.8 Hz, 2H, ArH), 7.48 (t, *J* 1= 7.8 Hz, 1H, ArH), 3.69 (s, 4H, 2 × CH_2, imidaz.)[a]
3d	13.07 (brs, 1H, $NH^{\oplus}$), 9.17 (s, 1H, N=CH), 8.83 (brs, 2H, 2 × NH), 8.15 (d, *J* = 7.3 Hz, 1H, ArH), 8.07 (d, *J* = 7.8 Hz, 1H, ArH), 7.67 (t, *J* = 7.3 Hz, 1H, ArH), 7.63-7.60 (m, 2H, ArH), 3.75 (s, 4H, 2 × CH_2, imidaz.)[a]
3e	13.02 (brs, 1H, $NH^{\oplus}$), 8.80 (brs, 2H, 2 × NH), 8.48 (s, 1H, N=CH), 8.19-8.13 (m, 2H, ArH), 7.99-7.93 (m, 3H, ArH), 7.60-7.55 (m, 2H, ArH), 3.74 (s, 4H, 2 × CH_2, imidaz.)
3f	12.00 (s, 1H, $NH^{\oplus}$), 8.52 (brs, 2H, 2 × NH), 7.98 (d, *J* = 8.1 Hz, 2H, ArH), 7.48 (d, *J* = 8.1 Hz, 2H, ArH), 3.73 (s, 4H, 2 × CH_2, imidaz.), 2.34 (s, 3H, CH_3)
3g	10.62 (brs, 1H, NH^{L}), 8.50 (brs, 2H, 2 × NH), 7.61-7.50 (m, 5H, Ph), 7.41-7.23 (m, 5H, Ph), 3.70 (s, 4H, 2 × CH_2, imidaz.)
3h	10.57 (s, 1H, $NH^{\oplus}$), 9.31 (brs, 2H, 2 × NH), 7.61 (d, *J* = 7.3 Hz, 2H, ArH), 7.44-7.39 (m, 5H, Ph), 7.21 (d, *J* = 7.3 Hz, 2H, ArH), 3.72 (s, 4H, 2 × CH_2, imidaz.), 2.42 (s, 3H, CH_3)[a]
3i	10.78 (s, 1H, $NH^{\oplus}$), 8.59 (brs, 2H, 2 × NH), 7.69-7.59 (m, 4H, ArH), 7.42-7.35 (m, 5H, Ph), 3.72 (s, 4H, 2 × CH_2, imidaz.)
3j	10.62 (s, 1H, $NH^{\oplus}$), 8.50 (brs, 2H, 2 × NH), 7.62-7.59 (m, 2H, Ph), 7.42-7.38 (m, 3H, Ph), 7.26 (d, *J* = 8.4 Hz, 2H, ArH), 7.15 (d, *J* = 8.4 Hz, 2H, ArH), 3.84 (s, 3H, OCH_3), 3.71 (s, 4H, 2 × CH_2, imidaz.)
3k	11.04 (s, 1H, $NH^{\oplus}$), 8.40 (brs, 2H, 2 × NH), 7.73-7.53 (m, 6H, ArH), 7.51 (d, *J* = 1.7 Hz, 2H, ArH), 7.07 (d, *J* = 1.6 Hz, 2H, ArH), 3.66 (s, 4H, 2 × CH_2, imidaz.)
3l	13.19 (s, 1H, $NH^{\oplus}$), 8.93 (brs, 2H, 2 × NH), 8.62 (d, *J* = 4.9 Hz, 1H, H-6, pyr.), 8.33 (s, 1H, N=CH), 8.20 (d, *J* = 8.3 Hz, 1H, H-3, pyr.), 7.93-7.90 (m, 1H, H-5, pyr.), 7.46-7.44 (m, 1H, H-4, pyr.), 3.74 (s, 4H, 2 × CH_2, imidaz.)[a]
3m	13.40 (brs, 1H, $NH^{\oplus}$), 9.01 (brs, 2H, 2 NH), 8.50-8.33 (m, 3H, N=CH, 2H, quin.), 7.99-7.06 (m, 2H, quin.), 7.84-7.75 (m, 1H, quin.), 7.69-7.61 (m, 1H, qiun.), 3.76 (s, 4H, 2 × CH_2, imidaz.)
3n	12.11 (s, 1H, $NH^{\oplus}$), 8.70 (brs, 2H, 2 × NH), 8.60 (d, *J* = 4.2 Hz, 1H, H-6, pyr.), 8.39 (d, *J* = 8.1 Hz, 1H, H-3, pyr.), 7.87-7.83 (m, 1H, H-5, pyr.), 7.46-7.41 (m, 1H, H-4, pyr.), 3.75 (s, 4H, 2 × CH_2, imidaz.), 2.42 (s, 3H, CH_3)
3o	10.80 (brs, 1H, $NH^{\oplus}$), 8.51 (d, *J* = 7.8 Hz, 1H, H-6, pyr.), 8.50 (d, *J* = 3.9 Hz, 1H, H-3, pyr.), 7.93 (t, *J* = 7.3 Hz, 1H, H-5, pyr.), 7.55-7.54 (m, 3H, Ph), 7.42 (t, *J* = 5.8 Hz, 1H, H-4, pyr.) 7.31 (d, *J* = 5.7 Hz, 2H, Ph), 3.74 (s, 4H, 2 × CH_2, imidaz.)[a]
3p	9.38 (brs, 2H, 2 × $NH^{\oplus}$), 8.65-8.63 (m, 1H, H-6, pyr.), 8.39 (d, *J* = 4.7 Hz, 1H, H-3, pyr.), 8.01 (s, 1H, N=CH), 7.96-7.87 (m, 1H, H-5, pyr.), 7.49-7.42 (m, 1H, H-4, pyr.), 3.79 (s, 4H, 2 × CH_2, imidaz.), 3.53 (s, 3H, N-CH_3)
3r	9.54 (brs, 2H, 2 × $NH^{\oplus}$), 8.56 (d, *J* = 8.5 Hz, 1H, quin.), 8.48 (d, *J* = 8.5 Hz, 1H, quin.), 8.19 (s, 1H, N=CH), 8.04 (t, *J* = 6.5 Hz, 2H, quin.), 7.82 (t, *J* = 7.3 Hz, 1H, quin.), 7.67 (t, *J* = 7.3 Hz, 1H, quin.), 3.82 (s, 4H, 2 × CH_2, imidaz.), 3.62 (s, 3H, N-CH_3)
3s	9.05 (brs, 2H, 2 × $NH^{\oplus}$), 8.04 (s, 1H, N=CH), 7.90 (s, 1H, H-5, furane), 7.09 (d, *J* = 3.5 Hz, 1H, H-3, furan), 6.72-6.66 (m, 1H, H-4, furan), 3.74 (s, 4H, 2 × CH_2, imidaz.), 3.45 (s, 3H, N-CH_3)
3t	9.06 (brs, 2H, 2 × $NH^{\oplus}$), 8.38 (s, 1H, N=CH), 7.75 (d, $J_{5,4}$ = 4.8 Hz, 1H, H-5, thiophene), 7.60 (d, $J_{3,4}$ = 3.8 Hz, 1H, H-3, thiophene), 7.17 (dd, $J_{4,3}$ = 3.8 Hz, $J_{4,5}$ = 4.8 Hz, 1H, H-4, thiophene), 3.74 (s, 4H, 2 × CH_2, imidaz.), 3.48 (s, 3H, N-CH_3)
3u	8.86 (brs, 2H, 2 × $NH^{\oplus}$), 8.69 (d, *J* = 3.9 Hz, 1H, H-6, pyr.), 8.24 (d, *J* = 7.7 Hz, 1H, H-3, pyr.), 7.97-7.89 (m, 1H, H-5, pyr.), 7.59-7.53 (m, 1H, H-4, pyr.), 3.71 (s, 4H, 2 × CH_2, imidaz.), 3.36 (s, 3H, N-CH_3), 2.47 (s, 3H, CH_3)

Table 2. continuation

Compd. No.	^{1}H NMR (DMSO-d_6, δ ppm)
4a	6.06 (s, 1H, NH), 5.96 (s, 1H, NH), 3.27 (brs, 4H, 2 × CH_2, imidaz.), 2.69-2.59 (m, 1H, CH), 0.98-0.88 (m, 1H, CH), 0.86-0.66 (m, 6H, 3 × CH_2), 0.57-0.44 (m, 2H, CH_2) **4b** 7.95 (s, 1H, N=CH), 7.69 (d, *J* = 8.4 Hz, 2H, ArH), 7.37 (d, *J* = 8.4 Hz, 2H, ArH), 6.89 (s, 1H, NH), 6.52 (s, 1H, NH), 3.39 (brs, 4H, 2 × CH_2, imidaz.)
4c	8.14 (s, 1H, N=CH), 7.46 (d, *J* = 8.0 Hz, 2H, ArH), 7.27 (t, *J* = 8.0 Hz, 1H, ArH), 6.66 (s, 1H, NH), 6.38 (s, 1H, NH), 3.39 (s, 4H, 2 × CH_2, imidaz.)
4d	8.76 (d, *J* = 7.8 Hz, 1H, ArH), 8.71 (s, 1H, N=CH), 7.99 (d, *J* = 7.3 Hz, 1H, ArH), 7.93 (d, *J* = 7.8 Hz, 1H, ArH), 7.85 (d, *J* = 7.8 Hz, 1H, ArH), 7.58-7.49 (m, 3H, ArH), 6.83 (s, 1H, NH), 6.56 (s, 1H, NH), 3.46-3.42 (m, 4H, 2 × CH_2, imidaz.)[a]
4e	8.14-8.08 (m, 2H, N=CH and ArH), 7.93-7.82 (m, 4H, ArH), 7.52-7.42 (m, 2H, ArH), 6.93 (s, 1H, NH), 6.53 (s, 1H, NH), 3.47-3.42 (m, 4H, 2 × CH_2, imidaz.) **4f** 7.98 (d, *J* = 7.9 Hz, 2H, ArH), 7.34 (d, *J* = 7.9 Hz, 2H, ArH), 6.79 (s, 1H, NH), 6.54 (s, 1H, NH), 3.38 (brs, 4H, 2 × CH_2, imidaz.), 2.17 (s, 3H, CH_3)
4g	7.52-7.13 (m, 10H, N=CH and ArH), 6.86 (s, 1H, NH), 6.55 (s, 1H, NH), 3.40-3.38 (m, 4H, 2 × CH_2, imidaz.)
4h	7.53-7.05 (m, 9H, N=CH and ArH), 6.84 (s, 1H, NH), 6.52 (s, 1H, NH), 3.40 (brs, 4H, 2 × CH_2, imidaz.), 2.34 (s, 3H, CH_3)
4i	7.53-7.48 (m, 2H, Ph), 7.44 (d, *J* = 8.4 Hz, 2H, ArH), 7.32-7.25 (m, 3H, Ph), 7.18 (d, *J* = 8.4 Hz, 2H, ArH), 6.91 (s, 1H, NH), 6.56 (s, 1H, NH), 3.44-3.35 (m, 4H, 2 × CH_2, imidaz.)
4j	7.68-7.49 (m, 2H, Ph), 7.38-7.21 (m, 3H, Ph), 7.12 (d, *J* = 7.5 Hz, 2H, ArH), 6.94 (d, *J* = 7.5 Hz, 2H, ArH), 6.82 (s, 1H, NH), 6.50 (s, 1H, NH), 3.78 (s, 3H, OCH_3), 3.34 (brs, 4H, 2 × CH_2, imidaz.)
4k	7.55-7.24 (m, 8H, ArH), 6.88 (s, 2H, ArH), 6.54 (s, 1H, NH), 6.38 (s, 1H, NH), 3.34 (brs, 4H, 2 × CH_2, imidaz.)
4l	8.47 (d, *J* = 4.9 Hz, 1H, H-6, pyr.), 8.07 (d, *J* = 7.8 Hz, 1H, H-3, pyr.), 7.95 (s, 1H, N=CH), 7.73-7.70 (m, 1H, H-5, pyr.), 7.22-7.20 (m, 1H, H-4, pyr.), 7.04 (s, 1H, NH), 6.71 (s, 1H, NH), 3.46-3.40 (m, 4H, 2 × CH_2, imidaz.)
4m	8.32-8.20 (m, 2H, quin.), 8.09 (s, 1H, N=CH), 7.94-7.88 (m, 2H, quin.), 7.73-7.65 (m, 1H, quin.), 7.55-7.47 (m, 1H, quin.), 7.24 (s, 1H, NH), 6.85 (s, 1H, NH), 3.42 (s, 4H, 2 × CH_2, imidaz.)
4n	8.43 (d, *J* = 4.4 Hz, 1H, H-6, pyr.), 8.28 (d, *J* = 8.3 Hz, 1H, H-3, pyr.), 7.68-7.65 (m, 1H, H-5, pyr.), 7.22-7.20 (m, 1H, H-4, pyr.), 6.93 (s, 1H, NH), 6.73 (s, 1H, NH), 3.44-3.40 (m, 4H, 2 × CH_2, imidaz.), 2.24 (s, 3H, CH_3)[a]
4o	8.59 (d, *J* = 4.4 Hz, 1H, H-6, pyr.), 7.83-7.76 (m, 1H, H-3, pyr.), 7.45 (d, *J* = 3.8 Hz, 2H, H-5 and H-4, pyr.), 7.35-7.23 (m, 5H, Ph), 6.94 (s, 1H, NH), 6.57 (s, 1H, NH), 3.50-3.41 (m, 4H, 2 × CH_2, imidaz.)
4p	8.53-8.52 (m, 1H, H-6, pyr.), 8.13 (d, *J* = 8.3 Hz, 1H, H-3, pyr.), 7.80-7.77 (m, 1H, H-5, pyr.), 7.53 (s, 1H, N=CH), 7.30-7.27 (m, 1H, H-4, pyr.), 6.35 (s, 1H, NH), 3.67-3.60 (m, 2H, CH_2, imidaz.), 3.42-3.35 (m, 5H, CH_2 imidaz. and N-CH_3)[a]
4r	8.33 (s, 2H, N=CH and CH quin.), 7.97-7.94 (m, 2H, quin.), 7.77-7.71 (m, 2H, quin.), 7.60-7.53 (m, 1H, quin.), 6.69 (s, 1H, NH), 3.66-3.62 (m, 2H, CH_2, imidaz.), 3.45-3.40 (m, 5H, CH_2 imidaz. and N-CH_3)
4s	7.72 (s, 1H, N=CH), 7.51 (s, 1H, H-5, furan), 6.75 (d, *J* = 2.9 Hz, 1H, H-3, furan), 6.57 (s, 1H, H-4, furan), 6.11 (brs, 1H, NH), 3.55-3.46 (m, 4H, 2 × CH_2, imidaz.), 3.46 (s, 3H, N-CH_3)[a]
4t	7.83 (s, 1H, N=CH), 7.49 (d, $J_{5,4}$ = 4.9 Hz, 1H, H-5, thiophene), 7.30 (d, $J_{3,4}$ = 3.8 Hz, 1H, H-3, thiophene), 7.06 (dd, $J_{4,3}$ = 3.8 Hz, $J_{4,5}$ = 4.9 Hz, 1H, H-4, thiophene), 5.95 (s, 1H, NH), 3.61-3.50 (brs, 2H, CH_2, imidaz.), 3.40-3.26 (m, 5H, CH_2 imidaz. and N-CH_3)
4u	8.59 (d, *J* = 4.4 Hz, 1H, H-6, pyr.), 8.18 (d, *J* = 8.1 Hz, 1H, H-3, pyr.), 7.84-7.76 (m, 1H, H-5, pyr.), 7.44-7.38 (m, 1H, H-4, pyr.), 6.01 (brs, 1H, NH), 3.45 (s, 4H, 2 × CH_2, imidaz.), 3.22 (s, 3H, N-CH_3), 2.38 (s, 3H, CH_3)

Varian Gemini 200 spectrometer or [a] Varian Unity 500 spectrometer

Then, the appropriate hydrochloride **3p-u** (10 mmol) was dissolved in anhydrous methanol (10 mL) and treated with 5% methanolic NaOH solution (11 mmol, 9.0 mL). After stirring for 30 min the solvent was evaporated under reduced pressure and the solid residue was treated with CH_2Cl_2 (50 mL). The insoluble material was filtered off, and the filtrate was evaporated to dryness. The crude product thus obtained was purified by crystallization from suitable solvent. Physical and analytical data for compounds **4p-u** are presented in Tables 1 and 2.

4p: ^{13}C NMR (50 MHz, DMSO-d_6, δ ppm): 161.6 (C-2 imidaz.), 154.4 (N=CH), 149.0, 136.3, 134.7, 122.9, 119.3 (5C pyr.), 52.2, 44.1 (C-4, C-5 imidaz.), 31.5 (N-CH_3).
4r: ^{13}C NMR (50 MHz, DMSO-d_6, δ ppm): 161.6 (C-2 imidaz.), 154.8 (N=CH), 147.3, 136.0, 134.9, 129.7, 128.4, 127.9, 127.4, 126.5, 117.9 (9C quin.), 52.6, 45.2 (C-4, C-5 imidaz.), 31.5 (N-CH_3).
4t: ^{13}C NMR (50 MHz, DMSO-d_6, δ ppm): 161.8 (C-2 imidaz.), 140.9 (N=CH), 130.5, 127.9, 127.8, 126.6 (4C thiophene), 52.2, 45.9 (C-4, C-5 imidaz.), 31.7 (N-CH_3).
4u: ^{13}C NMR (50 MHz, DMSO-d_6, δ ppm): 165.4 (C-2 imidaz.), 158.7 (C=N), 155.6, 148.7, 136.6, 124.5, 121.2 (5C pyr.), 49.2 (C-4, C-5 imidaz.), 38.5 (N-CH_3), 15.9 (CH_3).

Pharmacology. Radioligand binding assays

I_1-Binding site assay

Kidneys were obtained post-mortem from male Sprague Dawley rats (250-280 g) and crude P_2 membranes were prepared according to methods of Lione et al. (36). [^{3}H]clonidine (3 nM, Perkin Elmer) was bound in the presence of 10 mM rauwolscine to preclude binding to α_2-adrenoceptors, the specific component was defined by 10 mM rilmenidine; under these conditions the site labeled is a model of the central I_1 binding site (37). Membrane aliquots (400 mL, 0.2-0.5 mg protein) were incubated with 11 concentrations of the test compound over the range 0.01mM – 100 mM. Incubations were carried out in 50 mM Tris-HCl buffer (pH 7.4) at room temperature for 45 min. Bound ligand and free radioactivities were separated by rapid filtration through pre-soaked (0.5% polyethylamine) glass-fibre filters (Whatman GFB). Trapped ligand was determined by liquid scintillation counting and data analyzed by GraphPad Prism version 3.02 for Windows (GraphPad Software, San Diego, California, USA) to yield IC_{50} values (the concentration of drug that displaces 50% of specifically bound [^{3}H]clonidine).

α_1-Binding site assay

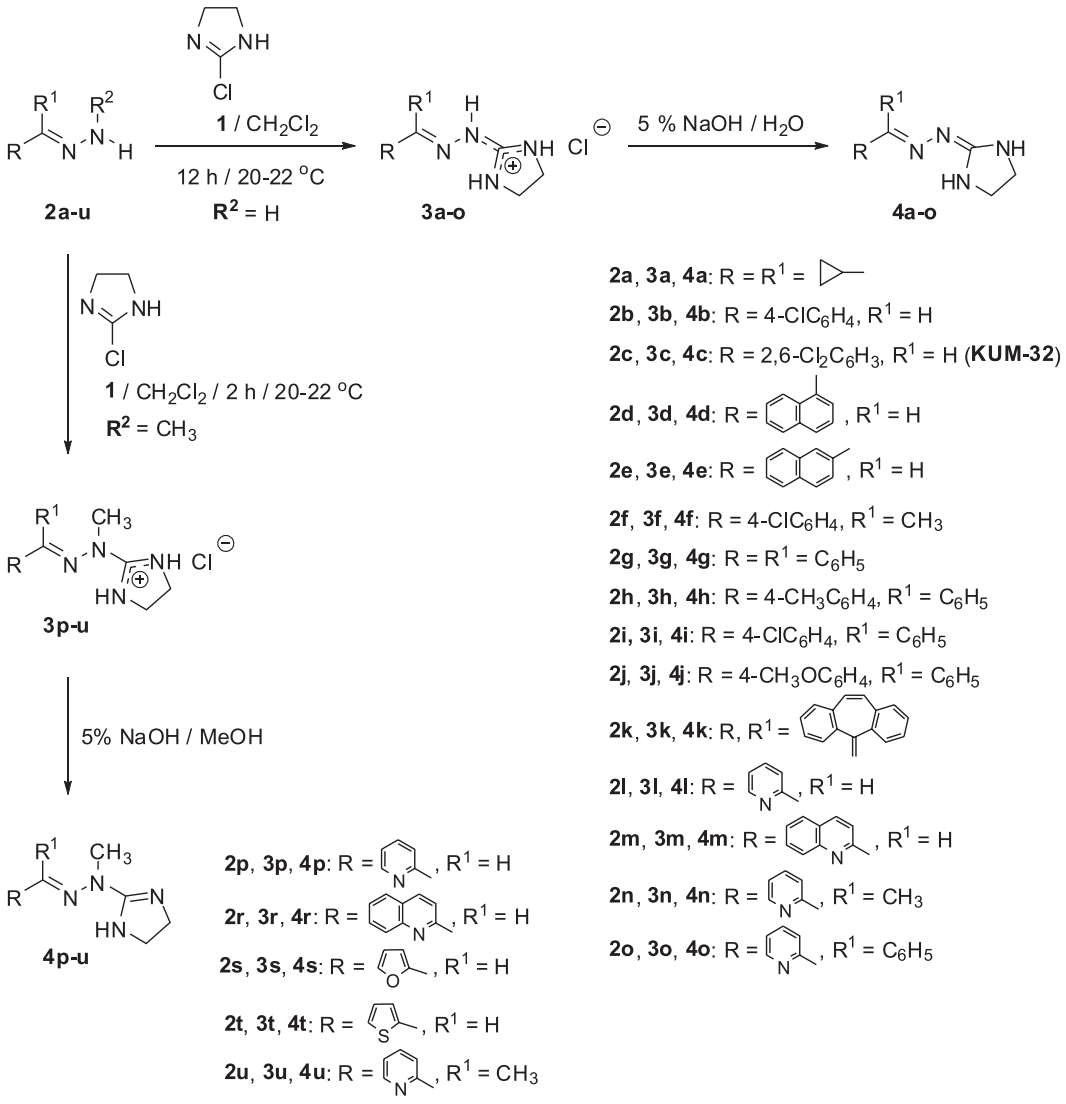
Crude P_2 brain membranes were prepared as follows. All procedures were carried out at 4^{o}C unless otherwise stated, rat brains (male Sprague Dawley rats, 250-280 g) were taken and homogenized in 10 volumes of ice-cold buffer (50 mM Tris-HCl, 1 mM $MgCl_2$ and 320 mM sucrose, pH 7.4). The homogenate was centrifuged (1000 × *g* for 10 min) and the precipitate discarded. The supernatant was centrifuged a second time (32000 × *g* for 20 min) and the supernatant discarded, with the remaining precipitate making up the crude P_2 membrane preparation. This was washed twice in an excess of buffer (50 mM Tris-HCl, 1mM $MgCl_2$) at room temperature, 30 mL were added, the precipitate re-suspended and centrifuged (32000 × *g* for 20 min). The washed membrane preparations were stored at –70^{o}C until use. Prior to use they were thawed and washed (as above) a further two times. Membrane aliquots (400 µL, 0.2-0.3 mg protein) were incubated with 11 concentrations of the test compound over the range 0.01 nM – 100 µM in the presence of the selective α_1-adrenoceptor ligand [^{3}H]prazosin (0.5 nM, Perkin Elmer) to final volume of 500 µL. Non-specific binding was determined using 10 µM phenylephrine. Each incubation was performed in triplicate, at room temperature and allowed to reach equilibrium (45 min). Bound and free radioactivities were separated by rapid filtration through pre-soaked (0.5% polyethyleneimine) glass-fibre filters (Whatman GF/B). Filters were then washed twice with 5 mL of ice-cold buffer and membrane bound radioactivity remaining on the filters was determined by liquid scintillation counting. Data were analyzed by iterative non-linear regression curve fitting procedures in GraphPad Prism version 3.02 for Windows (GraphPad Software, San Diego, California, USA). Each experiment was analyzed individually and the equilibrium dissociation constant (K_i), was determined by the method of Cheng and Prusoff (38).

α_2- and I_2-Binding site assays

These were conducted as described above for α_1-binding site using the selective I_2 binding site ligand [^{3}H]2BFI (1 nM) or the α_2-adrenoceptor antagonist [^{3}H]RX821002 (1 nM). Non-specific binding was determined using 10 µM BU224, I_2 binding and 10 µM rauwolscine, α_2-adrenoceptor binding. The equilibrium dissociation constant (K_i) was determined by the method of Cheng and Prusoff (38).

RESULTS AND DISCUSSION

The desired *N*-(imidazolidin-2-ylidene)hydrazones **3a-o** were obtained as depicted in Scheme 1 from 2-chloro-4,5-dihydroimidazole (**1**) and the corresponding aldehyde/ketone hydrazones **2a-o**. The reactions carried out in dichloromethane at room temperature for twelve hours gave the hydrochlorides **3a-o** in good yields. Analogous reactions of **1** with more reactive *N*-methylhydrazones **2p-u** required two hours at room temperature to provide the target *N*-(4,5-dihydro-1*H*-imidazol-2-yl)-*N*-methylhydrazone hydrochlorides **3p-u**. Free bases **4a-o** and **4p-u** were obtained upon treatment of the corresponding hydrochlorides **3a-o** and **3p-u** with aqueous or methanolic NaOH solution, respectively (Scheme 1).



Scheme 1. Synthesis of compounds **3a-u** and **4a-u**.

Structures of the final hydrochlorides **3a-u** and corresponding free bases **4a-u** were confirmed by elemental analysis as well as IR and NMR spectroscopic data (Table 1 and 2).

For example, in the ^{1}H NMR spectrum of *N*-(imidazolidin-2-ylidene)hydrazone **4b** the N-H protons of the imidazolidine ring appear as two separate singlet signals at d 6.89 ppm and d 6.52 ppm. Such a pattern is indicative of an intramolecular hydrogen bonding between the imidazolidine N-H group and the hydrazone nitrogen atom in DMSO-d_6 solution, which hinders the tautomeric process within the guanidine moiety. The methylene protons of the imidazolidine ring appear as a broad signal at δ 3.39 ppm and the methine =N-N=CH- proton is represented by a singlet at δ 7.95 ppm.

The ^{1}H NMR spectrum of *N*-(4,5-dihydro-1*H*-imidazol-2-yl)-*N*-methylhydrazone **4p** exhibits characteristic singlet of the N-H proton of the 2-substituted imidazoline moiety at δ 6.35 ppm. The methylene protons of the imidazoline ring are nonequivalent and appear as two separate multiplets at δ 3.67-3.60 ppm and δ 3.42-3.35 ppm. In the ^{13}C NMR spectrum of **4p** two signals at δ 52.2 ppm and 44.1 ppm appear for the two corresponding carbon atoms. Furthermore, the carbon resonances at δ 31.5 ppm, 154.4 ppm and 161.6 ppm are assigned to N-CH_3 and N=CH carbon atoms, and C-2 of the 2-imidazoline ring, respectively.

The *N*-(imidazolidin-2-ylidene)hydrazones **4a-o** could be regarded as structural analogues of guanylhydrazones of (hetero)aryl methyl ketones, which in DMSO-d_6 exist in the imino form (43). We have

examined the tautomers of **4b** by quantum chemical calculations using *ab initio* method at HF/6-31G** level (44). Calculations of the corresponding energies indicate that the imino-imidazolidine tautomer **4b/A** is more stable than the amino-imidazoline tautomer **4b/B** by 14.64 kcal/mol. Moreover, on the basis of their dipole moments, **4b/A** (m = 5.61 Debye) is predicted to predominate over **4b/B** (μ = 2.81 Debye) in polar solvents such as DMSO (Figure 2). These results are in agreement with the ^{1}H NMR study presented above for **4b** in DMSO-d_6 solution.

***In vitro* biological activity**

The prepared compounds were tested for their affinities to α-adrenergic (α_1 and α_2) and imidazoline (I_1 and I_2) receptors by radioligand binding assays using whole rat brain for α-adrenergic and imidazoline I_2 receptors, and rat kidney for imidazoline I_1 receptors. The results are presented in Table 3.

In general, the tested hydrazones showed variable affinities to the receptors investigated. As shown in Table 3, the dicyclopropyl derivative **3a**, which can be regarded as a partially constrained analogue of the well-known I_1/α_2 agonist *rilmenidine* (8), exhibited a moderate affinity to imidazoline I_1 receptors (K_i = 116.0 nM). Among the aryl aldehyde/ketone hydrazones **3b-k**, the 2,6-dichloro-substituted compound **3c** (**KUM 32**), previously described as a potent α_2-adrenergic agonist (14), in our studies showed good affinity for imidazoline I_2 receptors (K_i = 47.9 nM). The 4-chloro-substituted analogue **3b** retained a significant I_2 affinity (K_i = 72.8 nM), whereas its affinity for α_2-adrenoceptors was extremely decreased in comparison to that of **3c** (K_i = 4412.0 nM *vs*. K_i = 13.2 nM). On the other hand, reduction in binding affinity at I_2 receptors was observed for a series of compounds **3f-j** with either the methyl or phenyl substituent at the azomethine =N-N=CR^1- moiety (R^1 = CH_3, C_6H_5). Compounds **3f-i** exhibited binding affinities to imidazoline I_2 receptors with K_i values ranging from 230.1 to 657.9 nM and the compound **3j** showed very weak affinity (K_i = 2090.0 nM). Interestingly, replacement of the 4-chlorophenyl moiety in hydrazone **3b** with a 2-naphthalene ring (**3e**) resulted in good affinity to both α_2-adrenergic and imidazoline I_1 receptors (K_i = 94.3 nM and IC_{50} = 51.7 nM, respectively), while the 1-naphthyl analogue **3d** showed a moderate affinity for α_1-adrenoceptors (K_i = 247.0 nM) and lost its properties in comparison to **3e**. Furthermore, the α_1K_i value obtained for the derivative **3k** was almost equal with that of hydrazone **3d** (K_i = 263.0 nM *vs*. K_i = 247.0 nM).

We then investigated the binding affinity of heteroaryl hydrazones **3l-u**. As shown in Table 3, the 2-pyridyl derivative **3l** displayed a high α_1-adrenergic affinity (K_i = 24.6 nM) and moderate affinity at I_2 receptors (K_i = 409.4 nM). Foye and co-workers described previously that compound **3l** induced a gradual decrease in mean arterial blood pressure after intravenous administration to normotensive rats (45). The above result suggests that hypotensive effect of **3l** might be mediated through antagonist activity on α_1-adrenoceptors located on vascular smooth muscle (5). However, the analogue **3o** with a phenyl group at the azomethine =N-N=CR^1- moiety (R^1 = C_6H_5) showed affinity about 88-times lower at α_1-adrenoceptors (K_i = 2210.0 nM) and retained moderate I_2 affinity (K_i = 225.9 nM). Moreover, replacement of the phenyl substituent in the hydrazone **3l** with a methyl group (**3n**, R^1 = CH_3) resulted in an 8-fold decrease in binding affinity for I_2 receptors (K_i = 1881.0 nM). In addition, the 2-pyridyl derivatives **3p** and **3u** substituted at the hydrazone nitrogen atom with a methyl group (R^2 = CH_3) were almost lacking

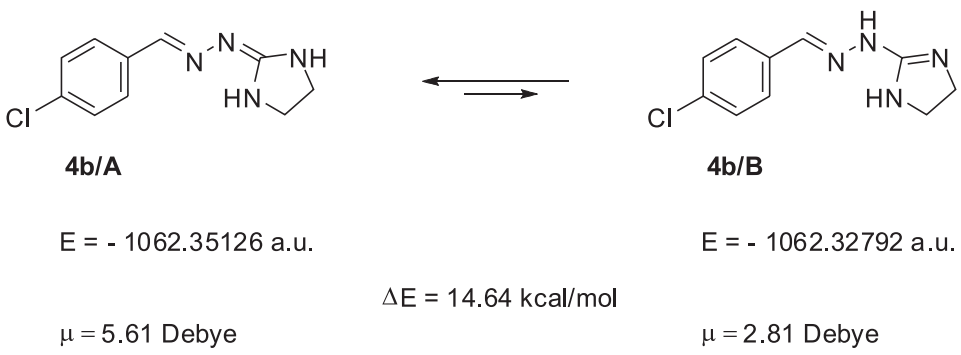


Figure 2. Calculated energies (E, a.u.), relative energy (DE, kcal/mol) and dipole moments (m, Debye) of tautomers **4b/A** and **4b/B**

Table 3. Binding affinities to a-adrenergic and imidazoline I_1 and I_2 receptors for compounds **3a-u**

Compd. No.	R	R^1	R^2	α_1 *K*i (nM)	α_2 *K*i (nM)	I_1 IC_{50} (nM)	I_2 Ki (nM)
3a			H	ND	5300.0	116.0	1120.0
3b	4-ClC_6H_4	H	H	2190.0	4412.0	3279.0	72.8
3c (**KUM-32**)	2,6-$Cl_2C_6H_3$	H	H	ND[a]	13.2[a]	2530.0	47.9
3d		H	H	247.0	ND	40400.0	6710.0
3e		H	H	1450.0	94.3	51.7	70600.0
3f	4-ClC_6H_5	CH_3	H	ND	2960.0	3680.0	340.0
3g	C_6H_5	C_6H_5	H	ND	31100.0	5660.0	230.1
3h	4-$CH_3C_6H_4$	C_6H_5	H	467.0	21860.0	23150.0	327.9
3i	4-ClC_6H_4	C_6H_5	H	ND	220000.0	11800.0	657.9
3j	4-$CH_3OC_6H_4$	C_6H_5	H	ND	106000.0	18100.0	2090.0
3k			H	263.0	17270.0	164400.0	3684.0
3l		H	H	24.6	1869.0	6716.0	409.4
3m		H	H	ND	22470.0	6145.0	26.7
3n		CH_3	H	ND	1310.0	15100.0	1881.0
3o		C_6H_5	H	2210.0	15440.0	46940.0	225.9
3p		H	CH_3	18700.0	71860.0	5623.0	6294.0
3r		H	CH_3	2940.0	25130.0	67120.0	706.6
3s		H	CH_3	11400.0	ND	ND	ND
3t		H	CH_3	2640.0	ND	ND	ND
3u		CH_3	CH_3	ND	16800.0	6600.0	29900.0

[a] Lit. α_1 IC_{50} = 3400.0 nM, α_2 IC_{50} = 48.0 nM (14). ND: not determined.

any activity at the receptors investigated (Table 3). Interestingly, the analogue **3m** with the 2-quinoline instead a pyridine ring (**3l**) displayed a high I_2 affinity (K_i = 26.7 nM) and selectivity as compared with α_2-adrenergic and imidazoline I_2 receptors (K_i = 22470.0 nM and IC_{50} = 6145.0 nM, respectively). Nevertheless, placement of a methyl group at the hydrazone nitrogen atom (**3r**, $R^2 = CH_3$) reduced I_2 affinity by about 25-fold (K_i = 706.6 nM *vs*. K_i = 26.7 nM). Moreover, the 2-thienyl analogue **3t** showed very weak affinity at α_1-adrenoceptors (K_i = 2640.0 nM) and affinity of the 2-furyl compound **3s** was almost abolished (K_i = 11400.0 nM).

The compounds **4p-u** were further evaluated for cytotoxic activity on six human cancer cell lines. None of the tested compounds exhibited cytotoxic properties. Full details on the method of testing have been described elsewhere (46, 47).

In summary, a series of 2-imidazolinylhydrazone derivatives, possessing variable activities at the receptors investigated, have been prepared. The 2-naphthyl compound **3e** elicited a significant affinity for both α_2-adrenergic and imidazoline I_1 receptors (K_i = 94.3 nM and IC_{50} = 51.7 nM, respectively), while its 2-quinolyl analogue **3m** was the most selective for imidazoline I_2 receptors with high affinity for these receptors (K_i = 26.7 nM). Interestingly, the 2-pyridyl derivative **3l** was found to be the most potent at α_1-adrenoceptors with a K_i value of 24.6 nM. Introduction either a methyl or phenyl group at the azomethine moiety (**3f-**

j, **3n**) led to a considerable reduction in binding affinity at the receptors investigated, whereas substitution of the hydrazone nitrogen atom with a methyl group resulted even in a loss of activity (**3p**, **3u**).

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