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ACID ASSISTED REACTIONS OF 1,2-DIHYDRO-2-(4,5-DIHYDROIMIDAZOL-2-YL)PHTHALAZIN-1-OL WITH ARYL(HETEROARYL) METHYL KETONES

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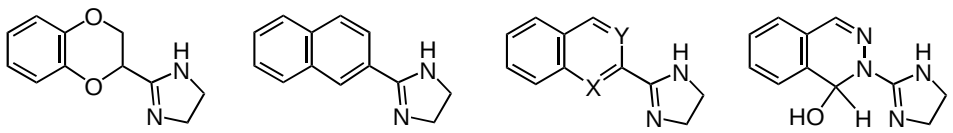
Abstract – A series of the 1-[2-(4,5-dihydro-1*H*-imidazol-2-yl)-1,2-dihydro-phthalazin-1-yl]-2-arylethanone hydrochlorides (**2a-i**) was synthesized by acid assisted reaction of phthalazine pseudobase (**1**) with aryl(heteroaryl) methyl ketones. A similar reactions of **1** with cyclohexanone and benzo-1,4-dioxan-2-one afforded 1, 2, 3, 4, 6, 7, 15b, 15c-octahydro-4a*H*-imidazo[1,2-*a*]phthalazino[2,1-*c*]quinazolin-4a-ol (**5**) and 7-[2-(4,5-dihydro-1*H*-imidazol-2-yl)-1,2-dihydro-phthalazin-1-yl]-1,4-benzodioxin-2(3*H*)-one (**6**), respectively. Structures of these compounds were confirmed by IR and NMR spectroscopy as well as X-Ray crystallographic analysis of the free base (**3a**). Biological activity of the compounds (**2**) was examined on rabbit aortic rings.

INTRODUCTION

It is well known that various imidazoline-containing compounds interact with adrenergic and/or imidazoline receptors and elicit a number of pharmacological effects on metabolism, secretion, ion transport, intraocular pressure dynamics and especially on cardiovascular function.[1,2] This class of compounds appears to be interesting in that minor structural modifications can considerably alter their pharmacological profiles, and include selective α_2-adrenoreceptor antagonist idazoxan[3] and highly selective to I_2 receptors benazoline,[4] BU224 and BU236[5] (Figure 1).



Idazoxan **Benazoline** **BU224**, X = N, Y = CH **BU236**, X = CH, Y = N **1**

Figure 1

We have previously reported the synthesis and reactions of 1,2-dihydro-2-(4,5-dihydroimidazol-2-yl)-phthalazin-1-ol (**1**) with active methylene compounds[6] and electron deficient acetylenes.[7] These results prompted us to investigate further both the reactivity of pseudobase (**1**) and biological properties of the newly prepared imidazoline derivatives.

RESULTS AND DISCUSSION

Heterocyclic pseudobasic carbinolamines are known to react with methyl ketones under alkaline conditions with elimination of water molecule to afford the corresponding condensation products. The mechanism is believed to involve initial dissociation of pseudobase into mesomeric aminium cation and hydroxide ion followed by nucleophilic attack of the carbanion derived from carbonyl compounds.[8]

We found that in the case of phthalazine pseudobase (**1**) bearing the electron-withdrawing imidazoline moiety at the N2 nitrogen atom, the nondissociated form is apparently favored in polar solvents under both neutral and alkaline conditions, and therefore, the analogous reaction is not feasible.

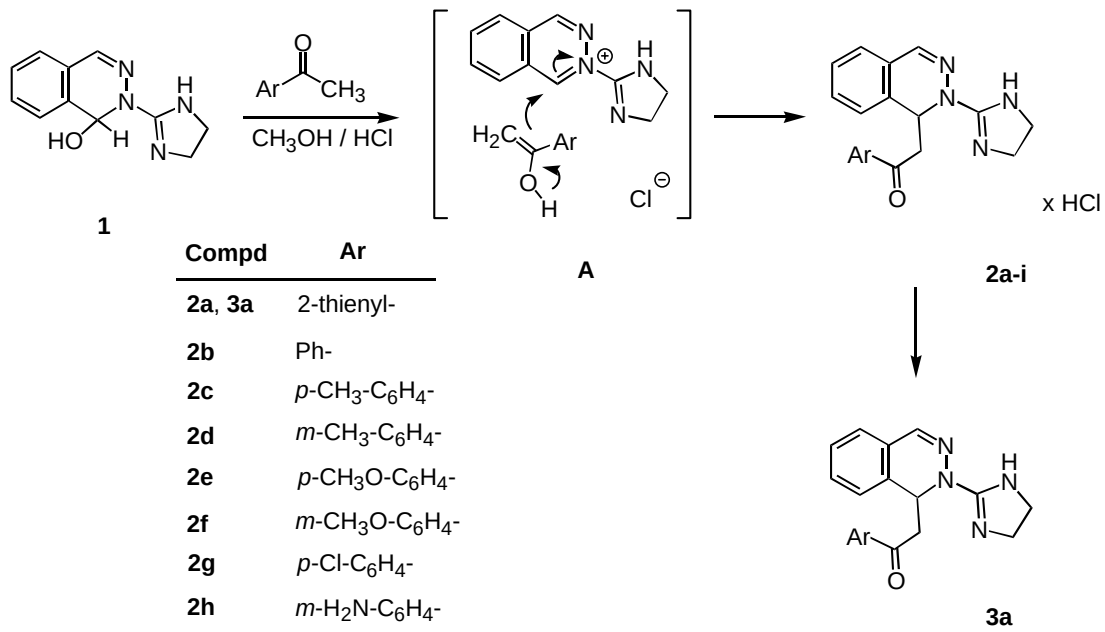
However, when the compound (**1**) was subjected to the reaction with aryl methyl ketones in 10% methanolic HCl solution, work-up the reaction mixture yielded 1-[2-(4,5-dihydro-1*H*-imidazol-2-yl)-1,2-dihydrophthalazin-1-yl]-2-arylethanone hydrochlorides (**2a-i**) in 39-79% overall yields (Scheme 1). The plausible mechanism seems to involve simultaneous acid-assisted enolization of the methyl ketone and dissociation of pseudobase (**1**) followed by nucleophilic alkylation to give the hydrochloride (**2**).

Treatment of hydrochloride (**2a**) with NaOH afforded the free base (**3a**). Structures of the compounds (**2**) and (**3**) were confirmed by elemental analyses, IR and NMR spectroscopic data (Table 1), MS spectrometry as well as X-Ray structure analysis of **3a**[9] (Figure 2).

It should be pointed out that under similar conditions aliphatic ketones such as acetone gave no expected alkylation product. However, the reaction of **1** with cyclohexanone proceeded smoothly with the formation of first the alkylation product (**B**), which subsequently underwent a spontaneous ring closure giving rise to formation of imidazo[1,2-*a*]phthalazino[2,1-*c*]quinazolin-4a-ol hydrochloride (**4**).

Table 1. Physico-chemical and spectroscopic data for compounds (**2a-i**)

Compd	Formula	mp [^{o}C]	Yield [%]	^{1}H-NMR (DMSO-d_6) [ppm]	IR (KBr) [cm^{-1}]	Elemental analysis C H N
2b	$C_{19}H_{19}N_4OCl$	235-239 ethanol	67	2.58-2.65 (dd, *J*=13.6 Hz, *J*=12.0 Hz,1H, CH), 3.09-3.18 (dd, *J*=13.6 Hz, *J*=3.3 Hz, 1H, CH), 3.28-3.71 (m, 4H, $2CH_2$), 5.43-5.50 (dd, *J*=12.0 Hz, *J*=3.3 Hz, 1H, CH), 7.41-7.70 (m, 10H, Ar, NH), 8.25 (s, 1H, CH=N), 9.62 (s, 1H, NH^+)	3416, 3162, 3018, 1641, 1548. 1448, 1293, 1106	Calcd: 64.31 5.40 15.79 Found: 64.15 5.22 15.88
2c	$C_{20}H_{21}N_4OCl$	224-229 DMF	77	2.34 (s, 3H, CH_3), 2.49-2.51 (dd, *J*=13.5 Hz, *J*=11.8 Hz, 1H, CH), 3.39 (dd, *J*=13.5 Hz, *J*=3.2 Hz, 1H, CH), 3.30-3.80 (m, 4H, $2CH_2$), 5.40-5.50 (dd, *J*=11.8 Hz, *J*=3.2 Hz, 1H, CH), 7.25-7.29 (d, *J*=8 Hz, 2H, Ar), 7.47-7.62 (m, 7H, Ar, NH), 8.24 (s, 1H, CH=N), 9.59 (s, 1H, NH^+)	3418, 3167, 3029, 2940, 1639, 1551, 1457, 1292	Calcd: 65.12 5.74 15.19 Found: 64.98 5.99 14.85
2d	$C_{20}H_{21}N_4OCl$	222-225 ethanol	53	2.36 (s, 3H, CH_3), 2.52 (dd, *J*=13.8 Hz, *J*=12.2 Hz, 1H, CH), 3.12 (dd, *J*=13.8 Hz, *J*=3.4 Hz, 1H, CH), 3.29-3.76 (m, 2H, $2CH_2$), 5.50 (dd, *J*= 12.2 Hz, *J*=3.4 Hz, 1H, CH), 7.2-7.62 (m, 8H, Ar), 7.75 (s, 1H, NH), 8.20 (s, 1H, CH=N), 9.60 (s, 1H, NH^+)	3402, 3145, 3028, 2990, 1638, 1545, 1340, 1292	Calcd: 65.12 5.74 15.19 Found: 65.01 5.87 15.43
2e	$C_{20}H_{21}N_4O_2Cl$	189-193 methanol	39	2.49-2.63 (dd, *J*=13.6 Hz, *J*=11.8 Hz, 1H, CH), 3.05-3.16 (dd, *J*=13.6 Hz, *J*=3.0 Hz, 1H, CH), 3.29-3.74 (m, 4H, $2CH_2$), 3.80 (s, 3H, OCH_3), 5.43-5.51 (dd, *J*=11.8 Hz, *J*=3.0 Hz, 1H, CH), 6.98 (d, *J*=8.8 Hz, 2H, Ar), 7.03-7.68 (m, 7H, Ar, NH), 8.24 (s, 1H, CH=N), 9.58 (s, 1H, NH^+)	4318, 3055, 2841, 1639, 1551, 1290, 1246, 1176	Calcd: 62.41 5.50 14.56 Found: 62.77 5.81 14.32
2f	$C_{20}H_{21}N_4O_2Cl$	211-214 methanol	47	2.55 (dd, *J*=13.2 Hz, *J*=12,8 Hz, 1H, CH), 3.12 (dd, *J*= 13.2 Hz, *J*=3.3 Hz, 1H, CH_2), 3.37-3.70 (m, 4H, $2CH_2$), 3.80 (s, 3H, OCH_3), 5.49 (dd, *J*=12.8 Hz, *J*=3.3 Hz, 1H, CH), 6.95-6.99 (m, 1H, Ar), 7.22-7.63 (m, 7H, Ar), 7.77 (s, 1H, NH), 8.20 (s, 1H, CH=N), 9.60 (s, 1H, NH^+)	3406, 3083, 2925, 2842, 1939, 1600, 1555, 1489	Calcd: 62.41 5.50 14.56 Found: 62.11 5.19 14.65
2g	$C_{19}H_{18}N_4OCl_2$	220-223 DMF	46	2.58-2.66 (dd, *J*=13.6 Hz, *J*=12.0 Hz, 1H, CH), 3.09-3.17 (dd, *J*=13.6 Hz, *J*=3.6 Hz, 1H, CH), 3.37-3.73 (m, 4H, $2CH_2$), 5.39-5.47 (dd, *J*=12.0 Hz, *J*=3.6 Hz, 1H, CH), 7.44-7.72 (m, 9H, Ar, NH), 8.25 (s, 1H, CH=N), 9.60 (s, 1H, NH^+)	3413, 3030, 2901, 2848, 1640, 1552, 1491, 1292	Calcd: 58.62 4.66 14.39 Found: 59.01 4.56 14.44
2h	$C_{19}H_{21}N_5OCl_2$	216-219 ethanol	55	2.42-2.55 (dd, *J*=13.7 Hz, *J*=11.4 Hz, 1H, CH), 3.05-3.14 (dd, *J*=13.7 Hz, *J*=3.3 Hz, 1H, CH), 3.39-3.72 (m, 4H, $2CH_2$), 5.23 (s, 3H, NH_3^+), 5.43 (dd, *J*=11.4, *J*=3.3 Hz, 1H, CH), 6.57 (d, *J*=7.9 Hz, 1H, Ar), 6.72 (d, *J*=7.7 Hz, 1H, Ar), 6.87 (s, 1H, Ar), 7.08 (t, *J*=7.9 Hz, 1H, Ar), 7.46-7.60 (m, 5H, Ar , NH), 8.23 (s, 1H, CH=N), 9.57 (s, 1H, NH^+)	3392, 3252, 3021, 2849, 2595, 1639, 1581, 1549	Calcd: 56.16 5.21 17.24 Found: 55.92 5.17 17.59
2i	$C_{19}H_{19}N_4O_2Cl$	181-184 methanol	60	2.54-2.60 (dd, *J*=13.7 Hz, *J*=12.0 Hz, 1H, CH), 3.03-3.12 (dd, *J*=13.7 Hz, *J*=3.3 Hz, 1H, CH), 3.39-3.71 (m, 4H, $2CH_2$), 5.39-5.40 (dd, *J*=12.0 Hz, *J*=3.3 Hz, 1H, CH), 6.81-6.87 (d, *J*= 7.7 Hz, 2H, Ar), 7.34-7.76 (m, 7H, NH), 8.23 (s, 1H, CH=N), 9.55 (s, 1H, NH^+), 9.79 (s, 1H, OH)	3511, 3448, 3187, 3042, 2979, 2672, 1641, 1553	Calcd: 61.54 5.16 15.11 Found: 61.24 5.37 15.49



Compd	Ar
2a, **3a**	2-thienyl-
2b	Ph-
2c	*p*-CH_3-C_6H_4-
2d	*m*-CH_3-C_6H_4-
2e	*p*-CH_3O-C_6H_4-
2f	*m*-CH_3O-C_6H_4-
2g	*p*-Cl-C_6H_4-
2h	*m*-H_2N-C_6H_4-
2i	*p*-HO-C_6H_4-

Scheme 1

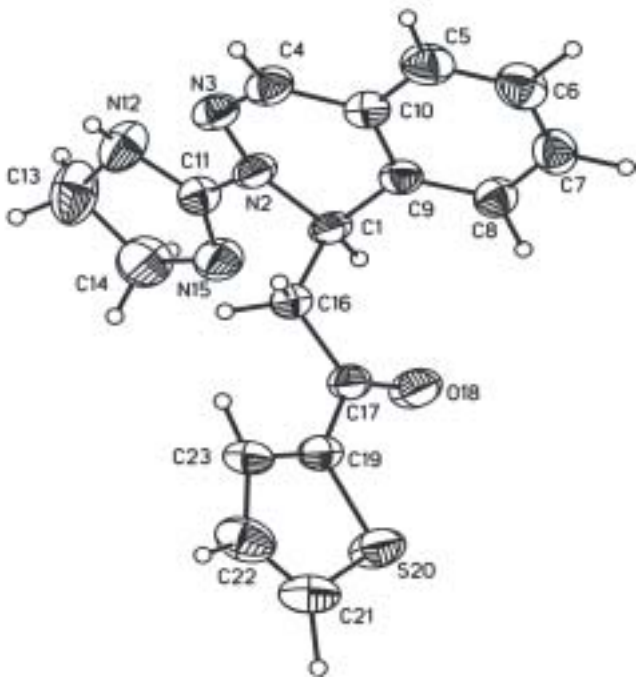
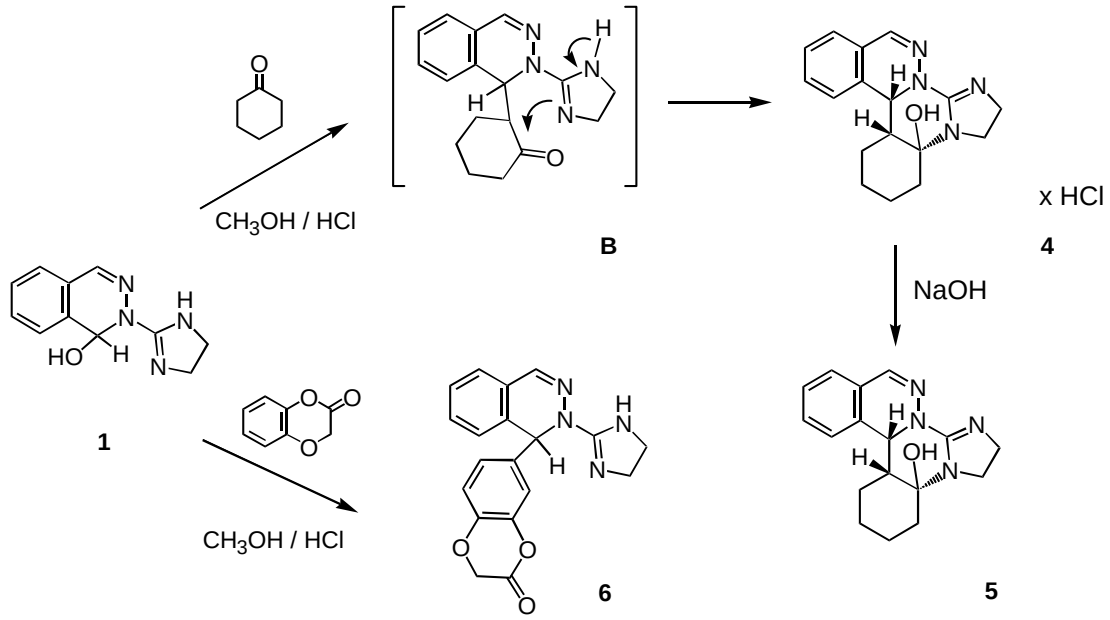


Figure 2. Ortep drawing of molecule (**3a**)

For analysis of conformational preference of compound 4, after complete assignment of all the protons using the HH-COSY, HSQC and HMBC spectra, the connection mode and the stereochemistry of the pentacyclic ring system was investigated using a ROESY experiment. As shown in Figure 3, the strong

ROEs effects between O-H and both C15b-H and C15c-H indicate that cyclohexane and pyrimidine rings of the central quinazoline moiety exist in a *cis*-fused configuration. In this configuration OH group adopts equatorial position with respect to cyclohexane ring and axial position with respect to pyrimidine ring. The reverse arrangement is found for C15c-H proton, and C15b-H is in axial position of pyrimidine ring. Four large three-bond coupling constants between aksjal protons at C15c, C1, C2, C3 and C4 ($^3J_{aa}$~12.5-13.5 Hz) demonstrate that cyclohexane ring is in the chair conformation. The proton at C15b has a coupling constant of J = 2.9 Hz with C15c-H, which is in agreement with the results of structural quantum chemical calculations [10] which revealed that the dihedral angle between these C-H bonds is 52°.

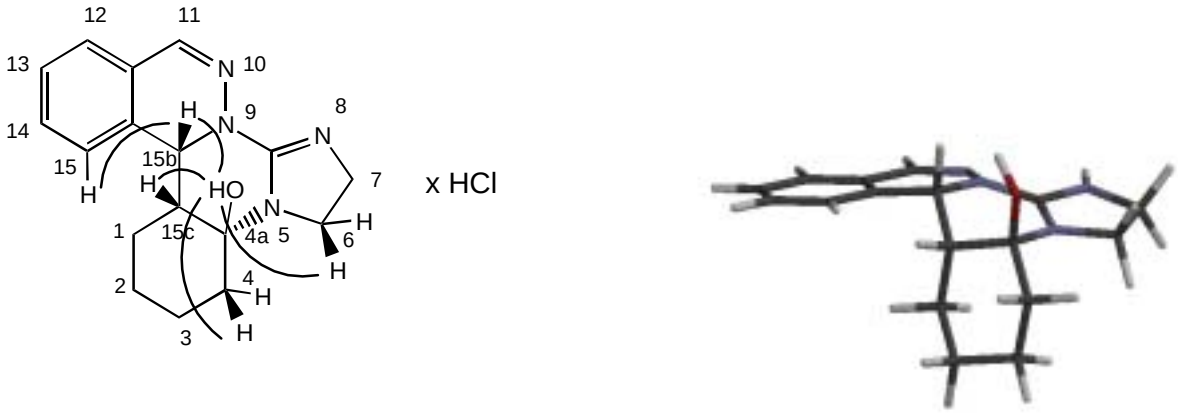


Scheme 2

The salt (**4**) could be converted by NaOH into the corresponding free base (**5**) (Scheme 2).

We also investigated the acid assisted reaction of pseudobase (**1**) with benzo-1,4-dioxan-2-one. The ^{1}H-NMR spectrum of the product showed the presence of 7-substituted benzo-1,4-dioxan-2-one (**6**) which was formed by electrophilic attack of the phthalazinium mesomeric cation at the aromatic ring.

However, the above reaction could, in principle, give rise to either 7- or 6-substituted benzo-1,4-dioxan-2-one and these isomers cannot be easily distinguished on the basis of NMR spectral data. With the aim to confirm the reaction mechanism, we investigated the electronic properties of phthalazinium cation (**A**), benzo-1,4-dioxan-2-one (**C**) and its enol form (**D**) by using a molecular orbital *ab initio* method.[10] Total energies, dipole moments, atomic charges on selected atoms and absolute values of HOMO and LUMO mapped on the van der Waals contact surface are shown in Figure 4.



Scheme 3. The strong ROE relationships found for hydrochloride (**4**) (*left*), and the minimum energy structure of the stereoisomer (4a*S*,15b*R*,15c*R*) of **4**.

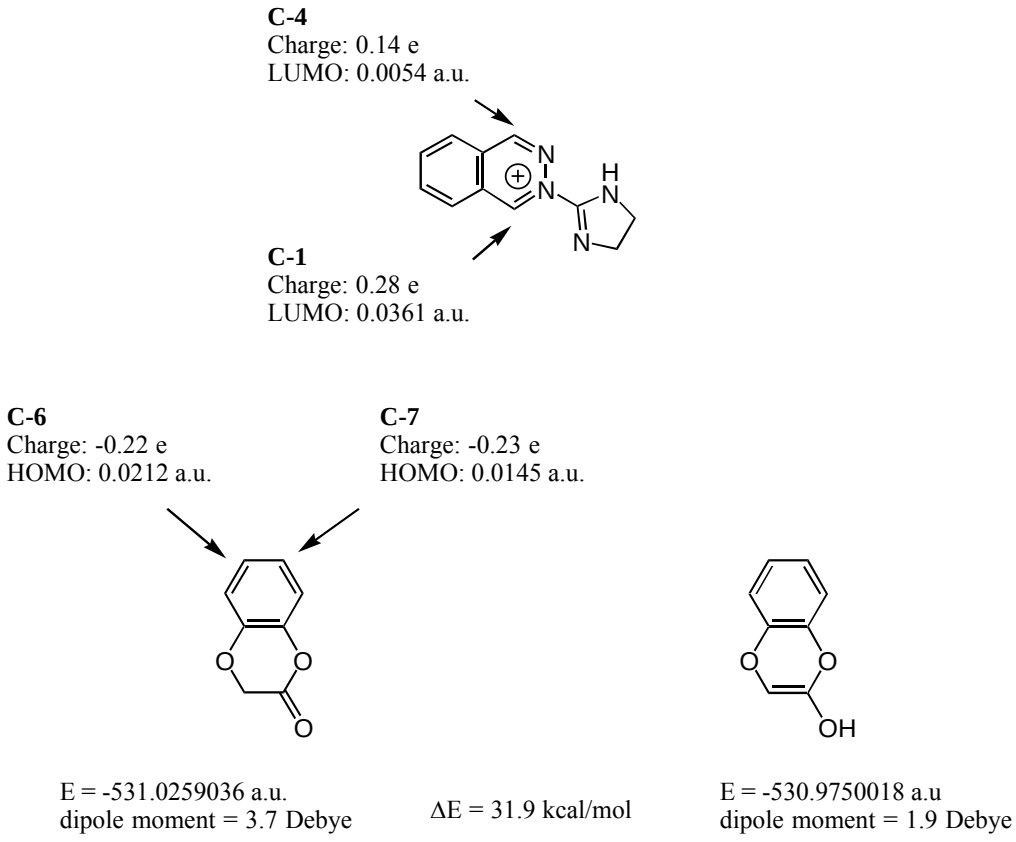


Figure 4. Atomic charges and absolute values of the HOMO and LUMO on the electron density isosurface corresponding to the van der Waals surface calculated for phthalazinium cation (**A**) and benzo-1,4-dioxan-2-one (see text for details).

According to *ab initio* computed electronic structure of phthalazinium cation (**A**), both positive charge (0.28 e) and LUMO (0.0361 a.u.) have the highest contribution for C1 carbon atom, which must be involved in the reaction with nucleophiles.

On the other hand, the relative low stability and lower dipole moment of tautomer (**D**) would make tautomer (**C**) more favored in polar methanolic solution, and therefore, the product formed from the reaction should be derived from the ketone (**C**) rather than the enol form (**D**).

The magnitudes of the calculated negative charges at C6 and C7 of ketone (**C**) are very close (-022 e and –0.23 e, respectively) which suggests that the electrostatically-controlled reaction with phthalazinium cation should give rise to the formation of a mixture of 6- and 7-substituted products. However, the reaction of phthalazinium cation with soft nucleophiles would be the orbital-controlled reaction. As seen in Figure 4, the C7 carbon atom in ketone (**C**) (HOMO = 0.0212a.u.) is more active than the C6 (HOMO = 0.0145a.u.), and therefore, the orbital-controlled reaction at this position is possible.

The biological activity of the compounds (**2**) was examined on rabbit aorta. We found that neither contractile nor dilatatory effect was elicited by these compounds but they enhanced vasocontractile response to phenylephrine. As exemplified in Figure 5, compound (**2c**) at concentrations 10^{-7} and 10^{-6} mol/L enhanced contraction response to phenylepinephrine ($3x10^{-4}$ mol/L) by 19 and 38%, respectively. The enhancing effect was abolished by rimalkalim, the K_{ATP} channel opener. These results confirmed the observations made by other authors that a variety of imidazoline-based agents antagonize the vasodilatatory effect of K^+-channel openers.[11,12]

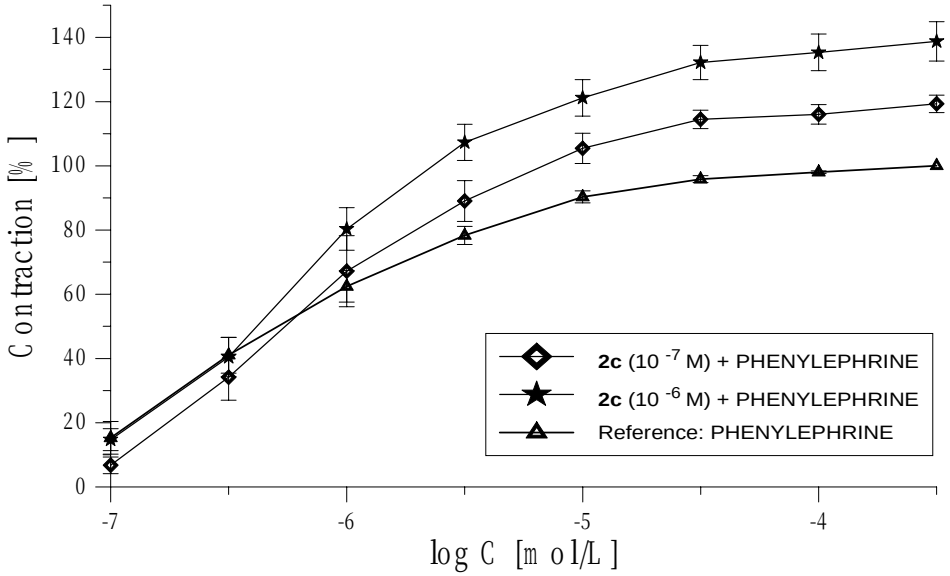


Figure 5 The influence of the compound (**2c**) on the contraction responce to the phenylepinephrine in isolated rabbit aortic rings (Means and ±SEM from 7 experiments).

EXPERIMENTAL

Melting points were determined on a Boetius apparatus and are not corrected. IR spectra were obtained on a Perkin-Elmer FT 1600 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded in DMSO-d_6 with Varian Gemini 200 spectrometer. Chemical shifts were measured relative to residual solvent signal at 2.50 ppm and 39.5 ppm, respectively. 2D NMR spectra were recorded on a Varian Unity 500 spectrometer at 295 K. ROESY experiments were made with a mixing time of 350 msec. MS spectra were recorded on a LKB 9000 spectrometer.

Synthesis of 1-[2-(4,5-dihydro-1*H*-imidazol-2-yl)-1,2-dihydrophthalazin-1-yl]-2-(2-thienyl)ethanone hydrochloride (2a) (Typical Procedure)

2-Acetylthiphene (0.4 ml, 3.7 mmol) was added to a solution of compound (**1**)[7] (0.5 g, 2.3 mmol) in 10% methanolic HCl solution (5 mL), and the reaction mixture was kept at room temperature for 3 days. The solid that precipitated was filtered off, washed with cold methanol, and crystallized from methanol to give **2a**; yield 0.66 g, (79%); mp 213-216 ^{o}C; IR ($CHCl_3$): 3420, 3080, 3024, 1644, 1552, 1295, 1232, 1104 (cm^{-1}). Anal. Calcd for $C_{17}H_{17}N_4OClS$: C, 56.58; H, 4.75; N, 15.53. Found: C, 56.38; H, 4.33, N, 15.12. Analogously were obtained hydrochlorides (**2b**-**i**) (Table 1).

1-[2-(4,5-Dihydro-1*H*-imidazol-2-yl)-1,2-dihydrophthalazin-1-yl]-2-(2-thienyl)ethanone (3a)

The above described hydrochloride **(2a**) (0.66 g, 1.72 mmol) was dissolved in methanol (5 mL) and treated with 5% methanolic solution (1.4 mL, 1,75 mmol) of NaOH to pH = 9. The solvent was evaporated under reduced pressure, and the solid residue was washed with water (20 mL), dried and purified by crystallization from acetone; yield 0.48 g (72.7%); mp 179-182 ^{o}C; IR: 3392, 2984, 1648, 1632, 1612, 1568, 1404, 1284, 1152, 1120 (cm^{-1}); ^{1}H-NMR ($CDCl_3$) δ 3.22-3.26 (dd, 1H, CH, *J* = 14 Hz, *J* = 4.5 Hz), 3.38-3.42 (dd, 1H, CH, *J* = 14 Hz, *J* = 9 Hz), 3.44-3.79 (m, 2H, CH_2), 3.79-3.92 (m, 2H, CH_2), 5.17 (s, 1H, NH), 6.17-6.21 (dd, 1H, CH, *J* = 9 Hz, *J* = 4.5 Hz),6.80 (t, 1H, Ar, *J* = 5 Hz), 7.16 (d, 1H, Ar, *J* = 7.2 Hz), 7.20 (d, 1H, Ar, *J* = 7.2 Hz), 7.27-7.34 (m, 2H, Ar), 7.48 (s, 1H, CH=N), 7.59 (d, 1H, Ar, *J* = 5 Hz), 7.83 (d, 1H, Ar, *J* = 3.5 Hz); ^{13}C-NMR ($CDCl_3$) δ 43.09, 45.39, 52.82, 124.24, 125.51, 127.01, 128.47, 128.58, 131.45, 121.84, 133.07, 134.17, 139.12, 144.92, 161.29, 190.02. (324.40); Anal. Calcd for $C_{17}H_{16}N_4OS$: C, 62.94; H, 4.97; N, 17.27. Found: C, 62.72; H, 4.66; N, 17.01.

Synthesis of (4a*SR*,15b*RS*,15c*RS*)-1,2,3,4,6,7,15b,15c-octahydro-4a*H*-imidazo[1,2-*a*]phthalazino-[2,1-*c*]quinazolin-4a-ol hydrochloride (4)

Cyclohexanone (0.26 mL, 2.5 mmol) was added to a solution of pseudobase (**1**) (0.5 g, 2.3 mmol) in 10% methanolic HCl solution (5 mL), and the reaction mixture was stirred at rt for 2 days. The crude product (**4**) that precipitated was collected by filtration, washed with cold methanol, dried and recrystallized from DMF; yield 0.52 g (68%); mp 166-168^{o}C; IR (KBr): 3483, 1883, 1636, 1563, 1520, 1472, 1456, 1163, 992 (cm^{-1}); ^{1}H-NMR (DMSO-d$_6$) δ 1.00-1.1 (m, 1H, CH), 1.18-1.28 (m, 1H, CH), 1.3-1.4 (m, 1H, CH), 1.52-1.6 (m 1H, CH), 1.6-1069 (m, 3H, CH), 2.16-2.21 (d, 1H, CH_2, *J* = 13.6 Hz), 2.80-2.85 (m, 1H, CH), 3.65-3.72 (m, 1H, CH), 3.75-3.84 (m, 2H, CH), 3.86-3.93 (m, 1H, CH), 5.61 (d, *J* = 2.9 Hz, 1H, CH), 7.46-7.50 (m, 2H, Ar), 7.55-7.58 (m, 1H, Ar), 7.60-7.64 (m, 1H, Ar), 8.05 (s, 1H, CH=N), 9.42 (s, 1H, $N^{+}H$); ^{13}C-NMR (DMSO-d$_6$) δ 21.74, 22.54, 23.46, 34.95, 40.89, 41.09, 42.64, 51.84, 81.09, 122.88, 124.52, 128.34, 128.61, 129.89, 133.18, 145.42, 155.25. Anal. Calcd for $C_{17}H_{21}N_4OCl$: C, 61.34; H, 6.36; N, 16.83. Found: C, 61.11; H, 6.59; N, 16.52.

(4a*SR*,15b*RS*,15c*RS*)-1, 2, 3,4,6,7,15b,15c-Octahydro-4a*H*-imidazo[1,2-*a*]phthalazino[2,1-*c*]-quinazolin-4a-ol (5)

The above described hydrochloride (**4**) (0.5 g, 1.5 mmol) was dissolved in water (5 mL) and treated with 5% aqueous NaOH (1.25 mL, 1.55 mmol) to pH = 9. The solid thus obtained was separated by filtration, washed with water and dried to give pure product (**5**); yield 0.4 g (90%); mp 180-183 ^{o}C (methanol); IR (KBr): 3471, 3148, 2943, 1642, 1560, 1451, 1299, 1072, 1020, 782 (cm^{-1}); ^{1}H-NMR (DMSO-d$_6$) δ 1.00-1.65 (m, 6H, 3CH_2), 2.16-2.19 (d, 1H, CH_2, *J* = 13.6 Hz), 2.80-2.82 (d, 1H, CH), *J* = 11.7 Hz), 3.67-3.94 (m, 6H, 2CH_2, CH, OH), 5.61 (s, 1H, CH), 7.43-7.60 (m, 4H, Ar), 8.03 (s, 1H, CH); ^{13}C-NMR ($CDCl_3$) δ 22.48, 23.25, 24.18, 35.69, 41.64, 41.91, 43.33, 52.54, 123.62, 125.28, 129.03, 129.34, 130.63, 133.9, 146.09; MS (70 eV) *m/z* (%): 296 (M^{+}, 8), 278 (M^{+} -H_2O, 31.1), 277 (20.9), 200 (18.2), 199 (100), 156 (7.5), 117 (8.9), 116 (6.4). Anal. Calcd for $C_{17}H_{20}N_4O$: C, 68.89; H, 6.80; N, 18.90. Found: C, 68.67; H, 6.44; N, 18.77.

Synthesis of 7-[2-(4,5-dihydro-1*H*-imidazol-2-yl)-1,2-dihydrophthalazin-1-yl]-1,4-benzodioxin-2(3*H*)-one (6)

Benzo-1,4-dioxan-2-one (0.37 g, 2.5 mmol) was added to a solution of pseudobase (**1**) (0.5 g, 2.3 mmol) in 10% methanolic HCl solution (5 mL), and the reaction mixture was kept at rt for 3 days. The solvent was evaporated to dryness under reduced pressure. The crude hydrochloride thus obtained was dissolved in water (10 mL) and neutralized with 5% aqueous NaOH. The amorphous product was filtered off, washed with cold water, dried and recrystallized from methanol to give pure product (**6**); yield 0.34 g (42%); mp 195-198 ^{o}C; IR (KBr): 3376, 2392, 2352, 1636, 1520, 1484, 1343, 1284, 1184, 980 (cm^{-1}); ^{1}H-

NMR (DMSO-d_6) δ 3.75 (m, 4H, $2CH_2$), 4.6 (m, 2H, CH_2), 6.46-6.81 (m, 4H, CH), 7.31-7.63 (m, 4H, Ar), 8.2 (s, 1H, CH=N), 9.22 (s, 1H, NH); MS (70 eV) *m/z* (%): 348 (M^+, 100), 320 (M^+-CO, 14). 199 (5.4), 190 (8.8), 144 (12.7), 131 (7), 117 (11.6), 76 (5.3). Anal. Calcd for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.63; N, 16.08. Found: C, 65.29; H, 4.54; N, 15.93.

X-Ray structure analysis of 3a

Crystal data for $C_{17}H_{16}N_4OS$: monoclinic, space group *C*2/c, *a*=25.431(1), *b*=8.118(1), *c*=17.431(1) Å, *β*=121.50(1)°, *V*=3068.3(4) $Å^3$, *Z*=8, d_x =1.404 $g.cm^{-3}$, *T*=294K. Data were collected for a crystal with dimensions 0.6x0.5x0.1 mm on a KumaCCD diffractometer using graphite monochromated Mo K_α radiation. Final R indices for 2649 reflections with $I>2\sigma(I)$ and 227 refined parameters are: R_1=0.0570, wR_2=0.1633 (R_1=0.0689, wR_2=0.1800 for all 2690 data). Atom labeling is shown in Figure 2.

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9. Crystallographic data for **3**a have been deposited with the Cambridge Crystallographic DATA Centre, CCDC deposition number:193201 Copies of this information may be obtained free of charge from:

The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax:+44-1223-3360033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

10. The structures of **4**, phthalazinium cation (**A**), benzo-1,4-dioxan-2-one (**C**) and its enol form **(D**) were fully optimized in the gas phase. Assignment of atomic charges and obtaining graphs that show the values of the HOMO and LUMO on the electron density isosurface corresponding to a van der Waals contact surface were performed using *ab initio* module (direct Hartree-Fock method, 6-31g** basis set) as implemented into SPARTAN v. 5.0 program installed on a Silicon Graphics O_2 workstation.
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