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Synthesis, structure and antiaggregatory effects of some *N*-(4,5-dihydro-1*H*-imidazol-2-yl)indoles

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Abstract

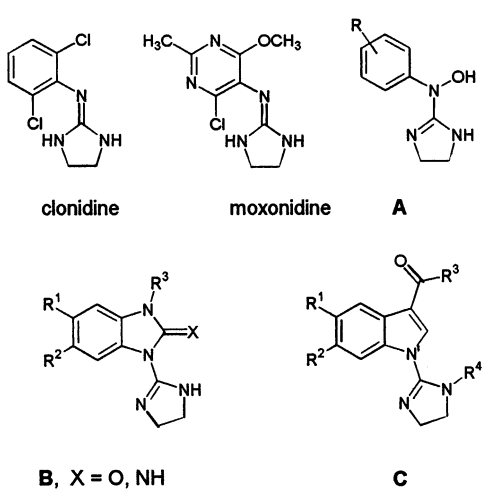
A series of 1-(4,5-dihydro-1*H*-imidazol-2-yl)indole derivatives was prepared in order to evaluate their antiaggregatory activity in human platelets. The compounds **4a**–**m** were prepared by reacting *N*-aryl-*N*-(4,5-dihydro-1*H*-imidazol-2-yl)hydroxylamines (**2a**–**d**) with monosubstituted acetylene derivatives **3a**–**b**. Imidazoline derivatives **4** were further acetylated or sulfonylated to give amides **5a**–**c** and sulfonamides **6a**–**c** and **7a**–**c**, respectively. Eight compounds were taken as representative aryliminoimidazoline analogs. Among them only one, **4m**, showed a good concentration-dependent action against the primary or α_2-adrenoreceptor mediated phase of noradrenaline-induced aggregation in platelets.

Keywords: *N*-(4,5-Dihydro-1*H*-imidazol-2-yl)indoles; Synthesis; X-ray structure; Antiaggregatory activities

1. Introduction

The imidazoline class of drugs interacting with adrenergic [1–3] and/or imidazoline [4] receptors is known to mediate a variety of biological actions including lowering blood pressure, sedation, anxiety reduction, analgesia, hypothermia, decreased salivary secretion and mydriasis. Moreover, previous reports demonstrated that synthetic imidazolines act either as inhibitors of α_2-mediated events in platelets [5,6] or inducers of platelet activation [7,8]. The prototypical agents in the series of aryliminoimidazolines are *clonidine* and *moxonidine* depicted in Chart 1.

We previously reported the synthesis and pronounced antiaggregatory activity of aryliminoimidazoline analogues bearing a hydroxyl group at the exocyclic nitrogen atom (structure **A**, Chart 1) [9]. The effects of incorporation of the exocyclic nitrogen atom into 1,3-dihydrobenzimidazole ring system to form structure **B** have also been described [10].



(Chart 1)

We now report our investigations on the synthesis, structure and ability to inhibit proaggregatory responses to adrenaline in human platelets of the compounds in which the exocyclic nitrogen atom was incorporated into an indole ring system (structure **C**, Chart 1).

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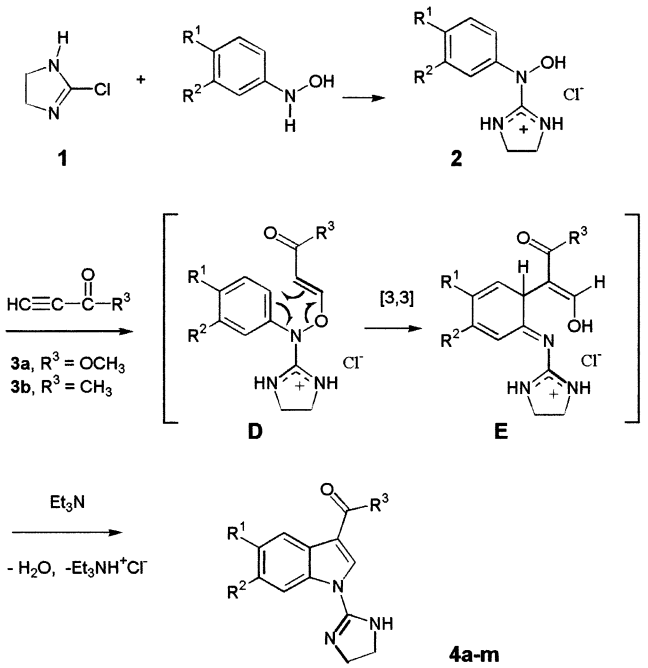
2. Chemistry

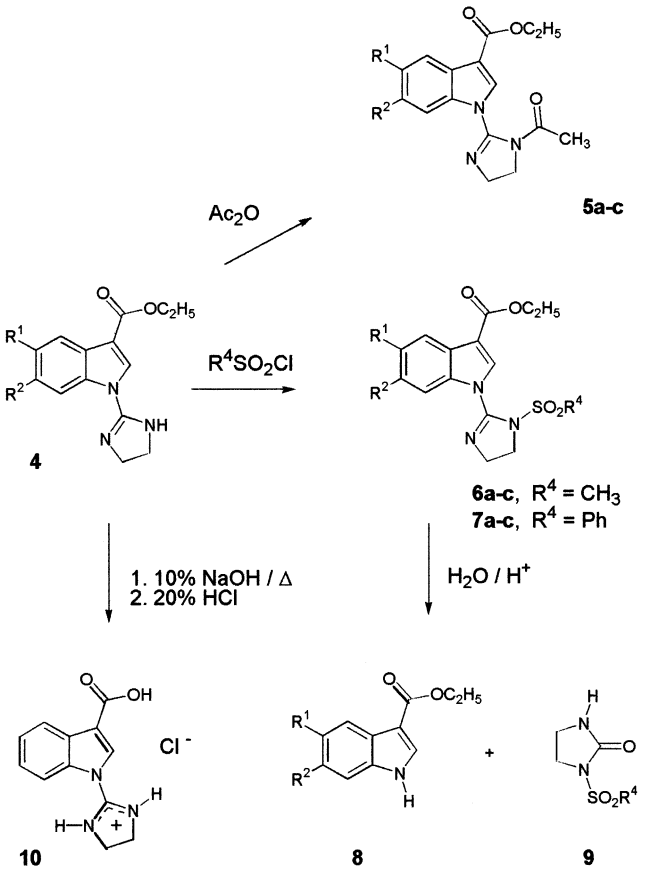
Usually, the incorporation of the 2-imidazoline moiety into various molecules with biological activity can be achieved by the nucleophilic displacement of the chlorine atom of 2-chloro-4,5-dihydroimidazole (**1**) with amines, phenols or thiophenols. Preparation of *N*-(4,5-dihydroimidazol-2-yl)azoles can be also realized by 'aliphatic aldehyde assisted' *N*-heteroalkylation of an azole with **1** [11]. However, attempted reactions of **1** with indoles using either of these methods failed. Therefore, the indoles discussed in this paper were prepared via an alternative approach starting from *N*-aryl-*N*-(4,5-dihydro-imidazol-2-yl)hydroxylamines (**2**), which are potentially useful substrates in polyhetero-Cope reactions [12,13].

We used a method developed by Toyota and Fukumoto [14–16] to assemble the indole subunit. Initially, the intermediate hydroxylamines **2a**–**d** were prepared from 2-chloro-4,5-dihydroimidazole (**1**) and suitable *N*-arylhydroxylamines [9] and were then treated with monosubstituted acetylene derivatives **3a**,**b** to afford the desired *N*-(4,5-dihydro-1*H*-imidazol-2-yl)indoles (**4a**–**m**) (Scheme 1). The first step of the reaction sequence is the formation of an adduct **D**, which undergoes [3,3] sigmatropic shift (formation of **E**) followed by ring closure upon loss of a water molecule.

The imidazoline derivatives **4** were further subjected to reactions with acetic anhydride, mathanesulfonyl chloride and phenylsulfonyl chloride (Scheme 2). The structures of the amides **5a**–**c**, as well as sulfonamides



Scheme 1.



Scheme 2.

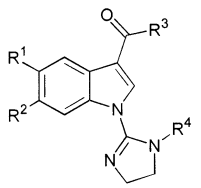
6a–**c** and **7a**–**c** obtained, were confirmed by elemental analysis and spectral data. It is worth noting that these compounds proved to be rather unstable in aqueous solution. This behavior might be explained by the high susceptibility of the imidazoline C-2 carbon atom towards nucleophilic attack by a water molecule leading to decomposition products of type **8** and **9** (Scheme 2).

Ethyl 1-(4,5-dihydro-1*H*-imidazol-2-yl)indole-3-carboxylate (**4a**) was hydrolyzed under basic conditions to give the corresponding carboxylic acid derivative **10**. However, attempted thermal decarboxylation of **10** failed and an intractable mixture of products was formed upon heating the substrate at 190°C. Physicochemical properties and spectroscopic data for all the compounds prepared are shown in Tables 1–3.

2.1. Crystal structure of *4b*

In the crystal, molecules of **4b** lie on a mirror plane passing through all non-H atoms. However, for some atoms, especially N11 and O16, it may be a statistical mirror plane, what is evident from the shape of their anisotropic displacement ellipsoids, which are strongly elongated in the direction perpendicular to the plane. We have estimated that deviation of about 0.2 Å of

Table 1
Physico-chemical properties of the indole derivatives **4a–m**, **5a–c**, **6a–c** and **7a–c**



Comp.	R^1	R^2	R^3	R^4	Yield (%)	M.p. (°C)	Analysis
4a	H	H	OC_2H_5	H	65	154–155 [a] (MeOH–H_2O)	$C_{14}H_{15}N_3O_2$ (257.28)
4b	CH_3	H	OC_2H_5	H	44	190–191 (MeOH)	$C_{15}H_{17}N_3O_2$ (271.31)
4c	OCH_3	H	OC_2H_5	H	38	166–167 (MeOH)	$C_{15}H_{17}N_3O_3$ (287.31)
4d	C_2H_5	H	OC_2H_5	H	40	140–143 (*i*-PrOH)	$C_{16}H_{19}N_3O_2$ (285.33)
4e	CH_3	CH_3	OC_2H_5	H	55	165–168 (EtOH–H_2O)	$C_{16}H_{19}N_3O_2$ (285.33)
4f	Cl	H	OC_2H_5	H	51	198 (EtOH)	$C_{14}H_{14}ClN_3O_2$ (291.72)
4g	Cl	Cl	OC_2H_5	H	49	233–236 (AcOEt)	$C_{14}H_{13}Cl_2N_3O_2$ (326.17)
4h	H	H	CH_3	H	28	211–214 (MeOH)	$C_{13}H_{13}N_3O$ (227.25)
4I	CH_3	H	CH_3	H	37	210–213 (MeOH)	$C_{14}H_{15}N_3O$ (241.28)
4j	OCH_3	H	CH_3	H	22	178–182 (MeOH)	$C_{14}H_{15}N_3O_2$ (257.28)
4k	C_2H_5	H	CH_3	H	28	168–170 (MeOH)	$C_{15}H_{17}N_3O$ (255.31)
4l	Cl	H	CH_3	H	38	219–222 (MeOH)	$C_{13}H_{12}ClN_30$ (267.7)
4m	Cl	Cl	CH_3	H	37	235–239 (*i*-PrOH)	$C_{13}H_{11}Cl_2N_3O$ (302.15)
5a	H	H	OC_2H_5	$COCH_3$	54	118–120 (MeOH–H_2O)	$C_{16}H_{17}N_3O_3$ (299.32)
5b	CH_3	H	OC_2H_5	$COCH_3$	77	158–160 (MeOH)	$C_{17}H_{19}N_3O_3$ (313.34)
5c	OCH_3	H	OC_2H_5	$COCH_3$	52	155–156 (MeOH)	$C_{17}H_{19}N_3O_4$ (329.34)
6a	H	H	OC_2H_5	SO_2CH_3	69	151–152 (MeOH)	$C_{15}H_{17}N_3O_4S$ (335.37)
6b	CH_3	H	OC_2H_5	SO_2CH_3	84	134–135 (MeOH)	$C_{16}H_{19}N_3O_4S$ (349.39)
6c	OCH_3	H	OC_2H_5	SO_2CH_3	80	145–146 (MeOH–H_2O)	$C_{16}H_{19}N_3O_5S$ (365.39)
7a	H	H	OC_2H_5	SO_2Ph	53	169–170 (MeOH)	$C_{20}H_{19}N_3O_4S$ (397.47)
7b	CH_3	H	OC_2H_5	SO_2Ph	45	170–171 (MeOH)	$C_{21}H_{21}N_3O_4S$ (411.46)
7c	OCH_3	H	OC_2H_5	SO_2Ph	55	131 (MeOH)	$C_{21}H_{21}N_3O_5S$ (427.46)

[a] Ref. [16]; m.p. 154–155°C.

N11 from this plane would improve significantly the otherwise short bond lengths to this atom.

A search of the Cambridge Structural Database (CSD) [17] gave 12 molecules with carbonyl substituent at the indole position 3 and unsubstituted positions 2 and 4. In all cases the carbonyl group lies approximately in the indole plane with a maximum value for the torsion angle C9–C3–C15–O16 of 13.8°. The mean value of the C_{ar}–C_{sp^2} bond length, 1.445(8) Å, indicates for these compounds strong coupling between the carbonyl group and the indole π-electron systems. As the C_{ar}–C_{sp^2} bond has partial double bond character two isomers, *Z* and *E*, are possible. In all 12 molecules found in the CSD, the configuration around this bond is *Z*, while for compound **4b** this bond has the *E* configuration.

Recently we reported the crystal structure of a compound which had an exocyclic nitrogen atom of the iminoimidazoline system incorporated in a 1,3-dihydro-2-oxo-benzimidazole ring [10]. We concluded that the approximately coplanar arrangement of the guanidine moiety and 1,3-dihydro-2-oxo-benzimidazole system results from conjugation of their π-electron systems and intramolecular N–H···O and C–H···N hydrogen bond interactions.

In compound **4b**, the exocyclic N atom of iminoimidazolidine is incorporated into the indole ring. The geometry of the guanidine fragment (bond lengths and angles) in this compound is very similar to that observed in the 2-oxo-benzimidazole derivative [10] (except for the geometry around N11, for reasons given above). Therefore the degree of conjugation of the π-electron systems should be very similar in both compounds. In compound **4b**, however, additional stabilization of the planar structure results from intermolecular rather then intramolecular hydrogen bond interactions.

There are two pairs of N–H···O=C and C–H···O=C type hydrogen bonds, which join the molecules of **4b** into a centrosymmetric dimer (Fig. 1). Taking into account the geometry of the C2–H2···O16 hydrogen bond [C2···O16 3.188(3) Å, H2···O16($1-x$, $-y$, $1-z$) 2.20 Å, $<$C2–H2···O16($1-x$, $-y$, $1-z$) 166°], this relatively strong C–H···O interaction, together with the N–H···O H-bond, should be an important factor stabi-

Table 2
Spectroscopic data for the indole derivatives **4a**–**m**

Comp.	IR (KBr)	^{1}H NMR (DMSO-d_6)	^{13}C NMR (DMSO-d_6)
4a [a]	3152, 2880, 1708, 1636, 1552, 1500, 1200, 1072	1.35 (t, 3H, CH_3); 3.7 (s, 4H, CH_2); 4.3 (q, 2H, CH_2); 7.3–7.4 (m, 3H); 8.0–8.1 (m, 1H); 8.4 (s, 1H); 8.5–8.6 (m, 1H)	14.3; 48.5; 59.7; 109.6; 115.8; 120.7; 123.3; 124.3; 126.4; 132.0; 135.5; 155.4; 163.5
4b	3336, 3136, 2880, 1680, 1632, 1552, 1520, 1472, 1280, 1216	1.35 (t, 3H, CH_3); 2.4 (s, 3H, CH_3); 3.52 (m, 2H, CH_2); 3.91 (m, 2H, CH_2); 4.3 (q, 2H, CH_2); 7.16 (dd, 1H, $J_{6,7} = 8.6$ Hz, $J_{6,4} = 1.7$ Hz); 7.25 (s, 1H); 7.85 (d, 1H, $J_{4,6} = 1.7$ Hz); 8.35 (s, 1H); 8.4 (d, 1H, $J_{7,6} = 8.6$ Hz)	14.3; 21.1; 43.4; 53.6; 59.98; 109.2; 115.4; 120.3; 125.6; 126.7; 131.9; 132.3; 133.8; 155.4; 163.5
4c [b]	3152, 2992, 1696, 1648, 1568, 1488, 1204, 1152, 1072	1.4 (t, 3H, CH_3); 3.65 (m, 2H, CH_2); 3.88 (s, 3H, CH_3); 4.05 (m, 2H, CH_2); 4.36 (q, 2H, CH_2); 6.95 (dd, 1H, $J_{6,7} = 9.2$ Hz, $J_{6,4} = 2.5$ Hz); 7.26 (s, 1H); 7.63 (d, 1H, $J_{4,6} = 2.5$ Hz); 8.04 (s, 1H); 8.13 (d, 1H, $J_{7,6} = 9.2$ Hz)	
4d	3344, 3136, 2880, 1680, 1632, 1560, 1504, 1472, 1312, 1216	1.1–1.55 (m, 6H, CH_3); 2.65 (q, 2H, CH_2); 3.7 (s, 4H, CH_2); 4.3 (q, 2H, CH_2); 7.0–7.4 (m, 2H); 7.9 (d, 1H); 8.35 (s, 1H); 8.5 (d, 1H)	
4e	3144, 2888, 1696, 1632, 1544, 1472, 1296, 1216, 1168	1.35 (t, 3H, CH_3), 2.33 (s, 6H, CH_3); 3.5 (m, 2H, CH_2); 3.9 (m, 2H, CH_2); 4.3 (q, 2H, CH_2); 7.24 (s, 1H); 7.81 (s, 1H); 8.27 (s, 1H); 8.31 (s, 1H)	
4f	3136, 2976, 1712, 1632, 1552, 1504, 1452, 1296, 1232, 1200	1.35 (t, 3H, CH_3); 3.55 (m, 2H, CH_2); 3.9 (m, 2H, CH_2); 4.33 (q, 2H, CH_2); 7.36 (s, 1H); 7.4 (dd, 1H, $J_{6,7} = 8.9$ Hz, $J_{6,4} = 2.2$ Hz); 8.0 (d, 1H, $J_{4,6} = 2.2$ Hz); 8.47 (s, 1H); 8.55 (d, 1H, $J_{7,6} = 8.9$ Hz)	14.3; 43.5; 53.7; 60.0; 109.1; 117.5; 119.8; 124.4; 127.7; 128.0; 133.3; 134.0; 155.1; 163.1
4g	3120, 2940, 1696, 1632, 1536, 1488, 1428, 1312, 1248, 1200	1.35 (t, 3H, CH_3); 3.6 (m, 2H, CH_2); 3.84 (m, 2H, CH_2), 4.36 (q, 2H, CH_2); 7.43 (s, 1H); 8.15 (s, 1H), 8.5 (s, 1H), 8.8 (s, 1H)	
4h	3104, 2864, 1650, 1632, 1600, 1536, 1480, 1296, 1232, 1200	2.51 (s, 3H, CH_3); 3.73 (s, 4H, CH_2), 7.2–7.4 (m, 3H); 8.2–8.3 (m, 1H); 8.45–8.5 (m, 1H); 8.62 (s, 1H)	27.5; 48.6; 115.5; 118.4; 121.5; 123.6; 124.5; 126.3; 134.0; 135.7; 155.5; 193.3
4i	3344, 2910, 1650, 1632, 1532, 1472, 1296, 1212	2.4 (s, 3H, CH_3); 2.5 (s, 3H, CH_3); 3.7 (s, 4H, CH_2); 6.9–7.5 (m, 2H); 8.1 (d, 1H); 8.4 (d, 1H); 8.55 (s, 1H)	
4j	3144, 2930, 1650, 1632, 1548, 1536, 1504, 1352, 1296, 1264	2.5 (s, 3H, CH_3); 3.7 (s, 4H, CH_2); 3.8 (s, 3H, CH_3); 6.7–7.15 (m, 2H); 7.6 (d, 1H); 8.3 (d, 1H), 8.55 (s, 1H)	
4k [b]	3104, 2960, 1650, 1636, 1536, 1476, 1296, 1248, 1200, 1136	1.3 (t, 3H, CH_3); 2.45 (s, 3H, CH_3); 2.8 (q, 2H, CH_2); 3.85 (s, 4H, CH_2); 6.9–7.4 (m, 2H); 7.7–8.3 (m, 3H)	
4l	3136, 2900, 1664, 1600, 1536, 1504, 1440, 1360, 1264, 1232	2.5 (s, 3H, CH_3); 3.7 (s, 4H, CH_2); 7.25 (s, 1H); 7.4 (dd, 1H, t, $J_{6,7} = 9$ Hz, $J_{6,4} = 2$ Hz); 8.25 (d, 1H, $J_{4,6} = 2$ Hz); 8.55 (d, 1H, $J_{7,6} = 9$ Hz); 8.7 (s, 1H)	
4m	3168, 2880, 1664, 1600, 1536, 1504, 1360, 1312, 1248, 1200	2.5 (s, 3H, CH_3); 3.8 (s, 4H, CH_2); 7.4 (s, 1H); 8.6 (s, 1H); 8.9 (s, 1H); 9.0 (s, 1H)	

[a] MS (70 eV) $m/z = 257$ [M^+, 100%], 256 (27), 228 (12), 212 (27), 201 (16), 184 (25).
[b] ^{1}H NMR spectrum run in $CDCl_3$.

lizing the dimeric structure. The ester carbonyl group plays a role as the double H-bond acceptor and the five-membered chelate ring is formed. These chelating H-bond interactions are most probably the reason for the unusual *E* configuration of the carbonyl group, and an additional factor stabilizing the planar arrangement of the imidazolidine and indole rings.

In order to confirm that the planar arrangement found in the crystal structure of indole derivatives is due to hindered rotation and not packing forces, the molecular orbital calculations on **4b** were performed on an isolated molecule [18]. Energy minimization of **4b**, subject to the condition that the bond distance N1–C10 be fixed at experimentally determined value of 1.404 Å,

Table 3
Spectroscopic data for the indole derivatives **5a–c**, **6a–c** and **7a–c**

Comp.	IR (KBr)	^{1}H NMR ($CDCl_3$)	^{13}C NMR ($CDCl_3$)
5a	1704, 1648, 1540, 1504, 1456, 1408, 1376, 1312, 1208	1.4 (t, 3H, CH_3); 1.9 (s, 3H, CH_3); 4.0 (t, 2H, CH_2); 4.2 (t, 2H, CH_2); 4.4 (q, 2H, CH_2); 7.3–7.4 (m, 2H); 7.62–7.78 (m, 1H); 8.0 (s, 1H); 8.14–8.26 (m, 1H)	14.4; 23.5; 48.6; 51.1; 60.2; 111.8; 112.5; 122.0; 123.6; 124.7; 126.7; 132.8; 138.2; 148.9; 164.1; 168.1
5b	1696; 1540; 1456; 1376; 1312; 1216; 1136	1.4 (t, 3H, CH_3); 1.9 (s, 3H, CH_3); 2.5 (s, 3H, CH_3); 4.0 (t, 2H, CH_2); 4.2 (t, 2H, CH_2); 4.4 (q, 2H, CH_2); 7.16 (dd, 1H, $J_{6,7}=8.7$ Hz, $J_{6,4}=1.7$ Hz); 7.54 (d, 1H, $J_{7,6}=8.7$ Hz); 7.94 (s, 1H); 8.0 (d, 1H, $J_{4,6}=1.7$ Hz)	14.4; 21.4; 23.5; 48.5; 51.1; 60.0; 111.1; 112.3; 124.5; 126.0; 126.9; 132.8; 133.2; 134.4; 148.9; 164.2; 168.1
5c	1696; 1632; 1536; 1456; 1376; 1308; 1256; 1204; 1152	1.4 (t, 3H, CH_3); 1.9 (s, 3H, CH_3); 3.9 (s, 3H, CH_3); 4.0 (t, 2H, CH_2); 4.2 (t, 2H, CH_2); 4.4 (q, 2H, CH_2); 6.97 (dd, 1H, $J_{6,7}=8.\ 9$ Hz, $J_{6,4}=2.6$ Hz); 7.6 (d, 1H, $J_{7,6}=8.9$ Hz); 7.68 (d, 1H, $J_{4,6}=2.6$ Hz); 7.94 (s, 1H)	14.4; 23.5; 48.6; 51.1; 55.6; 60.1; 103.5; 111.4; 113.5; 114.6; 127.8; 130.6; 132.7; 148.9; 156.7; 164.2; 168.2
6a	1708; 1648; 1552; 1520; 1456; 1408; 1364; 1200; 1164	1.4 (t, 3H, CH_3); 3.0 (s, 3H, CH_3); 4.05–4.3 (m, 4H, CH_2); 4.4 (q, 2H, CH_2); 7.3–7.45 (m, 2H), 7.9–8.3 (m, 3H)	14.2; 39.6; 52.7; 62.1; 111.6; 113.3; 121.8; 123.8; 124.4; 127.1; 133.7; 136.1; 148.7; 163.9
6b	1704, 1648, 1552, 1504, 1472, 1408, 1328, 1200	1.4 (t, 3H, CH_3); 2.5 (s, 3H, CH_3); 3.0 (s, 3H, CH_3); 4.1 (t, 2H, CH_2); 4.2 (t, 2H, CH_2); 4.4 (q, 2H, CH_2); 7.2 (dd, 1H, $J_{6,7}=8.4$ Hz, $J_{6,4}=1.6$ Hz); 7.86 (d, 1H, $J_{7,6}=8.4$ Hz); 8.0 (d, 1H, $J_{4,6}=16$ Hz); 8.15 (s, 1H)	14.4; 21.5; 39.6; 52.8; 60.2; 111.2; 113.2; 121.6; 126.0; 127.4; 133.6; 134.0; 134.5; 148.9; 164.2
6c	1696; 1648; 1560; 1488; 1440, 1344; 1260; 1204; 1152	1.4 (t, 3H, CH_3); 3.0 (s, 3H, CH_3); 3.9 (s, 3H, CH_3); 4.0–4.25 (m, 4H, CH_2); 4.4 (q, 2H, CH_2); 6.98 (dd, 1H, $J_{6,7}=9.1$ Hz, $J_{6,4}=2.5$ Hz); 7.7 (d, 1H, $J_{4,6}=2.5$ Hz); 7.9 (d, 1H, $J_{7,6}=9.1$ Hz); 8.15 (s, 1H)	14.4; 39.7, 50.0; 52.8; 55.6; 80.1; 103.6; 111.3; 114.3; 114.4; 128.4; 130.9; 134.1; 149.0; 158.9; 164.2
7a [a]	1700; 1648; 1552; 1456; 1360; 1304; 1264; 1200	1.4 (t, 3H, CH_3); 3.4 (t, 2H, CH_2); 4.1 (t, 2H, CH_2); 4.4 (q, 2H, CH_2); 7.3–7.9 (m, 8H); 8.1–8.3 (m, 2H)	14.4; 48.8; 52.2; 60.1; 111.3; 113.8; 121.8; 123.9; 124.4; 127.3; 129.5; 134.2; 134.4; 136.2; 138.6; 149.1; 164.1
7b	1712; 1656; 1584; 1552; 1472; 1408; 1360; 1264; 1220	1.42 (t, 3H, CH_3); 2.5 (s, 3H, CH_3); 3.42 (t, 2H, CH_2); 4.1 (t, 2H, CH_2); 4.4 (q, 2H, CH_2); 7.34 (dd, 1H); 7.4–7.74 (m, 6H); 8.0 (d, 1H); 8.2 (s, 1H)	14.3; 21.4; 49.7; 52.0; 60.0; 110.7; 113.3; 121.4; 125.7; 127.1; 127.5; 129.4; 133.4; 136.4; 149.0; 164.1
7c	1700; 1648; 1584; 1532; 1480; 1360; 1296; 1264; 1204; 1168	1.43 (t, 3H, CH_3); 3.43 (t, 2H, CH_2); 3.9 (t, 2H, CH_2); 4.1 (t, 3H, CH_3); 4.4 (q, 2H, CH_2); 6.9 (dd, 1H); 7.4–7.8 (m, 7H); 8.2 (s, 1H)	14.4; 49.9; 52.1; 55.8; 60.1; 103.4; 110.9; 114.1; 114.5; 127.3; 128.5; 129.5; 130.7; 134.3; 134.7; 138.5; 149.2; 158.8; 164.2

[a] MS (70 eV) $m/z=397$ [M^+, 100%], 352 (15), 332 (14), 256 (18), 211 (18), 210 (16), 202 (31), 183 (19), 182 (35), 174 (40), 157 (10), 156 (11), 130 (20), 129 (18), 128 (11), 77 (40), 68 (96).

produced an imidazoline ring rotation of 7.1°. Thus, both X-ray crystallography and molecular orbital calculations indicate that the small torsional angle ($\sim$ 7°) do not place the N11 nitrogen atom of imidazoline in a suitable spatial arrangement with respect to the phenyl ring, which is characteristic for prototypical aryliminoimidazolines such as clonidine and moxonidine.

3. Experimental

3.1. Chemistry

Melting points are uncorrected and were recorded on a Buchi apparatus. IR spectra were recorded on a Specord M80 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Varian XL-200 instrument at 200

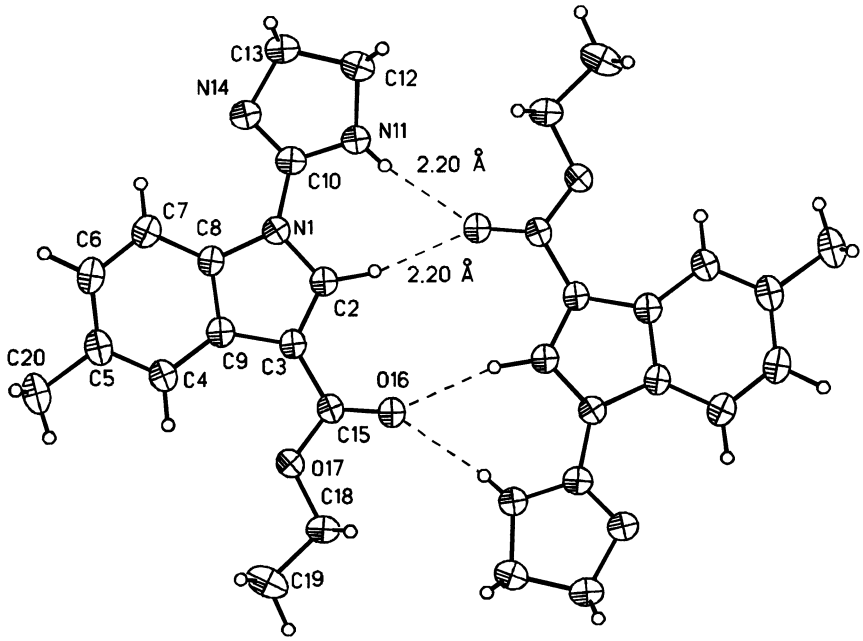


Fig. 1. Atomic labeling and H-bond interactions in crystals of 4b.

and 50 MHz, respectively using TMS as internal standard. MS spectra were taken with an LKB 9000S spectrometer. The results of elemental analyses for C and H were within $\pm$ 0.4% of the theoretical values.

*3.1.1. General procedure for preparation of indole derivatives **4a–m***

To a suspension of suitable *N*-(4,5-dihydro-1*H*-imidazol-2-yl)-*N*-phenylhydroxylamine hydrochloride (**2**) (4.7 mmol) prepared according to Ref. [9] in anhydrous acetone (15 ml) were added ethyl propiolate (**3a**) (or 3-butyn-2-one (**3b**), 4.7 mmol) and triethylamine (1.3 ml, 9.4 mmol). The reaction mixture was stirred at r.t. for 12 h, and then, the solvent was evaporated under reduced pressure to dryness. The crude product **4** thus obtained was purified by crystallization from suitable solvent. Analytical and spectroscopic data of the indoles **4a**–**m** are shown in Tables 1 and 2, respectively.

*3.1.2. General procedure for preparation of N-acetyl derivatives **5a–c***

To a solution of suitable indole **4** (3.9 mmol) in anhydrous THF (15 ml) were added acetic anhydride (1.47 ml, 13.6 mmol) and triethylamine (2.15 ml, 13.6 mmol). The mixture was stirred for 12 h and the solvent evaporated. To the oily residue was added 10% Na_2CO_3 (30 ml) and extracted with CH_2Cl_2 (2 $\times$ 20 ml). Then, the organic layer was dried with $MgSO_4$ and the solvent evaporated. The residue of crude product **5** was purified by crystallization from suitable solvent. Analytical and spectroscopic data of the amides **5a**–**c** are shown in Tables 1 and 3, respectively.

*3.1.3. Reactions of the indoles **4** with methanesulfonyl chloride. Preparation of sulfonamides **6a–c***

To a solution of suitable indole **4** (3.9 mole) in anhydrous pyridine (25 ml), methanesulfonyl chloride (1.22 ml, 15.6 mmol) was added at 0°C. The reaction mixture was stirred at room temperature (r.t.) for 12 h, and then poured into cold water (50 ml). The crude product **5** that precipitated was collected by filtration and purified by crystallization from suitable solvent. Analytical and spectroscopic data of the sulfonamides **6a**–**c** are shown in Tables 1 and 3, respectively.

*3.1.4. Reaction of the indoles **4** with benzenesulfonyl chlorides. Preparation of sulfonamides **7a–c***

To a solution of suitable indole **4** (3.9 mmol) in anhydrous THF (30 ml) were added benzenesulfonyl chloride (1.98 ml, 15.6 mmol) and triethylamine (2.16 ml, 15.6 mmol). The reaction mixture was stirred at r.t. for 12 h, and then the solvent evaporated to dryness under reduced pressure. The crude product **7** thus obtained was purified by crystallization from suitable solvent. Analytical and spectroscopic data for sulfonamides **7a**–**c** are shown in Tables 1 and 3, respectively.

*3.1.5. Preparation of 1-(4,5-dihydro-1H-imidazol-2-yl)-indolyl-3-carboxylic acid hydrochloride (**10**)*

The suspension of indole **4a** (1g, 3.9 mmol) in 10% NaOH (20 ml) was heated at 80°C for 1.5 h. After cooling to r.t., the pH of the solution was adjusted to 1 with 20% HCl. The solid crude product **10** that precipitated was separated by suction and purified by crystallization from H_2O. Yield 0.46 g (45%), m.p.

179–182°C. IR (KBr): $\nu = 3176, 1680, 1612, 1456, 1400, 1296, 1192$ cm^{-1}. ^{1}H NMR (DMSO-d_6): $\delta = 4.0$ (s, 4H, CH_2); 7.38–7.58 (m, 2H, aromat.); 7.94–8.06 (m, 1H, aromat.); 8.08–8.2 (m, 1H, aromat.); 11.0 (br s, 3H, 2 × NH + OH). ^{13}C NMR (DMSO-d_6): $\delta = 43.77, 114.0, 121.8, 124.97, 125.48, 127.33, 132.69, 134.43, 135.66, 154.85, 164.28$.

3.2. Pharmacology

Human blood was collected by venipuncture from healthy male volunteers into 3.8% sodium citrate (volume ratio 9:1). The blood was centrifuged at 150*g* for 20 min to obtain platelet-rich plasma (PRP). A portion of PRP was further centrifuged at 2000*g* for 10 min to obtain the platelet-poor plasma (PPP).

Platelet aggregation was studied by the turbidimetric method of Born [19]. The agents studied were dissolved in DMSO. A sample of the solution (1 μl), of fixed concentration, was added to 0.45 ml of PRP placed in a self-made aggregometer at 37°C with a stirring rate of 1000 rpm. After 2 min preincubation, changes in the light transmission were recorded. The percentage of aggregation was determined 6 min after the addition of an aggregating agent and was standardized by assuming that PPP represented 100% light transmission and PRP represented zero transmission. The maximum aggregatory effect was induced by adrenaline 10 μM added in 50 μl of saline. The determination of both primary and total aggregation was carried out according to Ding et al. [20] and Petrusewicz et al. [21].

3.3. X-ray structure analysis

Crystal data for $C_{15}H_{17}N_3O_2$ (1): monoclinic, space group $C2/m$, $a = 16.491(3)$, $b = 7.063(1)$, $c = 13.964(3)$ Å, $\beta = 120.85(2)°$, $V = 1396.3(4)$ Å^3, $Z = 4$, $D_x = 1.291$ g cm^{-3}, $T = 293$ K. Data were collected on a Kuma KM-4 diffractometer for crystals with dimensions 0.6 × 0.4 × 0.3 mm up to $2\theta_{max} = 160°$. Out of 2845 measured reflections 1542 were independent and used in further calculations. The structure was solved by direct methods using the program SHELXS-86 [22]. Full-matrix least-squares refinement was carried out on F^2 with SHELXL-93 [23]. Hydrogen atoms were located on a ΔF map and their parameters included in the refinement process. Final R indices for reflections with $I > 2\sigma(I)$ and 163 refined parameters are: $R_1 = 0.0456$, $wR_2 = 0.1221$ ($R_1 = 0.0495$, $wR_2 = 0.1252$ for all data). Final atomic coordinates, bond lengths and bond angles are listed in Tables 5 and 6, respectively. Atom labeling is shown in Fig. 1.

4. Results and discussion

The purpose of this investigation was to determine the antiaggregatory effects resulting from incorporation of the exocyclic nitrogen atom of the arylaminoimidazoline derivatives into the indole ring system.

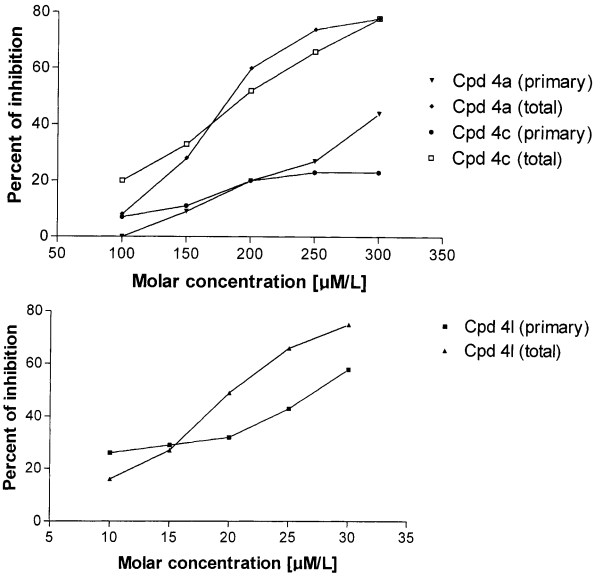


Fig. 2. Inhibitory effects of increasing concentrations of the indoles **4a**, **4c** and **4l** against the human blood platelet aggregation released by adrenaline at a concentration of 10 μM.

It is generally accepted that the initial interaction of adrenaline with platelet α_2-adrenoreceptors results in primary aggregation [24] and therefore, the primary aggregation by adrenaline can be used as an index of α_2-adrenoreceptor interactions in human platelets [8].

For all imidazoline derivatives tested no measurable aggregatory effect was detected in concentrations up to 300 μM. Concentration-dependant inhibition of platelet aggregation induced by the constant 10 μM concentration of adrenaline by selected compounds are presented in Fig. 2. Micromolar concentrations of the inhibitors causing 25% (IC_{25}) and 50% (IC_{50}) inhibition of the primary and total aggregatory response to the adrenaline are given in Table 4.

The data indicate that the compound **4l** with 3-acetyl-5-chloro substituents at indole ring was the most potent inhibitor of the adrenaline induced platelet aggregation in vitro ($IC_{50} = 27$ μM). The analogue **4i** substituted at position 5 with methyl group was slightly less active and the compound with 5-OCH_3 substituent **4j** was at least 30-fold less potent as an antagonist. The analogue unsubstituted at position 5 **4h** showed only weak activity (Table 4). This indicates that lipophilic substituents at this position are essential for antiaggregatory activity of this class of compounds and the Cl atom seems to be optimal at that position.

The replacement of the acetyl group of the indole ring of **4** with a carboethoxy group resulted in compounds with decreased inhibitory potency. These compounds

Table 4
Results of platelet aggregation tests for compounds **4**

Comp.	Primary aggregation		Total aggregation	
	pIC_{25}[a]	pIC_{50}[a]	pIC_{25}	pIC_{50}
4a	3.63 ± 0.04	–	3.84 ± 0.03	3.73 ± 0.04
4b	3.64 ± 0.03	–	3.55 ± 0.02	–
4c	–	–	3.92 ± 0.04	3.71 ± 0.05
4f	3.73 ± 0.06	–	3.69 ± 0.04	–
4h	[b]	–	[c]	–
4i	4.62 ± 0.09	–	4.55 ± 0.06	–
4j	3.52 ± 0.02	–	–	–
4l	>5	4.57 ± 0.05	4.85 ± 0.04	4.7 ± 0.02

[a] pIC_{25} and pIC_{50} = negative log molar IC_{25} and IC_{50} values respectively. Values are mean of $n = 4$–5.
[b] 13% of inhibition at concentration of 300 μM.
[c] 15% of inhibition at concentration of 300 μM.

Table 5
Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **4b**

	x	y	z	U_{eq}[a]
N(1)	2713(1)	0	2530(1)	39(1)
C(2)	3428(1)	0	3625(1)	41(1)
C(3)	3060(1)	0	4306(1)	40(1)
C(4)	1300(1)	0	3808(2)	44(1)
C(5)	383(1)	0	2929(2)	48(1)
C(6)	201(1)	0	1826(2)	50(1)
C(8)	1841(1)	0	2492(1)	38(1)
C(7)	921(1)	0	1588(2)	46(1)
C(9)	2047(1)	0	3599(1)	38(1)
C(10)	2845(1)	0	1613(1)	39(1)
C(12)	3669(2)	0	724(2)	57(1)
N(11)	3722(1)	0	1786(2)	79(1)
C(13)	2604(2)	0	−82(2)	48(1)
N(14)	2166(1)	0	611(1)	54(1)
C(15)	3649(1)	0	5517(1)	41(1)
O(16)	4505(1)	0	6026(1)	61(1)
O(17)	3146(1)	0	6015(1)	45(1)
C(18)	3672(1)	0	7221(2)	47(1)
C(19)	2955(2)	0	7580(2)	62(1)
C(20)	−430(2)	0	3137(2)	65(1)

[a] U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

blocked aggregation responses with IC_{25}s ranging from 184–235 μM.

However, comparing the known aryliminoimidazolines and the derivatives used in this study, it should be noted that incorporation of the exocyclic nitrogen atom into the indole ring system results in a reduced inhibitory potency of the molecules of type **4**. For comparison, clonidine inhibits platelet aggregation induced by adrenaline at a much lower concentration (IC_{50} = 0.048 μM) [25].

Table 6
Selected bond lengths (Å) and angles (°) for **4b**

Bond lengths			
N(1)–C(2)	1.371(2)	C(8)–C(7)	1.390(3)
N(1)–C(10)	1.404(2)	C(8)–C(9)	1.403(2)
N(1)–C(8)	1.412(2)	C(10)–N(14)	1.267(2)
C(2)–C(3)	1.365(2)	C(10)–N(11)	1.339(2)
C(3)–C(9)	1.440(3)	C(12)–N(11)	1.439(2)
C(3)–C(15)	1.456(2)	C(12)–C(13)	1.525(3)
C(4)–C(5)	1.375(3)	C(13)–N(14)	1.474(2)
C(4)–C(9)	1.405(2)	C(15)–O(16)	1.211(2)
C(5)–C(6)	1.411(3)	C(15)–O(17)	1.328(2)
C(5)–C(20)	1.509(3)	O(17)–C(18)	1.446(2)
C(6)–C(7)	1.388(2)	C(18)–C(19)	1.502(3)
Bond angles			
C(2)–N(1)–C(10)	124.8(2)	C(8)–C(9)–C(4)	119.1(2)
C(2)–N(1)–C(8)	108.54(13)	C(8)–C(9)–C(3)	107.20(14)
C(10)–N(1)–C(8)	126.6(2)	C(4)–C(9)–C(3)	133.7(2)
C(3)–C(2)–N(1)	110.0(2)	N(14)–C(10)–N(11)	117.4(2)
C(2)–C(3)–C(9)	107.2(2)	N(14)–C(10)–N(1)	123.1(2)
C(2)–C(3)–C(15)	122.6(2)	N(11)–C(10)–N(1)	119.6(2)
C(9)–C(3)–C(15)	130.2(2)	N(11)–C(12)–C(13)	101.5(2)
C(5)–C(4)–C(9)	119.7(2)	C(10)–N(11)–C(12)	109.0(2)
C(4)–C(5)–C(6)	119.7(2)	N(14)–C(13)–C(12)	106.4(2)
C(4)–C(5)–C(20)	120.5(2)	C(10)–N(14)–C(13)	105.8(2)
C(6)–C(5)–C(20)	119.8(2)	O(16)–C(15)–O(17)	123.1(2)
C(7)–C(6)–C(5)	122.2(2)	O(16)–C(15)–C(3)	124.4(2)
C(7)–C(8)–C(9)	122.4(2)	O(17)–C(15)–C(3)	112.6(2)
C(7)–C(8)–N(1)	130.6(2)	C(15)–O(17)–C(18)	116.55(14)
C(9)–C(8)–N(1)	107.0(2)	O(17)–C(18)–C(19)	106.5(2)
C(6)–C(7)–C(8)	116.9(2)		

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