Synthesis of New Bis-3,5-diphenylpyrazolines Derivatives Linked with Alkyl Chains

Braulio Insuasty,[a*] Henry Martinez,[a] Jairo Quiroga,[a] Rodrigo Abonía,[a] Manuel Nogueras[b*] and Justo Cobo[b]

[a]Grupo de Investigación de Compuestos Heterocíclicos, Department of Chemistry, Universidad del Valle, A. A. 25360 Cali, Colombia
[b]Department of Inorganic and Organic Chemistry, Universidad de Jaén, 23071 Jaén, Spain.
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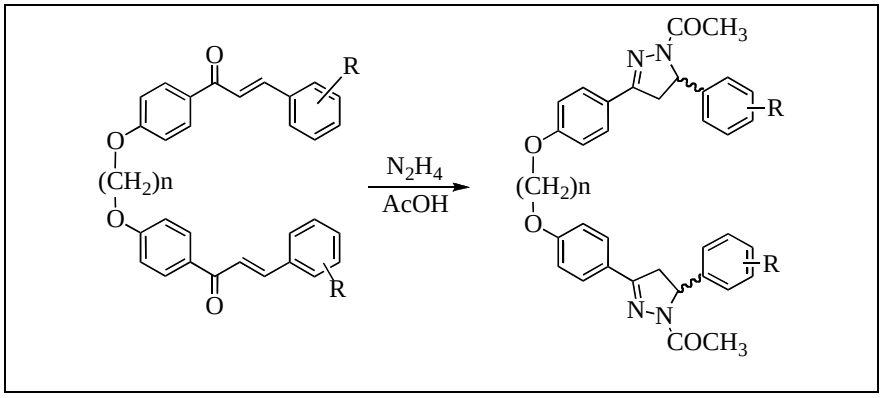

New bis-3,5-diphenylpyrazoline derivatives have been synthesized according to Elway [1] (1999) and Sangwan's [2] (1992) methodology. Most of them were obtained in good yields, from the reaction between an alkyl linked bis-chalcones and hydrazine in acetic acid. The activity of some bis-pyrazolines was evaluated against *Helicobacter pylori*.

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INTRODUCTION

Recently, considerable interest has been focused on pyrazoline system, specially, 3,5-diarylpyrazoline derivatives, which have displayed a tremendous spectrum of biological activity; for example, antitumoral activity [3], human Acyl-CoA inhibitors (anti-atherosclerosis) [4] with an important activity (MIC_{50} between 14.7-164.3 μM), anti-depressant agents [5] or as bactericide (anti-*Helicobacter pylori*, with MIC_{90} between 8-64 μg/mL) [6]. With respect to the anti-depressant activity, the authors [5] found that the presence of 4-chlorophenyl group at position 3 of the pyrazoline system increased the anti-depressant activity. More recently Azam and co-workers [7] reported the synthesis of bis-pyrazolines with a great activity as inhibitors of the growth of *Entamoeba histolytica*, a potent pathogen, which causes approximately 100,000 deaths annually.

The bis-pyrazolines **4a-f** were prepared using a previous methodology reported by Elway [1] and Sangwan [2] by the reaction of bis-chalcones **3a-f** with hydrazine in acetic acid. For some of them its anti- *H. Pylori* activity was evaluated.

RESULTS AND DISCUSSION

The bis-chalcones derivatives **3a-f** were obtained according to Claisen-Schmidt reaction by treating diketone **1** and aromatic aldehydes **2** in ethanol with catalytic amounts of sodium hydroxide [8]. All bis-chalcones were obtained in good yields.

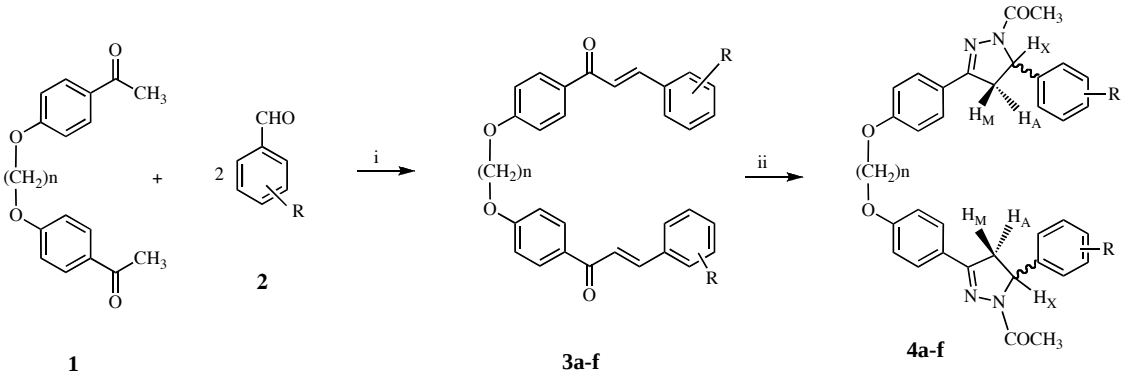
The synthesis of the bis-pyrazolines was carried out with hydrazine, and acetic acid as a solvent, obtaining the N-acetylated final products (Scheme 1), consistent with a previous work [2].

The spacers of methylenes chains that liked both pyrazolines were varied in order to analyze any possible influence on biological activity.

The structure of new bis-chalcones **3a-f** were established by usual analytical and spectroscopic methods (1D and 2D-NMR mainly, MS and elemental analysis, see experimental section). The IR spectra of compounds **3a-f** showed a strong C=O stretching band at interval 1659 and 1668 cm^{-1}, as usual for this kind highly conjugated C=O. The ^1H NMR spectra of compounds **3a-f** showed the aromatic protons between 6.84-7.84 ppm, two doublets at 7.40-7.93 ppm (J=15.6–15.7 Hz) corresponding to the *trans* vinyl protons of the α,β-unsaturated system. Additionally, proton signals of -O-$(CH_2)_n$-O- fragment appear at 4.10-4.28 and 1.96-2.35 ppm for the CH_2-groups connected to the oxygen and for the interior CH_2-groups respectively.

The structures of **4a-f** were established by the usual analytical and spectroscopic methods given above. Where, the IR spectra of compounds **4a-f** showed a strong stretching band at interval 1660-1666 cm^{-1}, that resulted

Scheme 1



i) EtOH/NaOH, rt; ii) N_2H_4/CH_3COOH/Reflux

Comp.	3a/4a	3b/4b	3c/4c	3d/4d	3e/4e	3f/4f
n	3	3	3	4	4	4
R	3,4,5-Tri-OMe	4-OMe	4-CF_3	3,4,5,Tri-OMe	4-OMe	4-CF_3
t. r. (hours)	8/28	10/32	9/25	7/27	9/28	8/26

the C=O amide type (acetyl group). The ^{1}H NMR spectra of compounds **4a-f** showed aromatic protons at interval 6.42-7.60 ppm, three doublet of doublets corresponding to an AMX system characteristic of pyrazolines, where H_A appear at interval 3.12–3.40 ppm, H_M at interval 3.66–3.75 ppm and H_X at interval 5.50–5.62 ppm, with three coupling constants around $J_{AM(gem)}$=17.7 Hz, $J_{AX(trans)}$=4.7 Hz and $J_{MX(cis)}$=11.8Hz.

As recorded previously, Helicobacter Pylori, an S-shaped spiral microaerophilic, Gram-negative bacterium first isolated in human gastric mucosa in 1982, is considered to be the major causative agent of several gastric pathologies, such as chronic gastritis, peptic ulcer disease and gastric cancer [6]. Due to these different biological activities, the compounds **4a, 4d**, **4e** and metronidazole were evaluated with against 20 *H. pylori* strains, including metronidazole resistant strains. But unfortunately those compounds did not show an important biological activity compare with metronidazole. There was not significant difference between spacers of 3 and 4 methylenes.

In summary, the alkyl spacers bis-chalcones **3** were obtained by a Claisen-Schmidt reaction with arylaldehyde, a diketone, and catalytic amounts of sodium hydroxide, in high yields, which were used to provide new 1,3 and 1,4 bis-(4-((aryl)-*N*-acetyl-pyrazolin-5-yl)phenoxy)alkyl derivatives **4** by reaction with hydrazine, in good to excellent yields.

The anti-*H. pylori* activity was evaluated for some of those bis-pyrazolines, however low biological activity was obtained ($MIC_{90} \geq 128$ μg/mL). Even though, the activity against *H. Pyroli* was not successful, the great activity of pyrazolines and bis-pyrazolines warrants further study of other biological activities and small chemical modifications over these new compounds, in order to find an improvement in the activity.

EXPERIMENTAL

Melting points were taken on a Stuart SMP3 melting point apparatus and were not corrected. IR spectra were recorded on a Shimadzu FTIR-8400 using KBr discs. The ^{1}H- and ^{13}C NMR spectras were run on a BRUKER AVANCE spectrometer operating at 400 MHz and 100 MHz respectively in DMSO-d_6 using TMS as internal Standard (belong to the Servicios Técnicos de Investigación, Universidad de Jaén, STIUJA). The mass spectra were recorded on SHIMADZU GCMS201, by electronic impact operating at 70 eV. The elemental analyses have been obtained using a LECO CHNS-900 and an Thermo Finnigan FlashEA1112 CHNS-O (STIUJA) elemental analyzers. Diketones **1** were obtained according to methodology described in work [8].

General procedure for the synthesis of bis-chalcones 3a-f. To a solution of diketone **1** (1 mmol) and aromatic aldehyde **2** (2 mmol) in absolute ethanol (10 mL), a catalytic amount of sodium hydroxide (0.100 g) was added, and the reaction mixture was stirred at room temperature until the precipitate formation. The precipitate was isolated by filtration and washed with hot ethanol.

1,3-Bis(4-((3,4,5-(trimethoxy)phenyl)-acryloyl)phenoxy)-propane 3a. This compound was obtained according to general procedure as a yellow solid; Yield 93%; m.p: 146-148 ºC. IR (KBr) cm^{-1}: (C=O) 1665; EIMS: *m/z* (70 eV): 668 (20, M$^+$), 490 (78), 459 (100), 457 (58). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 2.33 (m, 2H), 4.26 (t, 4H), J=6.3 Hz, 6.88 (s, 4H), 3.90 (s, 6H), 3.92 (s, 12H), 8.04 (d, 4H), 6.98 (d, 4H), J=8.9 Hz., 7.42 (d, 2H), 7.71 (d, 2H), J=15.6Hz. ^{13}C NMR (DMSO-d_6, ppm): 188.6

(C_1), 162.6 ($C_{p'}$), 153.5 (C_m), 144.2 (C_3), 140.4 (C_p), 131.3 ($C_{i'}$), 130.8 ($C_{o'}$), 130.5 (C_i), 121.2 (C_2), 114.3 ($C_{m'}$), 105.7 (C_o), 64.5 (OCH_2), 61.0 (OCH_3(p)), 56.3 (OCH_3(m)), 29.1 (CH_2). Elem. *Anal*. for $C_{39}H_{40}O_{10}$, Calculated (%): C, 70.05; H, 6.03; found: C, 70.17; H, 5.97.

1,3-Bis(4-((4-(methoxy)phenyl)-acryloyl)phenoxy)propane 3b. This compound was obtained according to general procedure as yellow solid; Yield 95 %; m.p: 139-141 ºC. IR (KBr) cm^{-1}: (C=O) 1675; EIMS: *m/z* (70 eV): 548 (80, M^+), 386 (100), 253 (53), 161 (90). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 2.25 (m, 2H), 4.24 (t, 4H), J=6.2 Hz, 3.84 (s, 6H), 7.77 (d, 4H), 6.98 (d, 4H), J=8.7 Hz, 8.08 (d, 4H), 7.08 (d, 4H), J=8.0 Hz, 7.63 (d, 2H), 7.56 (d, 2H), J=15.3 Hz. ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 188.5 (C_1), 143.5 (C_3), 120.7 (C_2), 162.8 ($C_{p'}$), 131.6 ($C_{i'}$), 131.0 ($C_{o'}$), 115.2 ($C_{m'}$), 55.9 (OCH_3), 161.9 (C_p), 130.7 (C_o), 128.1 (C_i), 115.1 (C_o), 65.5 (OCH_2), 30.8 (CH_2). Elem. *Anal*. for $C_{35}H_{32}O_6$, Calculated (%): C, 76.62; H, 5.88; found: C, 76.59; H, 5.93.

1,3-Bis(4-((4-(trifluoromethyl)phenyl)-acryloyl)phenoxy)-propane 3c. This compound was obtained according to general procedure as light yellow solid; Yield 90%; m.p: 189-190 ºC. IR (KBr) cm^{-1}: (C=O) 1659; EIMS: *m/z* (70 eV): 624 (23, M^+), 584 (20), 333 (28), 199 (100).). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 2.35 (m, 2H), 4.28 (t, 4H), J=5.8 Hz, 7.67 (d, 4H), 7.69 (d, 4H), J=7.9 Hz, 8.02 (d, 4H), 6.99 (d, 4H), J=8.5 Hz, 7.42 (d, 2H), 7.75 (d, 2H), J=15.7 Hz. ^{13}C NMR (DMSO-d_6, ppm): 188.2 (C_1), 163.0 ($C_{p'}$), 125.7 (C_o), 141.9 (C_3), 138.6 (C_p), 132.0 ($C_{i'}$), 131.0 ($C_{o'}$), 131.7 (C_i), 124.3 (C_2), 114.3 ($C_{m'}$), 125.9 (C_m), 122.7 (CF_3), 65.0(OCH_2), 29.2 (CH_2). Elem. *Anal*. for $C_{35}H_{26}F_6O_4$, Calculated (%): C, 67.31; H, 4.20; found: C, 67.39; H, 4.18.

1,4-Bis(4-((3,4,5-(trimethoxy)phenyl)-acryloyl)phenoxy)-butane 3d. This compound was obtained according to general procedure as yellow solid; Yield 95%; m.p: 196-197 ºC. IR (KBr) cm^{-1}: (C=O) 1668; EIMS: *m/z* (70 eV): 682 (25, M^+), 651 (95), 121 (100), 473 (48). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 2.05 (m, 4H), 4.12 (t, 4H), J=4,8 Hz, 6.87 (s, 4H), 3.92 (s, 12H), 3.90 (s, 6H) 8.04 (d, 4H), 6.99 (d, 4H), J=8.9 Hz, 7.40 (d, 2H), 7.73 (d, 2H), J=15.6 Hz. ^{13}C NMR (DMSO-d_6, ppm): 188.6 (C_1), 162.8 ($C_{p'}$), 153.5 (C_m), 144.2 (C_3), 140.4 (C_p), 131.2 ($C_{i'}$), 130.6 ($C_{o'}$), 130.6 (C_i), 121.2 (C_2), 114.3 ($C_{m'}$), 105.7 (C_o), 65.9 (OCH_2), 61.00 (OCH_3(p)), 56.3 (OCH_3(m)), 25.9 (CH_2). Elem. *Anal*. for $C_{40}H_{42}O_{10}$, Calculated (%): C, 70.37; H, 6.20; found: C, 70.48; H, 6.29.

1,4-Bis(4-((4-(methoxy)phenyl)-acryloyl)phenoxy)butane 3e. This compound was obtained according to general procedure as yellow solid; Yield 96 %; m.p: 137-138 ºC. IR (KBr) cm^{-1}: (C=O) 1677; EIMS: *m/z* (70 eV): 562 (35, M^+), 444 (72), 400 (100), 161 (72). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 1.96 (m, 4H), 4.20 (t, 4H), J=5.5 Hz, 3.83 (s, 6H), 7.72 (d, 4H), 7.00 (d, 4H), J=8.7 Hz, 8.04 (d, 4H), 7.06 (d, 4H), J=8.7 Hz, 7.57 (d, 2H), 7.64 (d, 2H), J=15.7 Hz. ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 187.2 (C_1), 142.0 (C_3), 120.0 (C_2), 161.8 ($C_{p'}$), 130.6 ($C_{i'}$), 129.8 ($C_{o'}$), 114.1 ($C_{m'}$), 54.8 (OCH_3), 160.8 (C_p), 129.5 (C_o), 127.2 (C_i), 114.0 (C_o), 67.3 (OCH_2), 24.8 (CH_2). Elem. *Anal*. for $C_{36}H_{34}O_6$, Calculated (%): C, 76.85; H, 6.09; found: C, 76.84; H, 6.11.

1,4-Bis(4-((4-(trifluoromethyl)phenyl)-acryloyl)phenoxy)-butane 3f. This compound was obtained according to general procedure as light yellow solid; Yield 90%; m.p: 192-194 ºC. IR (KBr) cm^{-1}: (C=O) 1662; EIMS: *m/z* (70 eV): 638 (6, M^+), 347 (100), 305 (45), 199 (32). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 1.96 (m, 4H), 4.21 (t, 4H), J=5.8 Hz, 7.74 (s, 4H), 7.99 (d, 4H), J=8.1 Hz, 8.07 (d, 4H), 7.07 (d, 4H), J=8.7 Hz, 7.67 (d, 2H), 7.86 (d, 2H), J=15.7 Hz. ^{13}C NMR (DMSO-d_6, ppm): 187.1 (C_1), 162.2 ($C_{p'}$), 125.0 (C_m), 140.1 (C_3), 138.4 (C_p), 131.9 ($C_{i'}$), 130.2 ($C_{o'}$), 129.9 (C_i), 124.8 (C_2), 114.1 ($C_{m'}$), 124.7 (C_o), 122.1 (CF_3), 67.3 (OCH_2), 24.7 (CH_2). Elem. *Anal*. for $C_{36}H_{28}F_6O_4$, Calculated (%): C, 67.71; H, 4.42; found: C, 67.82; H, 4.41.

General procedure for the synthesis of bis- pyrazolines 4a-f. A solution of bis-chalcone **3** (1 mmol) and hydrazine-hydrate (2 mmol) in 70 mL (aprox) of acetic acid was refluxed during 25-32 hours. The solution was cooled to room temperature, and then water was added until the formation of precipitate. A white solid was isolated by filtration, washed with cold ethanol and recrystallized from ethanol. In cases **4c, 4e** and **4f** chromatographical purification has been donde using silicagel 60 (0063-0.200 mm), eluent chloroform-acetate, 10:1.

1,3-Bis(4-((3,4,5-(trimethoxy)phenyl)-*N*-acetyl-pyrazolin-5-yl)phenoxy)-propane 4a. This compound was obtained according to general procedure as white solid; Yield 89%; m.p: 120-121 ºC. IR (KBr) cm^{-1}: (C=O) 1662; EIMS: *m/z* (70 eV): 780 (4, M^+), 737 (19), 528 (38), 487 (15), 43 (100). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 2.32 (m, 2H), 4.22 (t, 4H), J=6.0 Hz, 6.96 (d, 4H), 7.67 (d, 4H), J=8.89 Hz, 3.48 (dd, 2H), 3.66 (dd, 2H), J_{gem}=17.62 Hz, 5.51 (dd, 2H), J_{cis}=11.75 Hz, J_{trans}=4.75 Hz, 6.42 (s, 4H), 2.35 (s, 6H), 3.82 (s, 12H), 3.79 (s, 6H). ^{13}C NMR ($CDCl_3$, ppm): 64.4 (OCH_2), 29.1 (CH_2), 124.1 ($C_{i'}$), 128.2 ($C_{o'}$), 114.7 ($C_{m'}$), 160.6 ($C_{p'}$), 137.3 (C_i), 102.4 (C_o), 153.7 (C_m), 137.8 (C_p), 153.6 (C_1), 42.6 (C_2), 60.7 (C_3), 168.8 (C_4), 21.9 (C_5), 56.1 (OCH_3(m)), 60.0 (OCH_3(p)). Elem. *Anal*. for $C_{43}H_{48}N_4O10$, Calculated (%): C, 66.14; H, 6.20; N, 7.17; found: C, 66.19; H, 6.13; N, 6.98.

1,3-Bis(4-((4-(methoxy)phenyl)-*N*-acetyl-pyrazolin-5-yl)-phenoxy)propane 4b. This compound was obtained according to general procedure as white solid; Yield 56%; m.p: 125-126 ºC. IR (KBr) cm^{-1}: (C=O) 1660; EIMS: *m/z* (70 eV): 660 (15, M^+), 645 (12), 627 (100). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 2.34 (m, 2H), 4.25 (t, 4H), J=6.0 Hz, 6.94 (d, 4H), 7.61 (d, 4H), J=8.7 Hz, 3.20 (dd, 2H), 3.67 (dd, 2H), J_{gem}=17.7 Hz, 5.50 (dd, 2H), J_{cis}=11.7 Hz, J_{trans}=4.5 Hz, 7.28 (d, 4H), 6.84 (d, 4H), J=8.8 Hz, 2.37 (s, 6H), 3.85 (s, 18H), ^{13}C NMR ($CDCl_3$, ppm): 65.4 (OCH_2), 23.4 (CH_2), 124.1 ($C_{i'}$), 127.9 ($C_{o'}$), 114.6 ($C_{m'}$), 159.8 ($C_{p'}$), 134.2 (C_i), 126.9 (C_o), 114.5 (C_m), 158.8 (C_p), 153.6 (C_1), 42.3 (C_2), 59.3 (C_3), 167.9 (C_4), 21.4 (C_5), 56.2 (OCH_3). Elem. *Anal*. for $C_{39}H_{40}N_4O_6$, Calculated (%): C, 70.89; H, 6.10; N, 8.48; found: C, 70.84; H, 6.02; N, 8.26.

1,3-Bis(4-((4-(trifluoromethyl)phenyl)-*N*-acetyl-pyrazolin-5-yl)phenoxy)-propane 4c. This compound was obtained according to general procedure as white solid. Yield 59%; m.p: 103-104 ºC. IR (KBr) cm^{-1}: (C=O) 1663; EIMS: *m/z* (70 eV): 736 (5, M^+), 693 (100), 634 (29), 464 (36). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 2.31 (m, 2H), 4.20 (t, 4H), J=5.8 Hz, 6.97 (d, 4H), 7.66 (d, 4H), J=8.9 Hz, 3.12 (dd, 2H), 3.75 (dd, 2H), J_{gem}=17.7 Hz, 5.62 (dd, 2H), J_{cis}=11.8 Hz, J_{trans}=4.7 Hz, 7.33 (d, 4H), 7.60 (d, 4H), J=8.2 Hz, 2.42 (s, 6H). ^{13}C NMR ($CDCl_3$, ppm): 65.5 (OCH_2), 29.1 (CH_2), 123.9 ($C_{i'}$), 128.2 ($C_{o'}$), 114.7 ($C_{m'}$), 160.7 ($C_{p'}$), 145.8 (C_i), 126.0 (C_o), 125.9 (C_m), 130.0 (C_p), 153.5 (C_1), 122.6 (CF_3), 42.2 (C_2), 59.5 (C_3), 168.8 (C_4), 21.8 (C_5). Elem. *Anal*. for $C_{39}H_{34}F_6N_4O_4$, Calculated (%): C, 63.58; H, 4.65; N, 7.60; found: C, 63.51; H, 4.58; N, 7.47.

1,4-Bis(4-((3,4,5-(trimethoxy)phenyl)-*N*-acetyl-pyrazolin-5-yl)phenoxy)-butane 4d. This compound was obtained according to general procedure as white solid; Yield 92%; m.p:

188-190 ºC. IR (KBr) cm^{-1}: (C=O) 1666; EIMS: *m/z* (70 eV): 794 (5, M^+), 751 (15), 542 (39), 251 (84), 44 (100). ^1H NMR (400 MHz, $CDCl_3$, ppm): 2.04 (m, 4H), 4.13 (t, 4H), J=5.8 Hz, 6.95 (d, 4H), 7.69 (d, 4H), J=8.9 Hz, 3.15 (dd, 2H), 3.70 (dd, 2H), J_{gem}=17.7 Hz, 5.51 (dd, 2H), J_{cis}=11.7 Hz, J_{trans}=4.7 Hz, 6.43 (s, 4H), 2.55 (s, 6H), 3.82 (s, 12H), 3.80 (s, 6H). ^{13}C NMR ($CDCl_3$, ppm): 65.8 (OCH_2), 25.9 (CH_2), 123.9 ($C_{i'}$), 128.2 ($C_{o'}$), 114.6 ($C_{m'}$), 160.8 ($C_{p'}$), 137.3 (C_i), 102.4 (C_o), 153.8 (C_m), 137.8 (C_p), 153.6 (C_1), 42.6 (C_2), 60.7 (C_3), 168.8 (C_4), 21.9 (C_5), 56.1 (OCH_3(m)), 60.0 (OCH_3(p)). Elem. *Anal*. for $C_{44}H_{50}N_4O_{10}$, Calculated (%): C, 66.48; H, 6.34; N, 7.05; found: C, 66.54; H, 6.23; N, 6.92.

1,4-Bis(4-((4-(methoxy)phenyl)-*N*-acetyl-pyrazolin-5-yl)-phenoxy)butane 4e. This compound was obtained according to general procedure as white solid, Yield 86%; m.p: 139-140 ºC. IR (KBr) cm^{-1}: (C=O) 1660; EIMS: *m/z* (70 eV): 674 (25M^+), 659 (19), 631 (100), 84 (69). ^1H NMR (400 MHz, $CDCl_3$, ppm): 2.01 (m, 4H), 4.09 (t, 4H), J=5.7 Hz, 6.94 (d, 4H), 7.66 (d, 4H), J=8.7 Hz, 3.13 (dd, 2H), 3.68 (dd, 2H), J_{gem}=17.7 Hz, 5.53 (dd, 2H), J_{cis}=11.7 Hz, J_{trans}=4.4 Hz, 7.16 (d, 4H), 6.85 (d, 4H), J=8.9 Hz, 2.39 (s, 6H), 3.78 (s, 6H), ^{13}C NMR ($CDCl_3$, ppm): 67.6 (OCH_2), 25.9 (CH_2), 124.1 ($C_{i'}$), 128.3 ($C_{o'}$), 114.6 ($C_{m'}$), 160.7 ($C_{p'}$), 134.2 (C_i), 126.9 (C_o), 114.2 (C_m), 158.9 (C_p), 153.6 (C_1), 42.3 (C_2), 59.3 (C_3), 168.6 (C_4), 21.9 (C_5), 56.2 (OCH_3). Elem. *Anal*. for $C_{40}H_{42}N_4O_6$, Calculated (%): C, 71.20; H, 6.27; N, 8.30; found: C, 71.29; H, 6.19; N, 8.16.

1,4-Bis(4-((4-(trifluoromethyl)phenyl)-*N*-acetyl-pyrazolin-5-yl)phenoxy)-butane 4f. This compound was obtained according to general procedure as white solid; Yield 55%; m.p: 110-112 ºC. IR (KBr) cm^{-1}: (C=O) 1664; EIMS: *m/z* (70 eV): 750 (6, M^+), 707 (100), 689 (22.), 648 (27). ^1H NMR (400 MHz, $CDCl_3$, ppm): 2.04 (m, 4H), 4.09 (t, 4H), J=5.8 Hz, 6.95 (d, 4H), 7.61 (d, 4H), J=8.9 Hz, 3.13 (dd, 2H), 3.72 (dd, 2H), J_{gem}=17.7 Hz, 5.62 (dd, 2H), J_{cis}=11.8 Hz, J_{trans}=4.8 Hz, 7.33 (d, 4H), 7.59 (d, 4H), J=8.3 Hz, 2.42 (s, 6H). ^{13}C NMR ($CDCl_3$, ppm): 65.8 (OCH_2), 25.9 (CH_2), 122.7 ($C_{i'}$), 125.7 ($C_{o'}$), 114.9 ($C_{m'}$), 160.9 ($C_{p'}$), 145.8 (C_i), 126.9 (C_o), 128.2 (C_m), 130.0 (C_p), 153.5 (C_1), 122.6 (CF_3), 42.3 (C_2), 59.4 (C_3), 168.8 (C_4), 21.8 (C_5). Elem. *Anal*. for $C_{40}H_{36}F_4N_4O_4$, Calculated (%): C, 64.00; H, 4.83; N, 7.46; found: C, 64.09; H, 4.75; N, 7.23.

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