

REACTIVITY OF 7-AMINOINDAZOLE AS A BIDENDATE NUCLEOPHILE

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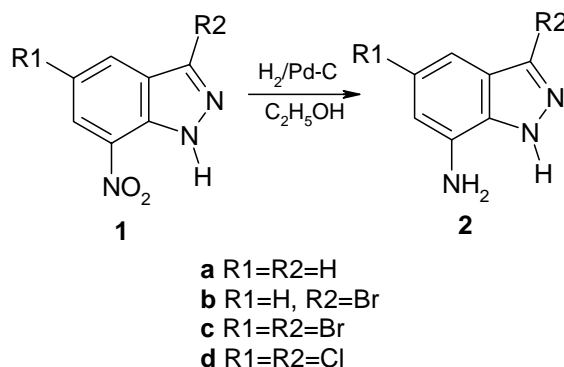
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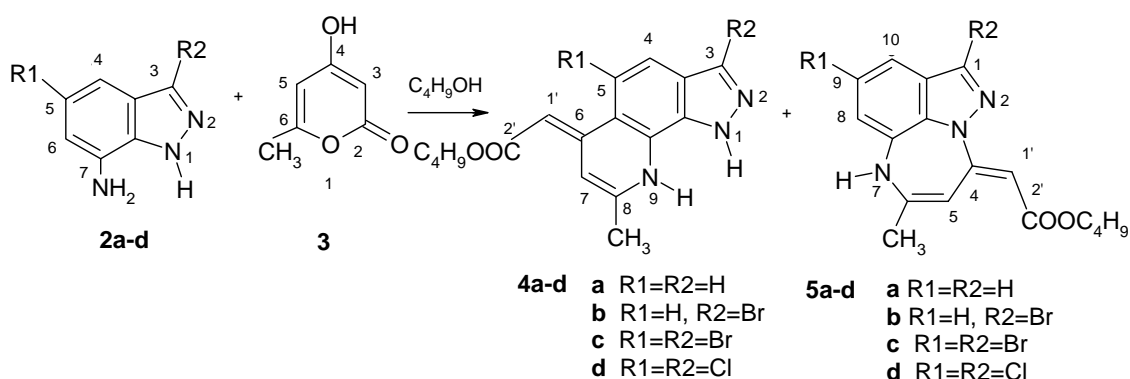
Abstract- A simple route for the preparation of two new classes of heterocyclic systems: halopyrazolo[4,5-*h*]quinolines and halopyrazolo[1,5,4-*ef*][1,5]-benzodiazepines, is presented. The effect of the solvent and the reactivity of pyrazolo-1,5-benzodiazepine were studied.

As a continuation of our research into the synthesis and reactivity of new derivatives of pyrazolo-1,5-benzodiazepine,¹⁻⁵ which have potentially pharmacological properties, we focused on the condensation of 7-aminoindazoles (**2a-d**) with the 4-hydroxy-6-methylpyran-2-one (**3**). The solvent effect was also studied to check its effect on the course of the reaction. The pyrone derivatives are electrophilic and highly reactive toward binucleophiles; their reactivity has been reported in the literature.⁶⁻¹² The 2, 4 and 6 positions of the pyrone are electrophilic centers: it is expected that three different compounds will be formed. Moreover, this system behaves like 1,3-dicarbonyl compounds and the pyrone may be opened by nucleophilic attack on C-2 or C-6 giving heterocyclic systems according to the literature.⁶⁻¹⁰ Scheme 1 shows the preparation of 7-aminoindazoles (**2a-d**) by catalytic reduction of the nitro derivatives (**1a-d**).¹³



Scheme 1

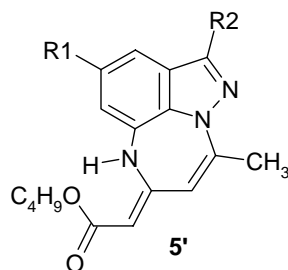
The reaction of 7-aminoindazoles (**2a-d**) with the 4-hydroxy-6-methylpyran-2-one (**3**) in refluxing *n*-butanol leads in all cases to the formation of a mixture of two products: pyrazolo[4,5-*h*]quinolines (**4a-d**) and pyrazolo[1,5,4-*ef*][1,5]benzodiazepines (**5a-d**) (Scheme 2). The structure of compounds (**4**) and (**5**) was consistent with their analytical data: ¹H NMR, IR, MS and elemental analyses.



Scheme 2

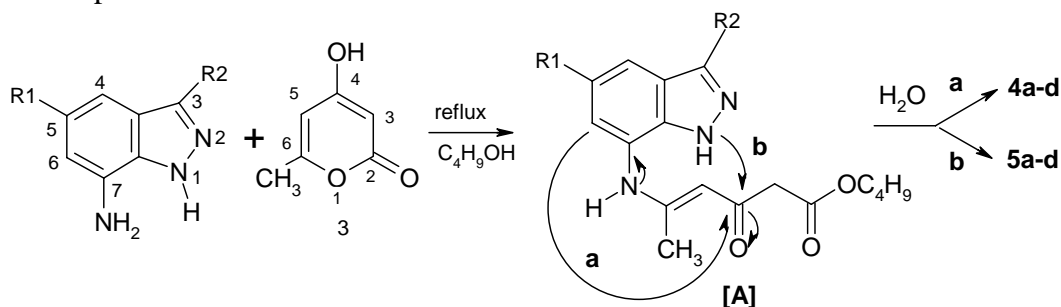
The ^1H NMR spectra of compounds (**4a-d**) show, in addition to signals due to ester group protons, two signals as singlets at 4.67-4.78 ppm and 4.76-4.85 ppm due to vinyl protons H-1' and H-7. For proton H-4, they signal appear as a doublet ($J = 8.30$ Hz and 8.24 Hz, respectively) for compounds (**4a-b**) and as a singlet for compounds (**4c-d**). This confirm that cyclisation occurred at 6 position of the indazole cycle. Analogous reactivity was observed for the 7-aminobenzimidazole.¹⁴

The ^1H NMR spectra of compounds (**5a-d**), other than the signals due to ester butyl group, have only one broad signal at 10.67-10.82 ppm, which correspond to the NH proton and two singlets at 4.77-4.88 ppm and 4.71-4.82 ppm due to vinylic protons H-5 and H-1'. It should be noted that structure (**5'**) is also conceivably an isomer of **5**. However, this structure was excluded on the basis of published results which show that the amino group of indazole is more reactive than the nitrogen *N*-1 of the pyrazolic ring toward 1,3-difunctionalized systems.^{1,2,5}



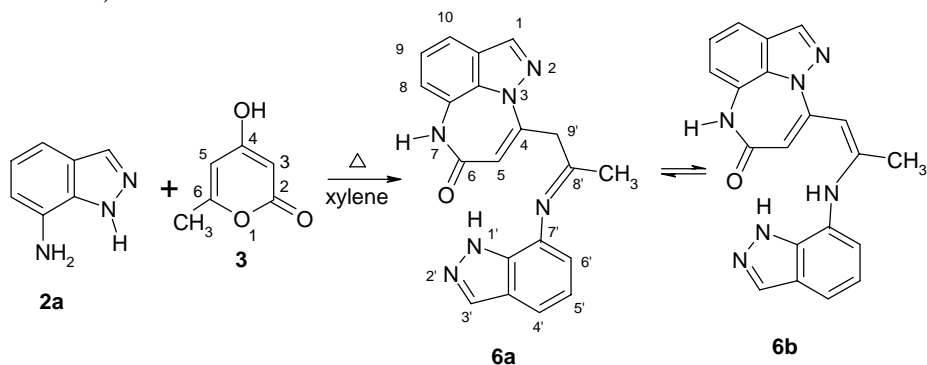
The IR spectra of the compounds (**4a-d**) and (**5a-d**) are mainly characterized by the presence of a band assigned to conjugated carbonyl groups at $1657\text{-}1670\text{ cm}^{-1}$.

The synthesis of compounds (**4** and **5**) can be explained by the following mechanism: initial attack of the amino group on C-6 of pyrone (**3**) followed by the opening of the pyranic cycle and formation of the intermediate [**A**]. Butanol (weak nucleophile) has an important function in this mechanism: it can cyclize in two different pathways to give compounds (**4a-d**) and (**5a-d**) (Scheme 3). In all cases compound (**5**) was the main compound isolated.



Scheme 3

In order to examine the solvent effect on the reaction, we studied the condensation of the 7-aminoindazole (**2a**) with the pyrone (**3**) in xylene. Under these conditions, only pyrazolo-1,5-benzodiazepine (**6**) was isolated. The formation of **6** suggests the attack of the amino group on position 2 of the pyrone (Scheme 4).



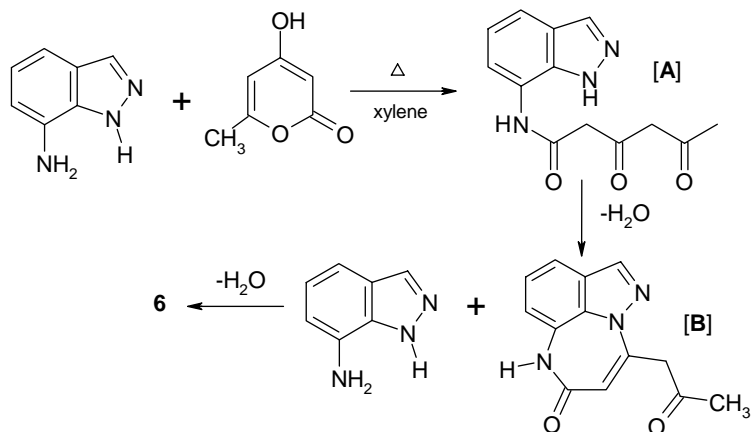
Scheme 4

The two tautomeric forms (**6a**) and (**6b**) were confirmed on the basis of spectral data: ^1H NMR, ^{13}C NMR, IR and MS (see Table 1).

Table 1: ^1H and ^{13}C NMR of compounds (**6a**) and (**6b**) (δ ppm, DMSO- d_6)

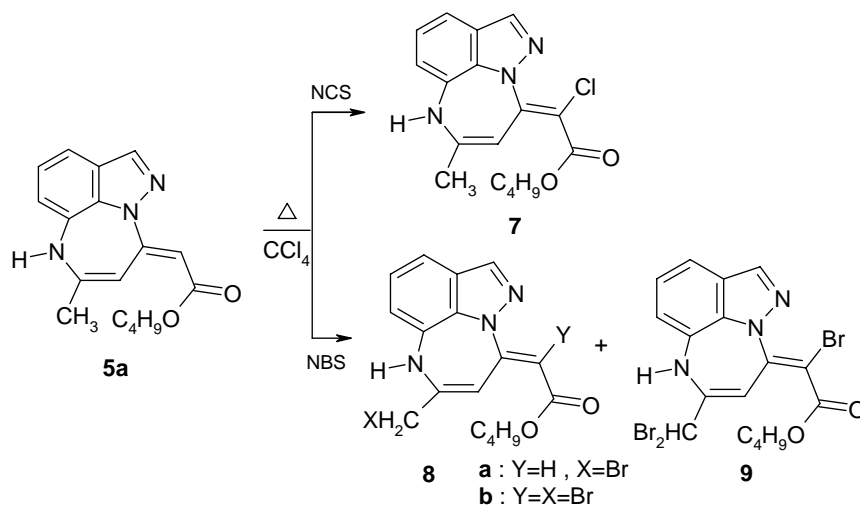
^1H NMR	CH₃	CH₂-9'	H-5	H-9'	H-Ar	H1, H3'	NH-7	NH-7'	NH-1'
6a	2.57	2.48	5.21	6.76-7.60	8.15; 8.21	10.02	12.73
6b	2.57	5.21	5.68			10.02	11.76	12.73
^{13}C NMR	CH₃	CH₂-9	C-5	CH-9'	C-4	C-8'	C=O		
6a	25.5	68.9	106.8	143.9	152.1	172.2		
6b	25.5	106.8	99.6	143.9	152.1	172.2		

To explain the formation of compound (**6**), we propose the following mechanism: the initial attack of the amino group takes place on the C-2 carbon of the pyrone (**3**) to give the intermediate [**A**]. The compound obtained cyclizes giving pyrazolo-1,5-benzodiazepine [**B**]. A subsequent reaction of **B** with a second 7-aminoindazole leads to compound (**6**) (Scheme 5). This result is in accord with the observation cited in the literature on,⁷ the condensation of the *ortho*-phenylenediamines with the 4-acetylidene-1,5-benzodiazepine. Therefore, the solvent effect is very important in this reaction. In the presence of *n*-butanol, condensation is initiated at the C-6 carbon of pyrone (**3**) (Scheme 3), whereas, in xylene, it is the C-2 position which is attacked in the first step (Scheme 5). Butanol, a weak nucleophile, reacts with the pyrone to give the corresponding ester, but non-nucleophilic solvents like xylene do not react with the pyrone. When xylene is used as solvent, the aminoindazole attacks directly the carbonyl group at **3**.



Scheme 5

We also examined the reactivity of **5a** with the *N*-halosuccinimides, 2,4-dinitrophenylhydrazine and *N*-*p*-chlorophenyl-*C*-ethoxycarbonylnitrile imine. Compound (**5a**) possesses several reactive sites: C-1', C-5, C-6, CH₃. We observed that the action of *N*-halosuccinimide depends of the halogenating agent used (Scheme 6).



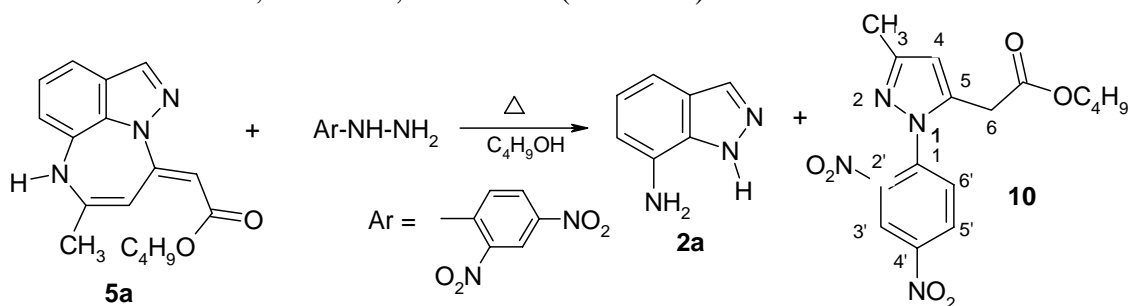
Scheme 6

When using NCS, the chlorination occurred at C-1' leading to compound (**7**) in good yield, whereas when NBS was used, bromination occurred at the methyl group and the vinyl carbon C-1' to give brominated compounds (**8a-b** and **9**). This difference in reactivity of NCS and NBS was previously reported by our research group.⁴

Compounds (**7**, **8** and **9**) were all characterized by ¹H NMR, ¹³C NMR, MS and elemental analyses. In the ¹H NMR spectrum of compound (**7**), we observed in particular the disappearance of the signal due to vinyl proton in position 1' and the lower magnetic field shift of the H-5 proton signal ($\delta_{\text{H-5}} = 5.89$ ppm). This is confirmed by the ¹³C NMR. In fact, the chemical shift of the carbon C-1', affected by the chlorine atom, changes from 93.0 ppm to 98.9 ppm. This lower magnetic field shift is observed in the ¹H and ¹³C NMR spectra of compounds (**8** and **9**) and is probably due to the electro-negativity and the anisotropy of bromine and chlorine atoms.⁴

In previous studies,^{3,15,16} we showed that, the 1,5-benzodiazepines easily react with binucleophile agents such as hydrazine, phenylhydrazine and hydroxylamine, leading to five-membered heterocycles.

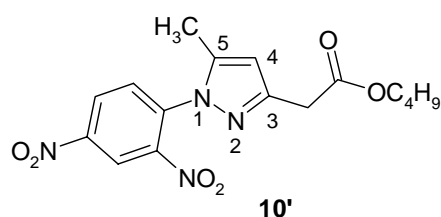
By reaction of the pyrazolo-1,5-benzodiazepine (**5a**) with 2,4-dinitrophenylhydrazine in refluxing *n*-butanol, compound (**10**) was isolated as a main product (61%) and a small quantity of **2a**, formed from **5a** by hydrolysis and degradation products was also detected. The structure of **10** was confirmed on the basis of its spectral data: ¹H NMR, ¹³C NMR, IR and MS (Scheme 7).



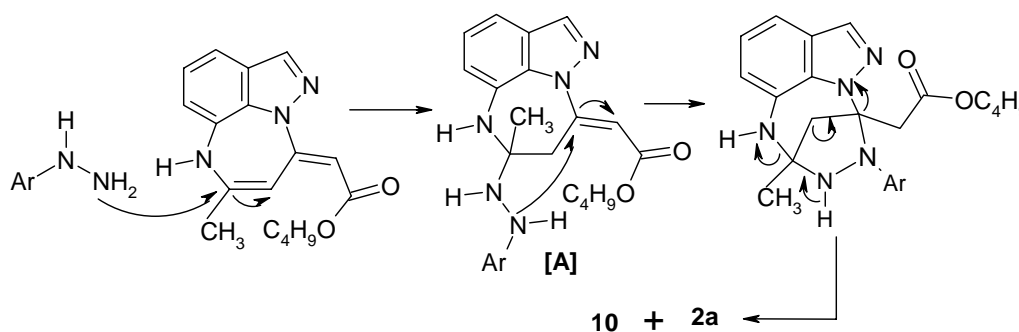
Scheme 7

It should be noted that, instead of compound (**10**), another isomeric structure (**10'**), possessing methyl substituent at the 5 position of the pyrazolic ring, is also conceivable. For discerning between both isomers, we employed a solvent effect on their ¹H NMR spectra. In fact, in accord with the literature,¹⁷

the variation of chemical shift in two different solvents (CDCl_3 , C_6D_6) is more significant for alkyl substituent at the 5 position of the pyrazole cycle (0.5-0.7 ppm) than the same substituent at 3 position (0.05-0.17 ppm). We observed for the methyl group of pyrazole a variation in chemical shift of about 0.19 ppm, which data excluded the proposed structure of isomer (**10'**).

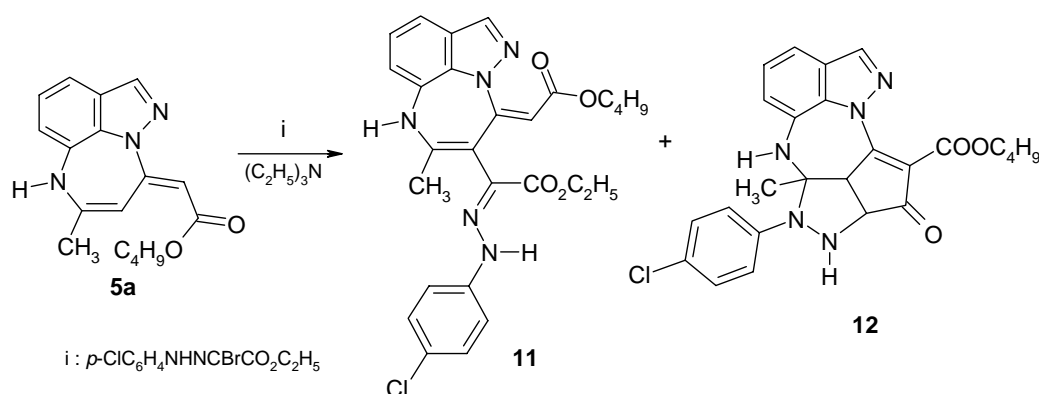


This result confirms that the 1,5-benzodiazepines are precursors of substituted pyrazoles. To support our hypothesis we propose the following mechanism: the initial stage corresponds to the attack of the amino group of the arylhydrazine at the 6 position of the diazepine system leading to the intermediate [A]. This proposed structure undergoes an intra-molecular reaction concerning the attack of the arylamino group on carbon C-4 of the tricyclic system. The tetracyclic compound thus formed undergoes reactions opening cyclic system, giving the 5-butoxycarbonylmethylen-4*H*-3-methyl-1-(2,4-dinitrophenyl)pyrazole (**10**), alongside the 7-aminoindazole (**2a**) (Scheme 8).



Scheme 8

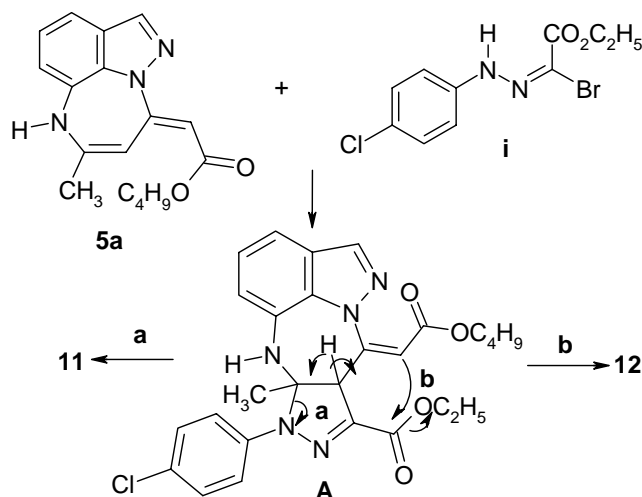
In parallel, we also studied the 1,3-dipolar cyclo-addition of nitrile imine **i** ($p\text{-ClC}_6\text{H}_4\text{NHNCBrCO}_2\text{C}_2\text{H}_5$) with **5a**. Compound **5a** has three possible sites: $\text{C}_6=\text{C}_5$ double bond, $\text{C}_4=\text{C}_1'$ and C_6-N_7 . Reaction of compound (**5a**) with nitrile imine (**i**) in dry benzene affords compounds (**11**) and (**12**) in 22% and 12% yields, respectively (Scheme 9). Analytical and spectral data of both compounds are consistent with the proposed structures.



Scheme 9

To explain the synthesis of compounds (**11**) and (**12**), we suggest the following mechanism: the initial phase of the reaction leads to a cyclo-adduct [A] resulting from the addition of dipole to the double bond

C6=C5. The pyrazole thus formed is not stable (Scheme 10). Consistently, the heterocyclic ring is easily opened by the migration of hydrogen atoms giving the compounds (**11**) (route **a**) and (**12**) (route **b**).



Scheme 10

Conclusion

In this study, we showed that 7-aminoindazoles behave like heterocyclic diamines towards 4-hydroxy-6-methylpyran-2-one (**3**). However, this reaction is an original way of synthesising a new series of heterocyclic compounds: halopyrazolo-1,5-benzodiazepines and halopyrazolo[4,5-*h*]quinolines consisted with very significant pharmacological properties. Mechanisms were proposed to explain the formation of these poly-condensed systems. New classes of pyrazolo-1,5-benzodiazepine derivatives were synthesized by the reaction of compound (**5a**) with *N*-halogenosuccinimide, arylhydrazine and nitrile imine as a 1,3-dipole.

EXPERIMENTAL

General: Melting points were determined using a Büchi-Tottoli apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 577 spectrometer using KBr disk, only noteworthy IR absorptions are listed (cm^{-1}). ^1H and ^{13}C NMR spectra were photorecorded in CDCl_3 solution (unless otherwise specified) with TMS as an internal reference using a Bruker AC 250 (^1H) or 62.89 MHz (^{13}C) and AC 500 (500 or 125 MHz) instruments, chemical shifts are given in δ ppm downfield from TMS; for ^{13}C NMR, the multiplicity was determined through DEPT sequence. MS were performed on the Kratos Concept IS at CSMUB (Centre de Spectroscopie Moléculaire, Université de Bourgogne) using EI. Column chromatography was carried out on SiO_2 (silica gel 60, Merck 0.063-0.200 mm). TLC was carried out on SiO_2 (silica gel 60F 254 Merck 0.063-0.200 mm) and the spots located with UV light. Elemental analyses were obtained from the Service Central d'Analyse du C.N.R.S. All solvents were dried by standard methods. Evaporation of solvents was accomplished with a rotary evaporator.

Synthesis of 7-aminoindazoles (**2b-d**)

To a hydrogenation reactor, the corresponding 7-nitroindazole (12.5 mmol), 0.5 g of palladium on carbon (10%) and 100 mL of ethanol were introduced. The mixture was stirred at rt. The air is removed under hydrogen atmosphere (1 atm). When absorption of hydrogen was stopped the solution is quickly filtered under vacuum and concentrated under reduced pressure.

7-Amino-3-bromoindazole (**2b**) was obtained as a white solid (2.45 g, 93%); **mp** 135°C (toluene); **Anal.**

Calcd for $\text{C}_7\text{H}_6\text{N}_3\text{Br}$: C, 39.65; H, 2.85; N, 19.82. Found: C, 39.76; H, 2.80; N, 19.86.

7-Amino-3,5-dibromoindazole (**2c**) was obtained as a white solid (3.32 g, 92%); **mp** 137°C (toluene);

Anal. Calcd for $\text{C}_7\text{H}_5\text{N}_3\text{Br}_2$: C, 28.90; H, 1.73; N, 14.44. Found: C, 29.10; H, 1.71; N, 14.55.

7-Amino-3,5-dichloroindazole (**2d**) was obtained as a white solid (2.38 g, 95%); **mp** 153°C (hexane / ethyl acetate); **Anal. Calcd** for C₇H₅N₃Cl₂: C, 41.61; H, 2.49; N, 20.80. Found: C, 41.73; H, 2.43; N, 20.82.

Synthesis of Pyrazolo[4,5-*h*]quinolines (**4 a-d**) and Pyrazolo[1,5,4-*ef*][1,5]benzodiazepines (**5a-d**).

General procedures: 4-Hydroxy-6-methylpyran-2-one (1.26 g, 10 mmol) was added to a solution of halo-7-aminoindazole (10 mmol) in 60 mL of *n*-butanol. The reaction mixture was refluxed for 24 h. After evaporation of solvent, the residue was then purified over silica gel column chromatography using a 80:20 mixture of hexane and dichloromethane as eluent.

6-Butoxycarbonylidene-1,9-dihydro-8-methylpyrazolo[4,5-*h*]quinoline (**4a**).

This compound was obtained from 7-aminoindazole (**2a**) as a yellow solid (0.53 g, 18%); **mp** 120-122°C (hexane / ethyl acetate); **IR:** 1670 (CO), 3210 (NH); **¹H NMR** (250 MHz): 0.95 (t, *J* = 7.2 Hz, 3H, CH₃), 1.41 (m, 2H, CH₂), 1.63 (m, 2H, CH₂), 2.38 (s, 3H, CH₃), 4.12 (t, *J* = 6.7 Hz, 2H, CH₂O), 4.73 (s, 1H, H-1'), 4.85 (s, 1H, H-7), 6.48 (d, *J* = 8.3 Hz, 1H, H-Ar), 6.92 (d, *J* = 8.3 Hz, 1H, H-Ar), 7.89 (s, 1H, H-3), 10.67 (s, 1H, NH); **¹³C NMR** (62.89 MHz): 14.4 (CH₃), 20.0 (CH₂), 22.8 (CH₃), 31.5 (CH₂), 64.3(CH₂O), 93.5 (C-1', CH), 104.3 (C-7, CH), 113.5 / 117.3 / 124.2 (C-4, C-5, C-6), 150.6 (C-8), 171.3 (CO); **MS(EI):** *m/z* 297 (M⁺); **Anal. Calcd** for C₁₇H₁₉N₃O₂: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.70; H, 6.40; N, 14.09.

4-Butoxycarbonylmethylidene-3,7-dihydro-6-methylpyrazolo[1,5,4-*ef*][1,5]benzodiazepine (**5a**)

This compound was obtained from 7-aminoindazole (**2a**) as a yellow solid (1.19 g, 40%); **mp** 82-84°C (hexane / ethyl acetate); **IR:** 1666 (CO), 3229 (NH); **¹H NMR** (250 MHz): 0.94 (t, *J* = 7.1 Hz, 3H, CH₃), 1.40 (m, 2H, CH₂), 1.64 (m, 2H, CH₂), 2.37 (s, 3H, CH₃), 4.11 (t, *J* = 6.6 Hz, 2H, CH₂O), 4.71 (s, 1H, H-1'), 4.77 (s, 1H, H-5), 6.57 (dd, *J*₁ = 7.0 Hz, *J*₂ = 1.2 Hz, 1H, H-Ar), 6.91 (dd, *J*₁ = 7.0 Hz, *J*₂ = 7.9 Hz, 1H, H-9), 7.02 (dd, *J*₁ = 7.9 Hz, *J*₂ = 1.2 Hz, 1H, H-Ar), 7.82 (s, 1H, H-1), 10.67 (s, 1H, NH); **¹³C NMR** (62.89 MHz): 14.4 (CH₃), 19.9 (CH₂), 23.0 (CH₃), 31.6 (CH₂), 64.1 (CH₂O), 92.9 (C-1', CH), 103.5 (C-5, CH), 113.1 / 113.2 / 125.1 (C-8, C-9, C-10, 3CH), 151.4 (C-6), 171.4 (CO); **MS(EI):** *m/z* 297 (M⁺); **Anal. Calcd** for C₁₇H₁₉N₃O₂: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.72; H, 6.41; N, 14.10.

3-Bromo-7-butoxycarbonylidene-1,9-dihydro-8-methylpyrazolo[4,5-*h*]quinoline (**4b**)

This compound was obtained from 7-amino-3-bromoindazole (**2b**) as a yellow solid (0.56 g, 15%); **mp** 130-132°C (toluene); **IR:** 1658 (CO), 3220 (NH); **¹H NMR** (250 MHz): 0.94 (t, *J* = 7.2 Hz, 3H, CH₃), 1.40 (m, 2H, CH₂), 1.65 (m, 2H, CH₂), 2.35 (s, 3H, CH₃), 4.10 (t, *J* = 6.7 Hz, 2H, CH₂O), 4.67 (s, 1H, H-1'), 4.77 (s, 1H, H-7), 6.35 (d, *J* = 8.2 Hz, 1H, H-Ar), 6.54 (d, *J* = 8.2 Hz, 1H, H-Ar), 10.52 (s, 1H, NH); **¹³C NMR** (62.89 MHz): 14.4 (CH₃), 20.0 (CH₂), 22.9 (CH₃), 31.6 (CH₂), 64.1 (CH₂O), 92.1 (C-1', CH), 104.7 (C-7, CH), 114.8 / 122.4 / 124.0 (C-4, C-5, C-6), 150.9 (C-8), 171.4 (CO); **MS(EI):** *m/z* 375, 377 (M⁺, Br); **Anal. Calcd** for C₁₇H₁₈N₃O₂Br: C, 54.27; H, 4.82; N, 11.17. Found: C, 54.42; H, 4.76; N, 11.23.

1-Bromo-4-butoxycarbonylmethylidene-3,7-dihydro-6-methylpyrazolo[1,5,4-*ef*][1,5]benzodiazepine (**5b**)

This compound was obtained from 7-amino-3-bromoindazole (**2b**) as a yellow solid (1.27 g, 34%); **mp** 92-94°C (toluene); **IR:** 1659 (CO), 3313 (NH); **¹H NMR** (250 MHz): 0.94 (t, *J* = 7.0 Hz, 3H, CH₃), 1.40 (m, 2H, CH₂), 1.63 (m, 2H, CH₂), 2.39 (s, 3H, CH₃), 4.13 (t, *J* = 6.7 Hz, 2H, CH₂O), 4.78 (s, 1H, H-1'), 4.82 (s, 1H, H-5), 6.69 (dd, *J*₁ = 7.3 Hz, *J*₂ = 1.2 Hz, 1H, H-Ar), 6.96 (dd, *J*₁ = 7.0 Hz, *J*₂ = 1.2 Hz, 1H, H-Ar), 7.07 (dd, *J*₁ = 7.3 Hz, *J*₂ = 7.0 Hz, 1H, H-9), 10.82 (s, 1H, NH); **¹³C NMR** (62.89 MHz): 14.4 (CH₃), 19.9 (CH₂), 22.7 (CH₃), 31.5 (CH₂), 64.2 (CH₂O), 93.5 (C-1', CH), 103.5 (C-5, CH), 112.3 / 114.1 / 125.6 (C-8, C-9, C-10, 3CH), 150.9 (C-6), 171.4 (CO). **MS(EI):** *m/z* 375, 377 (M⁺, Br); **Anal. Calcd** for C₁₇H₁₈N₃O₂Br: C, 54.27; H, 4.82; N, 11.17. Found: C, 54.35; H, 4.79; N, 11.18.

3,5-Dibromo-6-butoxycarbonylidene-1,9-dihydro-8-methylpyrazolo[4,5-*h*]quinoline (**4c**)

This compound was obtained from 7-amino-3,5-dibromoindazole (**2c**) as a yellow solid (0.77 g, 17% yield); **mp** 146-148°C (hexane / ethyl acetate); **IR**: 1660 (CO), 3285 (NH); **¹H NMR** (500 MHz): 0.93 (t, *J* = 7.5 Hz, 3H, CH₃), 1.38 (m, 2H, CH₂), 1.63 (m, 2H, CH₂), 2.38 (s, 3H, CH₃), 4.11 (t, *J* = 7.0 Hz, 2H, CH₂O), 4.76 (s, 1H, H-1'), 4.84 (s, 1H, H-7), 6.78 (s, 1H, H-4, H-Ar), 10.73 (s, 1H, NH); **¹³C NMR** (125 MHz): 14.2 (CH₃), 19.6 (CH₂), 22.6 (CH₃), 31.2 (CH₂), 64.2 (CH₂O), 93.9 (C-1', CH), 104.1 (C-7, CH), 111.0 / 117.1 / 121.0 (C-4, C-5, C-6), 150.0 (C-8), 171.0 (CO); **MS**(EI): *m/z* 453, 455, 457 (M⁺, 2Br); **Anal. Calcd** for C₁₇H₁₇N₃O₂ Br₂: C, 44.86; H, 3.76; N, 9.23. Found: C, 44.93; H, 3.71; N, 9.24.

1,9-Dibromo-6-butoxycarbonylmethylidene-3,7-dihydro-6-methylpyrazolo[1,5,4-*ef*][1,5]benzodiazepine (**5c**)

This compound was obtained from 7-amino-3,5-dibromoindazole (**2c**) as a yellow solid (1.63 g, 36%); **mp** 156-158°C (hexane / ethyl acetate); **IR**: 1665 (CO), 3300 (NH). **¹H NMR** (500 MHz): 0.94 (t, *J* = 6.7 Hz, 3H, CH₃), 1.39 (m, 2H, CH₂), 1.64 (m, 2H, CH₂), 2.38 (s, 3H, CH₃), 4.11 (t, *J* = 7.0 Hz, 2H, CH₂O), 4.80 (s, 1H, H-1'), 4.83 (s, 1H, H-5), 6.79 (d, *J* = 1.2 Hz, 1H, H-Ar), 7.06 (d, *J* = 1.2 Hz, 1H, H-Ar), 10.82 (s, 1H, NH); **¹³C NMR** (125 MHz): 14.2 (CH₃), 19.6 (CH₂), 22.4 (CH₃), 31.2 (CH₂), 64.2 (CH₂O), 94.6 (C-1', CH), 103.6 (C-5, CH), 114.2 / 116.5 / 118.1 (C-8, C-9, C-10), 149.9 (C-6), 171.0 (CO); **MS**(EI): *m/z* 453, 455, 457 (M⁺, 2Br); **Anal. Calcd** for C₁₇H₁₇N₃O₂Br₂: C, 44.86; H, 3.76; N, 9.23. Found: C, 45.04; H, 3.75; N, 9.25.

3,5-Dichloro-6-butoxycarbonylidene-1,9-dihydro-8-methylpyrazolo[4,5-*h*]quinoline (**4d**)

This compound was obtained from 7-amino-3,5-dichloroindazole (**2d**) as a yellow solid (0.36 g, 10%); **mp** 138-140°C (toluene); **IR**: 1655 (CO), 3280 (NH); **¹H NMR** (500 MHz): 0.93 (t, *J* = 7.0 Hz, 3H, CH₃), 1.40 (m, 2H, CH₂), 1.61 (m, 2H, CH₂), 2.36 (s, 3H, CH₃), 4.12 (t, *J* = 6.8 Hz, 2H, CH₂O), 4.78 (s, 1H, H-1'), 4.81 (s, 1H, H-7), 6.45 (s, 1H, H-4), 10.67 (s, 1H, NH); **¹³C NMR** (125 MHz): 14.1 (CH₃), 19.6 (CH₂), 22.6 (CH₃), 31.2 (CH₂), 64.1 (CH₂O), 94.0 (C-1', CH), 104.2 (C-7, CH), 115.0 / 119.1 / 120.8 (C-4, C-5, C-6), 150.2 (C-8), 171.0 (CO); **MS**(EI): *m/z* 365, 367, 369 (M⁺, 2Cl); **Anal. Calcd** for C₁₇H₁₇N₃O₂Cl₂: C, 55.75; H, 4.68; N, 11.47. Found: C, 55.74; H, 4.64; N, 11.47.

1,9-Dichloro-4-butoxycarbonylmethylidene-3,7-dihydro-6-methylpyrazolo[1,5,4-*ef*][1,5]benzodiazepine (**5d**)

This compound was obtained from 7-amino-3,5-dichloroindazole (**2d**) as a yellow solid (1.24 g, 34%); **mp** 150-152°C (toluene); **IR**: 1669 (CO), 3240 (NH); **¹H NMR** (500 MHz): 0.93 (t, *J* = 6.9 Hz, 3H, CH₃), 1.39 (m, 2H, CH₂), 1.64 (m, 2H, CH₂), 2.37 (s, 3H, CH₃), 4.11 (t, *J* = 7.0 Hz, 2H, CH₂O), 4.82 (s, 1H, H-1'), 4.88 (s, 1H, H-5), 6.68 (d, *J* = 2.0 Hz, 1H, H-Ar), 6.98 (d, *J* = 2.0 Hz, 1H, H-Ar), 10.73 (s, 1H, NH); **¹³C NMR** (125 MHz): 14.1 (CH₃), 19.6 (CH₂), 22.3 (CH₃), 31.2 (CH₂), 64.2 (CH₂O), 94.5 (C-1', CH), 103.7 (C-5, CH), 110.4 / 114.1 / 126.3 (C-8, C-9, C-10), 150.0 (C-6), 171.0 (CO); **MS**(EI): *m/z* 365, 367, 369 (M⁺, 2Cl); **Anal. Calcd** for C₁₇H₁₇N₃O₂Cl₂: C, 55.75; H, 4.68; N, 11.47. Found: C, 55.94; H, 4.68; N, 11.56.

Synthesis of Pyrazolo-1,5-benzodiazepin-6-one (**6**)

4-Hydroxy-6-methylpyran-2-one (2.52 g, 20 mmol) was added to a solution of 7-aminoindazole (**2a**) (2.66 g, 20 mmol) in 150 mL of xylene. The reaction mixture was refluxed for 48 h using an azeotropic separator. After evaporation of solvent, the residue was purified by chromatography on silica gel with petroleum ether and dichloromethane 70/30 as eluent. This compound was obtained in 35% yield (2.49 g) as a yellow solid; **mp** 224-226°C (toluene); **IR**: 1655 (CO), 3254 (NH), 1648 (CN); **MS**(EI): *m/z* 356 (M⁺); **Anal. Calcd** for C₂₀H₁₆N₆O: C, 67.39; H, 4.53; N, 23.58. Found: C, 67.44; H, 4.46; N, 23.61.

Halogenation of Pyrazolo-1,5-benzodiazepine (**5a**)

General procedures

A mixture of pyrazolo-1,5-benzodiazepine (**5a**) (0.89 g, 3 mmol) and of *N*-halosuccinimide (6 mmol) in carbon tetrachloride (50 mL) was refluxed for 4 h. Carbon tetrachloride was evaporated and the residue

was purified by column chromatography on silica gel with petroleum ether and dichromethane 70/30 as eluent.

1'-Chloro-4-butoxycarbonylmethylidene-3,7-dihydro-6-methylpyrazolo[1,5,4-ef][1,5]benzodiazepine (7)

This compound was obtained in 36% yield (0.36 g) as a orange solid; **mp** 86-88°C (hexane / ethyl acetate); **IR**: 1654 (CO), 3260 (NH); **¹H NMR** (500 MHz): 0.96 (t, *J* = 7.3 Hz, 3H, CH₃), 1.46 (m, 2H, CH₂), 1.71 (m, 2H, CH₂), 2.44 (s, 3H, CH₃), 4.20 (t, *J* = 6.4 Hz, 2H, CH₂O), 5.89 (s, 1H, H-5), 6.52 (dd, *J* = 7.0 Hz, *J* = 1.2 Hz, 1H, H-Ar), 6.96 (m, 2H, H-Ar), 7.84 (s, 1H, H-1), 11.32 (s, 1H, NH); **¹³C NMR** (125 MHz): 15.7 (CH₃), 21.1 (CH₂), 24.7 (CH₃), 32.6 (CH₂), 67.3 (CH₂O), 98.9 (C-1'), 100.2 (C-5, CH), 114.5 / 114.8 / 126.6 (C-8, C-9, C-10, 3CH), 150 (C-6), 169.9 (CO); **MS(EI)**: *m/z* 331, 333 (M⁺); **Anal. Calcd** for C₁₇H₁₈N₃O₂Cl: C, 61.54; H, 5.47; N, 12.66. Found: C, 61.09; H, 5.46; N, 13.05.

6-Bromomethylene-4-butoxycarbonylmethylidene-3,7-dihydro-6-methylpyrazolo[1,5,4-ef][1,5]benzodiazepine (8a)

This compound was obtained in 25% yield (0.28 g) as an orange solid; **mp** 126-128°C (toluene); **IR**: 1655(CO), 3235 (NH); **¹H NMR** (500 MHz): 0.95 (t, *J* = 7.3 Hz, 3H, CH₃), 1.42 (m, 2H, CH₂), 1.66 (m, 2H, CH₂), 4.13 (t, *J* = 6.6 Hz, 2H, CH₂O), 4.52 (s, 2H, CH₂Br), 4.86 (s, 1H, H-1'), 5.09 (s, 1H, H-5), 6.63 (dd, *J* orth = 7.3 Hz, *J* met = 1.6 Hz, 1H, H-Ar), 7.06 (m, 2H, H-Ar), 7.93 (s, 1H, H-1), 10.62 (s, 1H, NH); **¹³C NMR** (125 MHz): 15.7 (CH₃), 21.1 (CH₂), 32.5 (CH₂), 32.8 (CH₂Br), 65.7 (CH₂O), 97.1 (C-1', CH), 107.8 (C-5, CH), 114.8 / 115.1 / 126.7 (C-8, C-9, C-10, 3CH), 138.5 (C-1), 151.2 (C-6), 172.3 (CO); **MS(EI)**: *m/z* 375, 377 (M⁺, Br); **Anal. Calcd** for C₁₇H₁₈N₃O₂Br: C, 54.27; H, 4.82; N, 11.17. Found: C, 54.41; H, 4.77; N, 11.05.

1'-Bromo-6-bromomethylene-4-butoxycarbonylmethylidene-3,7-dihydro-6-methylpyrazolo[1,5,4-ef][1,5]benzodiazepine (8b)

This compound was obtained in 32% yield (0.43 g) as an orange solid; **mp** 120-122°C (toluene); **IR**: 1650 (CO), 3220 (NH); **¹H NMR** (500 MHz): 0.96 (t, *J* = 7.3 Hz, 3H, CH₃), 1.45 (m, 2H, CH₂), 1.71 (m, 2H, CH₂), 4.18 (t, *J* = 6.7 Hz, 2H, CH₂O), 4.53 (s, 2H, CH₂Br), 6.26 (s, 1H, H-5), 6.57 (dd, *J*₁ = 6.8 Hz, *J*₂ = 1.9 Hz, 1H, H-Ar), 7.03 (m, 2H, H-Ar), 7.92 (s, 1H, H-1), 11.49 (s, 1H, NH); **¹³C NMR** (125 MHz): 15.7 (CH₃), 21.2 (CH₂), 32.5 (CH₂), 32.8 (CH₂Br), 68.1 (CH₂O), 98.6 (C-1'), 109.2 (C-5, CH), 114.9 / 115.3 / 126.9 (C-8, C-9, C-10, CH), 138.5 (C-1), 150.7 (C-6), 169.9 (CO); **MS(EI)**: *m/z* 453, 455, 457 (M⁺, 2Br); **Anal. Calcd** for C₁₇H₁₇N₃O₂Br₂: C, 44.86; H, 3.76; N, 9.24. Found: C, 44.78; H, 3.90; N, 9.48.

1'-Bromo-6-dibromomethylene-4-butoxycarbonylmethylidene-5,7-dihydro-6-methylpyrazolo[1,5,4-ef][1,5]benzodiazepine (9)

This compound was obtained in 10% yield (0.16 g) as an orange solid; **mp** 98-100°C (toluene); **IR**: 1645 (CO), 3270 (NH); **¹H NMR** (500 MHz): 0.96 (t, *J* = 7.0 Hz, 3H, CH₃), 1.45 (m, 2H, CH₂), 1.71 (m, 2H, CH₂), 4.22 (t, *J* = 6.5 Hz, 2H, CH₂O), 5.85 (s, 1H, H-5), 6.60 (dd, *J*₁ = 6.4 Hz, *J*₂ = 1.7 Hz, 1H, H-Ar), 7.01 (m, 2H, H-Ar), 7.41 (s, 1H, CHBr₂), 7.93 (s, 1H, H-1), 11.47 (s, 1H, NH); **¹³C NMR** (125 MHz): 15.7 (CH₃), 21.2 (CH₂), 32.5 (CH₂), 36.5 (CHBr₂), 68.1 (CH₂O), 98.1 (C-1'), 108.1 (C-5, CH), 115.1 / 115.8 / 127.2 (C-8, C-9, C-10, 3CH), 139.1 (C-1), 148.0 (C-6), 169.8 (CO); **MS(EI)**: *m/z* 531, 533, 535, 537 (M⁺, 3Br); **Anal. Calcd** for C₁₇H₁₆N₃O₂Br₃: C, 38.23; H, 3.02; N, 7.87. Found: C, 38.10; H, 2.88; N, 7.97.

Reaction of 2,4-dinitrophenylhydrazine with pyrazolo-1,5-benzodiazepine (5a)

2,4-Dinitrophenylhydrazine (0.3 g, 1.50 mmol) was added to a solution of compound (5a) (0.4 g, 1.35 mmol) in 40 mL of *n*-butanol. The reaction mixture was refluxed for 24 h. After evaporation of solvent, the residue was purified by column chromatography on silica gel with petroleum ether and dichloromethane 20/80 as eluent.

5-Butoxycarbonylmethylene-4H-3-methyl-1-(2,4-dinitrophenyl)pyrazole (10)

This compound was obtained in 61% yield (0.30 g) as a brown solid; **mp** 100-102°C (toluene); **IR**: 1610 (CN), 1733 (CO); **¹H NMR** (500 MHz, CDCl₃): 0.90 (t, $J = 7.3$ Hz, 3H, CH₃), 1.31 (m, 2H, CH₂), 1.55 (m, 2H, CH₂), 2.26 (s, 3H, CH₃), 3.62 (s, 2H, CH₂-6), 4.07 (t, $J = 6.7$ Hz, 2H, CH₂O), 6.28 (s, 1H, H-4), 7.82 (d, $J_{H6'H5'} = 8.9$ Hz, 1H, H-6'), 8.52 (dd, $J_{H5'H3'} = 2.5$ Hz, $J_{H5'H6'} = 8.9$ Hz, 1H, H-5'), 8.79 (d, $J_{H3'H5'} = 2.5$ Hz, 1H, H-3'); **¹H NMR** (500 MHz, C₆D₆): 0.69 (t, $J = 7.3$ Hz, 3H, CH₃), 1.11 (m, 2H, CH₂), 1.28 (m, 2H, CH₂), 2.07 (s, 3H, CH₃), 3.24 (s, 2H, CH₂-6), 3.90 (t, $J = 6.7$ Hz, 2H, CH₂O), 6.06 (s, 1H, H-4), 6.98 (d, $J_{H6'H5'} = 8.9$ Hz, 1H, H-6'), 7.40 (dd, $J_{H5'H3'} = 2.5$ Hz, $J_{H5'H6'} = 8.9$ Hz, 1H, H-5'), 7.99 (d, $J_{H3'H5'} = 2.54$ Hz, 1H, H-3'). **¹³C NMR**(125 MHz): 15.6 (CH₃), 17.5 (CH₃), 21.0 (CH₂), 32.4 (CH₂), 33.8 (CH₂-6), 67.7 (CH₂O), 111.6 (C-6', CH), 122.9 (C-4, CH), 129.2 / 132.0 (C-2', C-4'), 139.5 (C-3), 148.7 (C-5), 154.4 (C-1'), 170.7 (CO); **MS**(EI): m/z 362 (M⁺); **Anal. Calcd** for C₁₆H₁₈N₄O₆: C, 53.04; H, 5.01; N, 15.46. Found: C, 52.99; H, 4.91; N, 15.45.

Reaction of nitrile imine with compound (5a)

A solution of triethylamine (2 mL, 9 mmol) in dry benzene (10 mL) was slowly added to a solution of pyrazolo-1,5-benzodiazepine (**5a**) (0.86 g, 2.9 mmol) and the corresponding nitrile imine (2.9 mmol) in dry benzene (80 mL). Then, the resulting mixture was refluxed for 48 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using hexane and chloroform as eluents (70:30).

Compound (11) was obtained as an orange solid in 22% yield (0.33 g); **mp** 192-194°C (toluene); **IR**: 1660, 1705 (CO), 3029, 3315 (NH); **¹H NMR** (200 MHz): 0.81 (t, $J = 6.8$ Hz, 3H, CH₃, butyl), 1.23 (m, 2H, CH₂), 1.33 (t, $J = 6.8$ Hz, 3H, CH₃, ethyl), 1.49 (m, 2H, CH₂), 2.25 (s, 3H, CH₃), 4.12 (q, $J = 6.8$ Hz, 2H, CH₂O, ethoxy), 4.30 (t, $J = 6.8$ Hz, 2H, CH₂O, butoxy), 4.65 (s, 1H, H-1'), 6.57 (d, $J = 6.4$ Hz, 1H, H-Ar), 6.95 (m, 2H, H-Ar), 7.23 (m, 4H, H-Ar), 7.80 (s, 1H, H-1), 8.31 (s, 1H, NH), 11.68 (s, 1H, NH); **¹³C NMR** (125 MHz): 15.5 (CH₃), 16.3 (CH₃), 20.9 (CH₂), 24.5 (CH₃), 32.5 (CH₂), 63.3 (CH₂O), 66.4 (CH₂O), 91.9 (C-1', CH), 99.5 (C-5), 133.8 (C-1), 166.9 (CO), 171.2 (CO); **MS**(EI): m/z 521, 523 (M⁺, Cl). **Anal. Calcd** for C₂₇H₂₈N₅O₄Cl: C, 62.13; H, 5.41; N, 13.42. Found: C, 61.80; H, 5.55; N, 13.34.

Compound (12) was obtained as a pale red solid in a 12% yield (0.16 g); **mp** 204-206°C (toluene); **IR**: 1638, 1669 (CO), 3065, 3310 (NH); **¹H NMR** (200 MHz): 1.02 (t, $J = 7.0$ Hz, 3H, CH₃), 1.57 (m, 2H, CH₂), 1.81 (m, 2H, CH₂), 2.60 (s, 3H, CH₃), 4.37 (t, $J = 6.4$ Hz, 2H, CH₂O), 7.06-7.56 (m, 7H, H-Ar), 8.09 (s, 1H, H-1), 9.01 (s, 1H, NH), 13.30 (s, 1H, NH); **¹³C NMR** (125 MHz): 14.3 (CH₃), 19.9 (CH₂), 23.2 (CH₃), 31.2 (CH₂), 65.0 (CH₂O), 96.6 (C-6), 106.5 (C-5), 137.3 (C-1), 139.9/141.5/142.7 (3C), 160.7 (CO), 163.7 (CO); **MS**(EI): m/z 475, 477 (M⁺, Cl); **Anal. Calcd** for C₂₅H₂₂N₅O₃Cl: C, 63.09; H, 4.66; N, 14.71. Found: C, 63.31; H, 4.53; N, 14.68.

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