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SYNTHESIS OF NEW BENZYLIC ETHERS OF OXIMES DERIVED FROM 1-PHENYL-PYRAZOLE COMPOUNDS

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ABSTRACT: In the scope of a research program aiming at the synthesis and pharmacological evaluation of new antithrombotic agents via rational molecular design, we describe in this paper the synthesis of benzyl ethers of aryl-pyrazolic oxime derivatives. Ethers' (2a-2c) and (3a-3c) are derived from 4-formyl-1-N-phenylpyrazole (4) in good yield. Designed as interphenylenic analogues of the ridogrel (1), one expects these compounds to present dual properties, i.e., thromboxane A_2 receptors antagonism and thromboxane synthetase inhibition.

In the scope of a research program aiming to the synthesis and pharmacological evaluation of new heterocyclic bioactive compounds[1-8] we describe in the present paper the synthesis and the anti-platelet behavior of benzylic ethers of pyrazolic oximes (2a-c) and (3a-c), designed as new analogues of ridogrel (1)[9-11] (Figure 1).

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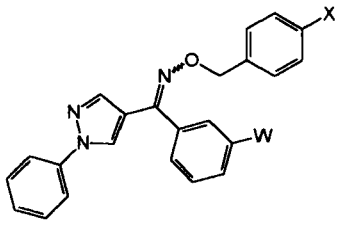
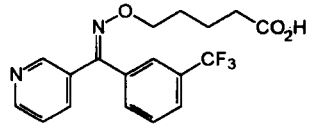




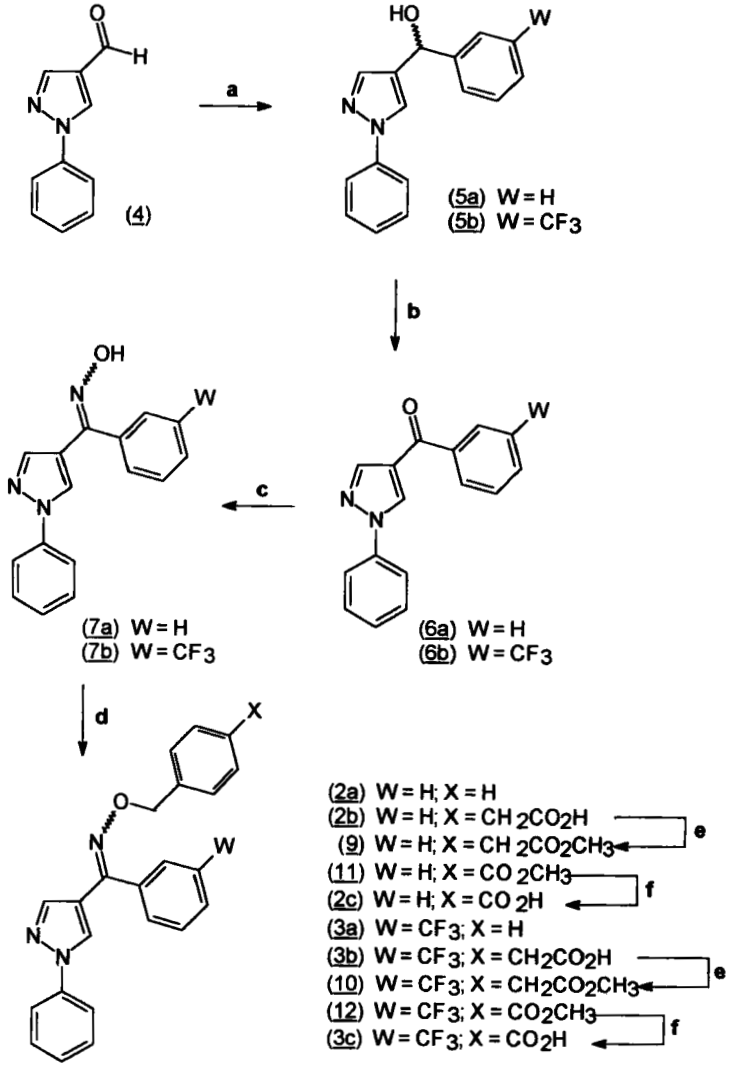
Ridogrel, (1)

(2a) W = H; X = H
(2b) W = H; X = CH_2CO_2H
(2c) W = H; X = CO_2H
(3a) W = CF_3; X = H
(3b) W = CF_3; X = CH_2CO_2H
(3c) W = CF_3; X = CO_2H

FIGURE 1

These new derivatives (2a-c) and (3a-c) were designed exploring the classical isosterism relationship between the pyridine nucleus of (1) and 1-phenyl-pyrazole ring present in (2a-c) and (3a-c)[2]. The variation of the **X** residue in these derivatives was made to determinate the importance of the carboxylic acid function as well as the distance from it to basic nitrogen atom of the pyrazole ring, in the antithrombotic activity, as ideally observed by Kato *et al.*[12] to TXSi activity. The oxime function present in (1) was maintained by characterize it as a pharmacoforic group to TPant activity[13]. Additionally, the proposed compounds (2a-c) and (3a-c) presents an interphenylene group in the carboxylic acid side chain of ridogrel (1) to favors it in an extended bioactive conformation[14] and reduce the metabolism by β-oxidation[15] pathway, increasing the half-life of the target compounds.

The synthetic route planned to these new derivatives (2) and (3) suggests the 4-formyl-1-phenyl-pyrazole (4), as a common key intermediate (Scheme 1). This



a) a) PhMgBr or 3-CF_3PhMgBr, THF, reflux, 1h; b) H_2CrO_4, acetone, 0°C, 30 min. c) $NH_2OH.HCl$, NaOH, EtOH, H_2O, reflux, 5 min.; d) NaH, THF, 3-X-$C_6H_4CH_2Y$, reflux, 3h; e) CH_2N_2, ethyl ether, r.t., 5 min.; f) 1N aq. LiOH, acetone, r.t., 3h.

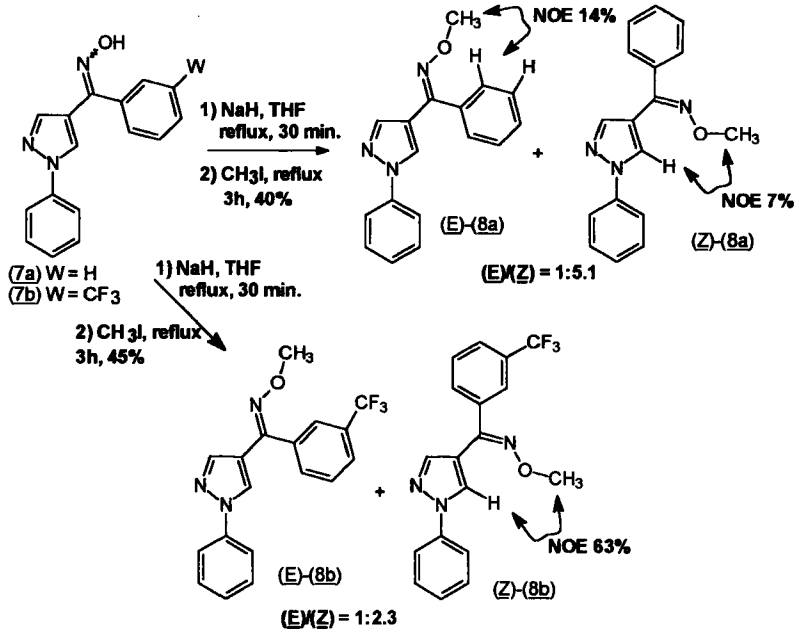
SCHEME 1

compound could be easily prepared in two steps by first condensation, at reflux under acidic conditions, of commercial phenylhydrazine and 1,1,3,3-tetramethoxypropane, followed by regiospecific Vilsmeyer-Haack formylation of the 4-position of the 1-phenyl-pyrazole, as described previously by Finar[16].

Treatment of (4) with the appropriate phenyl Grignard reagent in THF, produced the derived diarylmethanol derivatives (5a) and (5b), respectively in 68% and 94% yield[17]. These crystalline derivatives were oxidized employing a 8N solution of Jones reagent[18] to furnish in 92% and 86% yield, the corresponding diarylketone derivative (6a) and (6b), respectively. Condensation of (6a) and (6b) with hydroxylamine generated 'in situ' from hydrochloride salt in ethanol at reflux, for 5 minutes, afforded the diastereomeric mixture of the correspondent oxime derivatives (7a) and (7b), in 80% yield[19] (Scheme 1).

The E/Z-composition of the oxime derivatives (7a) and (7b) was determined after transformation in the respective O-methyl derivatives (8a) and (8b) by analysis of the ^{1}H NMR spectra. In both compounds, two singlets at δ 3.95 and δ 4.15 ppm, corresponding to methyl groups, in the relative proportion of 1:5.1 and 1:2.3, were displayed (Scheme 2). The downfield signal was attributed to the methyl group of the (Z)-diastereomer as confirmed by nOE experiments (Scheme 2). This is in agreement with previously reported data from Karabatsos[20].

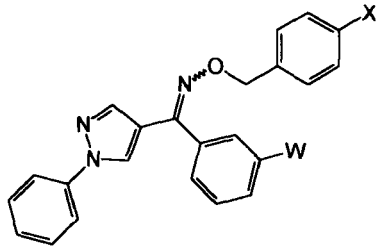
The key step to preparation of the new target derivatives (2) and (3) consisted in the O-alkylation of the oximes (7a) and (7b) with appropriate benzyl halides, *e.g.* benzyl chloride[21], 4-bromomethylphenylacetic acid[21] and methyl 4-iodomethyl-benzoate[22], using NaH as base in THF[23]. Employing this procedure



SCHEME 2

the derivatives (2a), (2b), (3a), (3b) were directly obtained, whereas the derivatives (2c) and (3c) were obtained in 77% yield after a mild exhaustive hydrolysis of the corresponding methyl esters (11) and (12) with lithium hydroxide in acetone[24] (Scheme 1).

The analysis of the ^{1}H NMR spectra of derivatives (2a), (3a), (11), (12) and the methyl esters (9) and (10), obtained by treatment of compounds (2b) and (3b) with diazomethane in ethyl ether[25], permit us to evidenciate the predominant formation of the isomer with the relative (Z) configuration. This diastereoselectivity could be rationalized as function of steric hindrance caused by O-benzyl ether group and 1-N-phenylpyrazole group, forcing the aromatic ring



(2a), (3a), (9), (10), (11), (12)

TABLE 1

COMPOUND	W	X	δ (ppm) (E)/(Z)	Relative proportion
2a	H	H	5.35	---[a)]
9	H	CH_2CO_2Me	5.15 / 5.35	1 : 2.8
11	H	CO_2Me	5.40	---[a)]
3a	CF_3	H	5.17 / 5.35	1 : 2.8
10	CF_3	CH_2CO_2Me	5.25 / 5.35	1 : 2.8
12	CF_3	CO_2Me	5.25 / 5.45	1 : 3.1

[a)] The signal referred to minority (E) diastereomer wasn't identified.

out of the conjugation plane and consequently stabilizing the (Z)-oximes[20] (Table 1).

Chemical shift of the benzylic methylene group present in the diastereomeric mixture of new benzyl ethers of pyrazolic oximes (2a), (3a), (9), (10), (11) and (12), determined by ^1H NMR analysis.

The platelet anti-aggregatory profile of these compounds will be described in due course.

Experimental Section

^{1}H NMR spectra are determined, unless otherwise stated, in deuteriochloroform containing *ca.* 1% tetramethylsilane as an internal standard with a Brucker AC 200, Brucker AG 50 and Brucker DRX 300 spectrometers at 200 MHz and 300 MHz, respectively. ^{13}C NMR are determined in the same spectrometers described above at 50 MHz and 75 MHz respectively, using deuteriochloroform as internal standard. Infrared spectra (IR) were obtained with Nicolet-205, Nicolet-550 Magna and Perkin-Elmer-257 spectrophotometers by using potassium bromide plates. Ultraviolet (UV) spectra were determined in methanol solution on a Shimadzu UV-1601 spectrophotometer. The mass spectra (MS) were obtained by electron impact with a GC/VG Micromass 12 spectrometer.

The progress of all reactions was monitored by tlc which was performed on 2.0 cm X 6.0 cm aluminum sheets precoated with silica gel 60 (HF-254, Merck) to a thickness of 0.25 mm. The developed chromatograms were viewed under ultraviolet light. For column chromatography Merck silica gel (70-230 mesh) was used. Solvents used in the reactions were generally redistilled prior to use and stored over 3-4 A molecular sieves. Reactions were generally stirred under a dry nitrogen atmosphere. The "usual work-up" means that the organic extracts prior to concentration, under reduced pressure, were treated with a saturated aqueous sodium chloride solution, referred to as brine, dried over anhydrous sodium sulfate and filtered.

4-Formyl-1-phenylpyrazole (4)[16].

A solution of 10.8 g (100 mmol) of phenylhydrazine, 16.4 g (100 mmol) of 1,1,3,3-tetramethoxypropane[21] in 100 mL of absolute ethanol containing 5 mL of conc. HCl, was refluxed for 1 h, then poured in a ice-water mixture and neutralized with 10% aq. NaOH. The resulting mixture was extracted with dicloromethane (5 X 50 mL) and the organic extracts were dried and evaporated to give an brown oily residue, which was distilled at reduced pressure (0.1 mmHg), furnishing 13.4 g (93%) of 1-phenylpyrazole as a light yellow oil.

To a Vilsmeyer-Haack complex formed, at 0°C, from 25.6 mL (330 mmol) of dry DMF and 21.6 mL (230 mmol) of phosphorus oxychloride was added dropwise, at room temperature, a solution of 4.4 mL (33 mmol) of 1-phenylpyrazole in 4 mL of dry DMF and the reaction mixture was heated until 100-110° C for 3 h. Then after cooling, a ice-water mixture was added and middle was carefully neutralized with 20% aq. NaOH. The resulting brown precipitate was filtered and chromatographed on a silica gel column to give 3.4 g (60%) of the aldehyde (4) as yellow crystals, mp 82° (lit.[16] mp 83°); **^{1}H NMR** (200 MHz): δ 7.37 (m, 1H, H-4'), 7.45 (m, 2, H-3'), 7.69 (m, 2, H-2'), 8.15 (s, 1, H-3), 8.44 (s, 1, H-5), 9.95 (s, 1, O=C<u>H</u>) ppm; **^{13}C NMR** (50 MHz): δ 119.7 (C-2'), 125.6 (C-4), 127.9 (C-4'), 129.6 (C-3'), 130.0 (C-5), 139.0 (C-1'), 184,0 (C=O); **IR** (KBr): ν CHO 2791, ν C=O 1678, ν C=N 1597 and 1545 cm^{-1}; **MS** (m/z): 172 (MH+, 95%), 171 (100%), 144 (4%), 77 (21%); **UV** (MeOH): λ 266.0 (ε, 16196) nm.

Anal. Calcd. for $C_{10}H_8N_2O$: C, 69.69; H, 4.64; N, 16.26. Found: C, 69.65; H, 4.62; N, 16.25.

General procedure for the reaction of (4) with phenyl Grignard derivatives[17].

To a suspension of 0.172 g (7.02 mmol) of pre-activated magnesium in 10 mL of dry THF containing a catalytic iodine crystal, were added 7.02 mmol of dry bromobenzene derivative. The reaction mixture was stirred until total consumption of the magnesium turnings and then a solution of 0.53 g (3.08 mmol) of 4-formyl-1-phenylpyrazole (4) in 25 mL of dry THF was added, dropwise, at 0 °C. The reaction mixture was refluxed for 1 h in water bath then poured in an ice-water mixture, neutralized with 4% aq. HCl (10 mL) and extracted with diethyl ether (3 X 30 mL). The organic extracts were submitted at usual work-up to give the respective diarylmethanol derivative (5) as described below;

[1-Phenyl-4-pyrazolyl(1-N-phenyl)]methanol (5a).

Obtained using 3.6 mL of bromobenzene, in 60% yield, as white precipitate, mp 114°; **^{1}H NMR** (200 MHz): δ 2.5 (br., 1H, D_2O exangeable, OH), 5.80 (s, 1H, CHOH), 7.21 (t, 2H, J = 2 Hz, H-2"), 7.25 (m, 2H, H-3"), 7.30 (m, 2H, H-3'), 7.34 (m, 1H, H-4"), 7.38 (m, 1H, H-4'), 7.50 (m, 1H, H-3), 7.55 (m, 2H, H-2'), 7.67 (s, 1H, H-5) ppm; **^{13}C NMR** (50 MHz): δ 69.0 (CHOH), 118.9 (C-2'), 125.1 (C-5), 126.2 (C-4"), 126.4 (C-4'), 127.4 (C-4), 127.8 (C-2"), 128.5 (C-3"), 129.3 (C-3'), 139.6 (C-3), 139.9 (C-1"), 143.3 (C-1') ppm; **IR** (KBr): ν O-H 3393, ν C=N 1596 and 1567, ν C-O 1124 cm^{-1}; **MS** (m/z): 250 (MH+, 84%), 233 (44%), 171 (100%), 145 (38%), 77 (58%).

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.71; H, 5.59; N, 11.18. Found: C, 76.69; H, 5.57; N, 11.17.

[1-(3'-Trifluoromethyl)phenyl-4-pyrazolyl(1-N-phenyl)] methanol (5b).

Obtained using 4.9 mL of 3-trifluoromethyl-1-bromobenzene, in 94 % yield, as yellow precipitate, mp 80°; **^{1}H NMR** (200 MHz): δ 3.10 (br., 1H, D_2O exangeable, OH), 5.91 (s, 1H, CHOH), 7.26 (m, 1H, H-4'), 7.37 (m, 2H, H-3'), 7.44 (m, 1H, H-5"), 7.49 (s, 1H, H-3), 7.54 (m, 1H, H-2"), 7.56 (m, 1H, H-6"), 7.57 (m, 2H, H-2'), 7.60 (m, 1H, H-4"), 7.72 (s, 1H, H-5) ppm; **^{13}C NMR** (50 MHz): δ 68.1 (CHOH), 119.0 (C-2'), 121.0 (CF_3), 124.5 (C-2"), 125.3 (C-5), 126.7 (C-4'), 126.8 (C-4), 128.9 (C-5"), 129.3 (C-3'), 129.5 (C-6"), 129.9 (C-4"), 131.0 (C-3"), 139.4 (C-3), 139.8 (C-1"), 144.3 (C-1') ppm; **IR** (KBr): ν O-H 3223, ν C=N 1600, ν C-F 1315, ν C-O 1124 cm^{-1}; **MS** (m/z): 318 (MH+, 100%), 301 (39%), 249 (3%), 172 (25%), 77 (34%).

Anal. Calcd. for $C_{17}H_{13}N_2OF_3$: C, 64.09; H, 4.08; N, 8.79. Found: C, 64.08; H, 4.08; N, 8.76.

General procedure for Jones oxidation of benzylic alcohols (5a) and (5b)[18].

To a solution of 2 mmol of alcohol derivative (5) in 4 mL of acetone were added dropwise, at 0°C, 2 mL of the 8N solution of Jones reagent. After 30 minutes, three drops of isopropanol were added and the reaction mixture was filtered through of anhydrous potassium carbonate column. The filtrate was concentrated at reduced pressure to obtain a residue which was diluted with 20 mL of a mixture of diethyl ether: water (2:1). The organic layer was separated and submitted to usual work-up to give the respective ketone derivative (6), as described below;

[1-Phenyl-4-pyrazolyl(1-N-phenyl)]methanone (6a).

This derivative was obtained in 92% yield, as a white precipitate, mp 112°; **^{1}H NMR** (200 MHz): δ 7.34 (t, 1H, J = 2 Hz, H-4'), 7.38 (t, 2H, J = 1.5 Hz, H-3'), 7.50 (m, 1H, H-4"), 7.70 (t, 2H, J = 1 Hz, H-2'), 7.85 (t, 2H, J = 2 Hz, H-3"), 7.90 (d, 2H, J = 1 Hz, H-2"), 8.13 (s, 1H, H-3), 8.43 (s, 1H, H-5) ppm; **^{13}C NMR** (50 MHz): δ 119.6 (C-2'), 123.9 (C-4), 127.6 (C-4'), 128.4 (C-3"), 128.7 (C-2"), 129.5 (C-3'), 130.6 (C-5), 132.3 (C-4"), 138.7 (C-1"), 139.1 (C-1'), 142.6 (C-3), 188.6 (C=O) ppm; **IR** (KBr): ν C=O 1637, ν C=N 1597 and 1540 cm^{-1}; **MS** (m/z): 248 (MH+, 45%), 171 (100%), 77 (33%); **UV** (MeOH): λ 279.0 (ε, 28167), 225.0 (ε, 27986) nm.

Anal. Calcd. for $C_{16}H_{12}N_2O$: C, 77.33; H, 4.83; N, 11.27. Found: C, 77.31; H, 4.84; N, 11.29.

[1-(3-Trifluoromethyl)phenyl-4-pyrazolyl(1-N-phenyl)]methanone (6b).

This derivative was obtained in 86% yield, as a white precipitate, mp 136°; **^{1}H NMR** (200 MHz): δ 7.26 (m, 1H, H-4'), 7.40 (m, 2H, H-3'), 7.52 (m, 1H, H-3"), 7.68 (m, 1H, H-6"), 7.72 (m, 2H, H-2'), 7.85 (m, 1H, H-2"), 7.90 (m, 1H, H-4"), 8.15 (m, 1H, H-3), 8.47 (s, 1H, H-5) ppm; **^{13}C NMR** (50 MHz): δ 119.7 (C-2'), 120.8 (C-4), 123.5 (CF_3), 126.3 (C-5"), 127.9 (C-4'), 128.7 (C-5), 129.2 (C-3"), 129.6 (C-3'), 130.7 (C-4"), 131.8 (C-2"), 139.0 (C-1"), 139.3 (C-1'), 142.5 (C-3), 187.1 (C=O) ppm; **IR** (KBr): ν C=O 1637, ν C=N 1535, ν C-F 1332 and 1260 cm^{-1}; **MS** (m/z): 316 (MH+, 45%), 297 (3%), 171 (100%); **UV** (MeOH): λ 281.0 (ε, 13210) 139.0 (ε, 14895) nm.

Anal. Calcd. for $C_{17}H_{11}N_2OF_3$: C, 64.49; H, 3.47; N, 8.85. Found: C, 64.51; H, 3.44; N, 8.84.

General procedure for oxymation of diaryl ketones derivatives (6a) and (6b)[19].

To a mixture containing 8 mmol of the ketone derivative (6), 1.21 g (17.4 mmol) of hydroxylamine hydrochloride, 4 mL of ethanol and 1 mL of water, were added slowly 2.25 g (56.5 mmol) of NaOH, under vigorous stirring. The reaction mixture was refluxed for 5 minutes, then poured in 10 mL of a 10% aqueous HCl solution. The resulting precipitate was filtered out, washed with 10 mL and air dried, furnishing the respective oxime derivative (7) as described below;

[1-Phenyl-4-pyrazolyl(1-N-phenyl)] methanone oxime (7a).

This derivative was obtained in 80% yield, as a white precipitate, mp 200°; **^{1}H NMR** (200 MHz): δ 7.42 (s, 1H, H-4'), 7.53 (m, 2H, H-3"), 7.59 (m, 2H, H-2"), 7.64 (m, 1H, H-4"), 7.68 (m, 2H, H-3'), 7.93 (t, 2H, J = 8 Hz, H-2'), 8.00 (s, 1H, H-3), 8.87 (s, 1H, H-5), 11.1 (s, 1H, D_2O exangeable, OH [isomer (E)]), 11.7 (s, 1H, D_2O exangeable, OH [isomer (Z)]) ppm; **^{13}C NMR** (50 MHz): δ 115.3 (C-4), 119.0 (C-2'), 126.8 (C-4'), 128.1 (C-3"), 128.3 (C-2"), 128.7 (C-3'), 129.5 (C-5), 129.6 (C-4"), 136.6 (C-1"), 139.1 (C-1'), 142.1 (C-3), 148.1 (C=N-OH) ppm; **IR** (KBr): ν O-H 3150, ν C=N 1589 and 1550, ν N-O 960 cm^{-1}; **MS** (m/z): 263 (MH+, 100%), 246 (74%), 171 (79%), 144 (75%), 77 (82%); **UV** (MeOH): λ 273.0 (ε, 21929), 213.0 (ε, 27128) nm.

Anal. Calcd. for $C_{16}H_{13}N_3O$: C, 72.92; H, 4.93; N, 15.95. Found: 72.90; H, 4.95; N, 15.94.

[1-(3-Trifluoromethyl)phenyl-4-pyrazolyl(1-N-phenyl)]methanone oxime (7b).

This derivative was obtained in 80% yield, as a white precipitate, mp 138°;

^{1}H NMR (200 MHz): δ 7.36 (m, 1H, H-5"), 7.40 (m, 1H, H-4"), 7.44 (m, 2H, H-3'), 7.47 (m, 1H, H-3), 7.53 (m, 1H, H-6"), 7.57 (m, 1H, H-4'), 7.59 (m, 1H, H-2"), 7.68 (m, 2H, H-2'), 7.87 (m, 1H, H-5), 8.55 (s, 1H, D_2O exangeable, OH) ppm; **^{13}C NMR** (50 MHz): δ 115.9 (C-4), 119.9 (C-2'), 121.3 (CF_3), 125.8 (C-2"), 126.4 (C-4'), 129.0 (C-4"), 129.6 (C-5"), 130.5 (C-5), 131.1 (C-3"), 131.7 (C-1"), 132.1 (C-3'), 137.2 (C-1'), 139.9 (C-6'), 142.7 (C-3), 149.6 (C=N) ppm; **IR** (KBr): ν O-H 3434, ν C=N 1599 and 1547, ν C-F 1167, ν N-O 969 cm^{-1}; **MS** (m/z): 331 (MH+, 80%), 314 (21%), 301 (10%), 144 (100%), 77 (27%); **UV** (MeOH): λ 272.0 (ε, 13893) nm.

Anal. Calcd. for $C_{17}H_{12}N_3OF_3$: C, 61.57; H, 3.62; N, 12.67. Found: C, 61.55; H, 3.61; N, 12.66.

General procedure for O-methylation of the pyrazolic oximes (7a) and (7b)[23].

An 80% suspension of sodium hydride in mineral oil (0.27 g, 11.5 mmol) was washed with dry n-hexane until a white pale solid was obtained which was suspended in 6 mL of dry THF. Then, a solution of 2.6 mmol of the oxime derivative (7) in 10 mL of dry THF was added dropwise and the reaction mixture was refluxed under stirring for 30 minutes. After this time, 1.88 g (13.3 mmol) of methyl iodide were added and the reaction was additionally refluxed for 3 hours then poured into an ice-water mixture containing 5 mL of an 10% aqueous HCl solution and extracted with ethyl ether (5 X 50 mL). The organic extracts were submitted at usual work-up, furnishing a crude oily residue which was purified by silica gel column chromatography, furnishing the respective oxyme methylether derivative (8) as described below;

Methyl ether of the [1-phenyl-4-pyrazolyl(1-N-phenyl)]methanone oxime (8a).

This derivative was obtained in 40% yield, as a colorless oil; **^{1}H NMR** (200 MHz): δ 3.90 (s, 3H, OCH$_3$ [isomer (E)]), 4.10 (s, 3H, OCH$_3$ [isomer (Z)]), 7.35 (t, 1H, J = 2 Hz, H-4'), 7.43 (m, 1H, H-4"), 7.45 (m, 2H, H-3"), 7.52 (m, 2H, H-3'), 7.60 (m, 2H, H-2"), 7.70 (m, 2H, H-2'), 7.90 (s, 1H, H-3), 8.5 (s, 1H, H-5) ppm; **^{13}C NMR** (50 MHz): δ 62.3 (OCH$_3$ (Z)), 62.1 (OCH$_3$ (E)), 115.0 (C-4), 119.5 (C-2'), 127.0 (C-4'), 128.1 (C-4"), 128.6 (C-3"), 129.1 (C-2"), 129.4 (C-3'), 130.0 (C-5), 136.0 (C-1"), 140.0 (C-1'), 142.9 (C-3), 150.0 (C=N) ppm; **IR** (KBr): ν C=N 1600 and 1560, ν C=C 1535, δ C-H 1500, ν C-O 1050 cm^{-1}; **MS** (m/z) 277 (MH+, 100%), 246 (17%), 77 (23%).

Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.56; H, 5.40; N, 15.14. Found: C, 73.57; H, 5.38; N, 15.15.

Methyl ether of the [1-(3-trifluoromethyl)phenyl-4-pyrazolyl(1-N-phenyl)]methanone oxime (8b).

This derivative was obtained in 45% yield, as a yellow oil; **^{1}H NMR** (200MHz): δ 3.95 (s, 3H, OCH$_3$ [isomer (E)]), 4.25 (s, 3H, OCH$_3$ [isomer (Z)]), 7.35 (m, 1H, H-4'), 7.40 (m, 1H, H-4"), 7.45 (m, 1H, H-5"), 7.52 (m, 2H, H-3'), 7.60 (m, 1H, H-6"), 7.70 (m, 1H, H-2"), 7.80 (m, 2H, H-2'), 7.85 (s, 1H, H-3), 8.5 (s, 1H, H-5) ppm; **^{13}C NMR** (50 MHz): δ 62.3 (OCH$_3$ (E)), 62.6 (OCH$_3$ (Z)), 114.9 (C-4), 121.0 (CF_3), 125.5 (C-2"), 125.9 (C-4'), 127.2 (C-4"), 128.9 (C-3'), 129.4 (C-5"), 130.0 (C-5), 130.5 (C-3"), 131.9 (C-6"), 136.8 (C-1"), 139.5 (C-1'), 142.5 (C-3), 148.0 (C=N) ppm.

Anal. Calcd. for $C_{18}H_{14}N_3OF_3$: C, 62.55; H, 4.05; N, 12.16. Found: C, 62.54; H, 4.04; N, 12.16.

General procedure for the O-alkylation reaction of the pyrazolic oximes (7a) and (7b) with benzyl halides[23].

An 80% suspension of sodium hydride in mineral oil (0.55 g, 23 mmol) was washed with dry n-hexane until a white pale solid was obtained which was suspended in 6 mL of dry THF. Then, a solution of 5.3 mmol of the oxime derivative (7) in 10 mL of dry THF was added dropwise and the reaction mixture was refluxed under stirring for 30 minutes. After this time, a solution of 7 mmol of the benzyl halide derivative in 10 mL dry THF was added and the reaction was additionally refluxed for 3 hours then poured into an ice-water mixture containing 7 mL of an 10% aqueous HCl solution and extracted with ethyl ether (5 X 50 mL). The organic extracts were submitted at usual work-up, furnishing the respective oxyme benzyl ether derivative as described below;

Benzyl ether of [1-phenyl-4-pyrazolyl(1-N-phenyl)]methanone oxime (2a).

This derivative was obtained using 0.89 g of benzyl chloride[21], in 50% yield, as a white precipitate, mp 130°; **^{1}H NMR** (200 MHz): δ 5.35 (s, 2H, CH_2Ph), 7.31 (m, 1H, H-4'), 7.36 (m, 2H, H-3"), 7.40 (m, 1H, H-4'"), 7.41 (m, 2H, H-2"), 7.44 (m, 2H, H-3'), 7.45 (m, 1H, H-4"), 7.48 (m, 2H, H-2'"), 7.52 (m, 1H, H-4'), 7.55 (m, 2H, H-3'"), 7.62 (m, 2H, H-2'), 7.95 (s, 1H, C-3), 8.45 (s, 1H, C-5) ppm; **^{13}C NMR** (50 MHz): δ 76.7 (CH_2Ph), 115.6 (C-4), 119.3 (C-2'), 127.0 (C-4'), 127.8 (C-2'"), 128.0 (C-4'"), 128.3 (C-3"), 128.7 (C--3'"), 129.0 (C-2"), 129.1

(C-3'), 129.4 (C-4"), 130.1 (C-5), 135.8 (C-1"), 137.5 (C-1'), 143.1 (C-3), 149.6 (C=N) ppm; **IR** (KBr): ν C=N 1594 and 1540, ν C-O 1045, ν N-O 953 cm^{-1}; **MS** (m/z): 353 (MH+, 48%), 91 (100%), 77 (32%).

Anal. Calcd. for $C_{23}H_{25}N_3O$: C, 76.77; H, 6.95; N, 11.68. Found: C, 76.75; H, 6.97; N, 11.69.

Benzyl ether of [1-(3-trifluoromethyl)phenyl-4-pyrazolyl(1-N-phenyl)]methanone oxime (3a).

This derivative was obtained using 0.89 g of benzyl chloride[21], in 86% yield, as a dark yellow oil; **^{1}H NMR** (200 MHz): δ 5.17 (s, 2H, C$\underline{H}_2$Ph (E)), 5.35 (s, 2H, C$\underline{H}_2$Ph (Z)), 7.35 (m, 2H, H-2'"), 7.38 (m, 1H, H-4'"), 7.39 (m, 1H, H-4"), 7.41 (m, 2H, H-3'), 7.43 (m, 1H, H-5"), 7.61 (m, 2H, H-2'), 7.64 (m, 1H, H-4'), 7.65 (m, 1H, H-6"), 7.71 (m, 1H, H-2"), 7.85 (m, 2H, H-3'"), 7.86 (s, 1H, C-3), 8.41 (s, 1H, C-5) ppm; **^{13}C NMR** (50 MHz): δ 77.0 ($\underline{C}H_2$Ph), 115.7 (C-4), 119.4 (C-2'), 121.0 (CF_3), 126.2 (C-2"), 126.5 (C-4'), 127.8 (C-2'"), 128.6 (C-4'"), 128.7 (C-4"), 129.0 (C-3'"), 129.5 (C-5"), 130.0 (C-3'), 130.4 (C-3"), 130.7 (C-5), 132.6 (C-6"), 136.8 (C-1"), 137.3 (C-1'), 139.4 (C-1'"), 142.6 (C-3), 148.5 (C=N) ppm; **IR** (KBr): ν C=N 1660 and 1560, ν C-O 1205 and 1069, N-O 890 cm^{-1}; **MS** (m/z): 421 (MH+, 25%), 402 (1%), 315 (2%), 300 (4%), 91 (100%), 77 (15%).

Anal. Calcd. for $C_{24}H_{24}N_3OF_3$: C, 67.37; H, 5.61; N, 9.82. Found: C, 67.37; H, 5.60; N, 9.81.

[1-Phenyl-4-pyrazolyl(1-N-phenyl)]methylene]amino]oxi]-4-methylenephenylacetic acid (2b).

This derivative was obtained using 1.62 g of 4-bromomethyl-phenylacetic

acid[21] in 52% yield, as a yellow oil; **IR** (KBr): ν O-H 3400, ν C=O 1740, ν C=N 1640, ν C-O 1290 cm^{-1}; **MS** (m/z): 411 (MH+, 35%), 394 (1%), 263 (9%), 247 (42%), 232 (7%), 77 (80%).

Anal. Calcd. for $C_{25}H_{21}N_3O_3$: C, 72.91; H, 5.10; N, 10.20. Found: C, 72.89; H, 5,13; N, 10.19.

[1-(3-Trifluoromethyl)phenyl-4-pyrazolyl(1-N-phenyl)] methylene] amino]oxi]-4-methylenephenylacetic acid (3b).

This derivative was obtained using 1.62 g of 4-bromomethyl-phenylacetic acid[21] in 52% yield, as a yellow oil; **IR** (KBr): ν O-H 3400, ν C=O 1714, ν C=N 1658, ν C-O 1264 cm^{-1}; **MS** (m/z): 479 (MH+, 2%), 331 (3%), 171 (29%), 77 (30%).

Anal. Calcd. for $C_{26}H_{20}N_3O_3F_3$: C, 65.07; H, 4.17; N, 8.76. Found: C, 65.08; H, 4.16; N, 8.77.

Methyl [1-phenyl-4-pyrazolyl(1-N-phenyl)]methylene]amino]oxi]-4-methylenebenzoate (11).

This derivative was obtained using 1.95 g of methyl 4-iodomethyl-benzoate[22] in 59% yield, as a yellow oil; **^{1}H NMR** (200 MHz): δ 3.90 (s, 3H, $OC\underline{H}_3$), 5.40 (s, 2H, $OC\underline{H}_2Ar$), 7.30 (m, 2H, H-2'''), 7.39 (m, 1H, H-4'), 7.44 (m, 2H, H-3'), 7.48 (m, 2H, H-2''), 7.53 (m, 2H, H-3''), 7.64 (m, 2H, H-2'), 7.95 (s, 1H, H-3), 8.03 (s, 2H, H-3'''), 8.07 (s, 1H, H-4''), 8.42 (s, 1H, H-5); **^{13}C NMR** (50 MHz): δ 51.9 ($O\underline{C}H_3$), 75.9 ($O\underline{C}H_2Ar$), 115.6 (C-4), 119.4 (C-2'), 127.0 (C-4'), 127.5 (C-2'''), 128.3 (C-3''), 129.2 (C-3'), 129.4 (C-3'''), 129.6 (C-4''), 130.0 (C-5), 135.5 (C-1''), 138.0 (C-4'''), 139.5 (C-4'), 143.0 (C-1'''), 143.1 (C-3), 150.0 (C=N),

167.0 (C=O); **IR** (KBr): ν CH 2910, ν CO 1725, 1600 and 1570, ν C=C 1530, δ CH_3 1500, ν C-O 1270 and 1100, ν N-O 950 cm^{-1}; **MS** (m/z): 411 (MH+, 6%), 171 (31%), 149 (87%), 77 (56%).

Anal. Calcd. for $C_{25}H_{21}N_3O_3$: C, 72.91; H, 5.10; N, 10.20. Found: C, 72.90; H, 5.08; N, 10.19.

Methyl [1-(3-trifluoromethyl)phenyl-4-pyrazolyl(1-N-phenyl)] methylene]amino]oxi]-4-methylenebenzoate (12).

This derivative was obtained using 1.95 g of methyl 4-iodomethylbenzoate[22] in 79% yield, as a yellow oil; **^{1}H NMR** (300 MHz): δ: 3.89 (s, 3H, OCH_3 (E)), 3.90 (s, 3H, OCH_3 (Z)), 5.25 (s, 2H, OCH_2Ar (E)), 5.45 (s, 2H, OCH_2Ar (Z)), 7.35 (m, 2H, H-2'''), 7.37 (m, 1H, H-4''), 7.45 (m, 2H, H-3'), 7.50 (m, 1H, H-5''), 7.64 (m, 2H, H-2'), 7.70 (m, 1H, H-4'), 7.75 (m, 1H, H-6''), 7.80 (s, 1H, H-2''), 7.89 (s, 1H, H-3), 8.10 (s, 2H, H-3'''), 8.45 (s, 1H, H-5) ppm; **^{13}C NMR** (75 MHz): δ 52.1 (OCH_3), 75.8 (OCH_2Ar (E)), 76.3 (OCH_2Ar (Z)), 115.1 (C-4), 119.3 (CF_3), 119.6 (C-2'), 125.6 (C-2''), 126.1 (C-4'), 127.3 (C-2'''), 127.5 (C-4''), 127.7 (C-5''), 129.0 (C-4'''), 129.5 (C-3'), 129.80 (C-3'''), 130.8 (C-3''), 131.9 (C-1''), 132.1 (C-6''), 130.1 (C-5), 136.7 (C-1'), 139.5 (C-1'''), 142.7 (C-3), 148.96 (C=N), 166.89 (C=O) ppm; **IR** (KBr): ν C=O 1722, ν C=N 1600, ν C-O 1278 and 1120, ν C-F 1027, ν N-O 952 cm^{-1}; **MS** (m/z): 479 (MH+, 15%), 331 (2%), 171 (20%), 77 (33%).

Anal. Calcd. for $C_{26}H_{20}N_3O_3F_3$: C, 65.07; H, 4.17; N, 8.76. Found: C, 65.06; H, 4.18; N, 8.77.

General procedure for esterification of the phenylacetic acid derivatives (2b) and (3b) with diazomethane[25].

To a solution of 0.32 mmol of acid (2b) or (3b) in 6 mL of dichloromethane were added dropwise an ethereal solution of diazomethane until that the tlc analysis indicated that all starting material had been consumed. Then, ca. 1 mL of concentrated acetic acid was added to reaction mixture until ceased the gaseous evolution. The organic layer was dried with anhydrous potassium carbonate, filtered and submitted at usual work-up affording the respective methyl ester derivative, as described below;

Methyl [1-phenyl-4-pyrazolyl(1-N-phenyl)]methylene]amino]oxi] 4-methylenephenylacetate (9).

This derivative was obtained in 98% yield, as a dark yellow oil; **^{1}H NMR** (200 MHz): δ 3.62 (s, 2H, $C\underline{H}_2COOCH_3$ (E)), 3.65 (s, 2H, $C\underline{H}_2COOCH_3$ (Z)), 3.68 (s, 3H, $OC\underline{H}_3$ (E)), 3.70 (s, 3H, $OC\underline{H}_3$ (Z)), 5.15 (s, 2H, $OC\underline{H}_2Ar$ (E)), 5.35 (s, 2H, $OC\underline{H}_2Ar$ (Z)), 7.30 (m, 2H, H-2'''), 7.42 (m, 1H, H-4'), 7.45 (m, 2H, H-3'), 7.49 (m, 2H, H-2''), 7.55 (m, 2H, H-3''), 7.63 (m, 2H, H-2'), 7.83 (m, 2H, H-3'''), 7.88 (m, 1H, H-4''), 7.95 (s, 1H, H-3), 8.45 (s, 1H, H-5) ppm; **^{13}C NMR** (50 MHz): δ 40.8 ($C\underline{H}_2COOCH_3$), 51.9 ($OC\underline{H}_3$), 76.4 ($O\underline{C}H_2Ar$), 115.7 (C-4), 119.4 (C-2'), 127.0 (C-4'), 128.1 (C-5), 128.3 (C-2'''), 128.7 (C-3''), 129.1 (C-2''), 129.3 (C-3'), 129.4 (C-3'''), 130.1 (C-4''), 132.4 (C-1''), 133.5 (C-4'''), 136.5 (C-1'), 139.9 (C-1'''), 143.1 (C-5), 149.6 (C=N), 171.8 (C=O) ppm; **IR** (KBr): ν C=O 1735, ν C=N 1600, ν C-O 1260 and 1160, ν N-O 960 cm^{-1}; **MS** (m/z): 425 (MH+, 11%), 171 (100%), 149 (75%), 77 (32%).

Anal. Calcd. for $C_{26}H_{23}N_3O_3$: C, 73.33; H, 5.40; N, 9.87. Found: C, 73.31; H, 5.41; N, 9.88.

Methyl [1-(3-trifluoromethyl)phenyl-4-pyrazolyl(1-N-phenyl)] methylene]amino]oxi]-4-methylenephenylacetate (11).

This derivative was obtained in 97% yield, as a dark yellow oil; **^{1}H NMR** (200 MHz): δ 3.63 (s, 2H, $C\underline{H}_2COOCH_3$ (E)), 3.66 (s, 2H, $C\underline{H}_2COOCH_3$ (Z)), 3.69 (s, 3H, $OC\underline{H}_3$ (E)), 3,70 (s, 3H, $OC\underline{H}_3$ (Z)), 5.25 (s, 2H, $OC\underline{H}_2Ar$ (E)), 5.35 (s, 2H, $OC\underline{H}_2Ar$ (Z)), 7.31 (m, 2H, H-2'''), 7.34 (m, 1H, H-4''), 7.41 (m, 2H, H-3'), 7.45 (m, 1H, H-5''), 7.62 (m, 2H, H-2'), 7.65 (m, 1H, H-4'), 7.69 (m, 1H, H-6''), 7.72 (m, 1H, H-2''), 7.88 (m, 2H, H-3'''), 7.89 (s, 1H, C-3), 8.45 (s, 1H, C-5) ppm; **^{13}C NMR** (50 MHz): δ 40.9 ($\underline{C}H_2COOCH_3$), 52.0 ($O\underline{C}H_3$), 76.2 ($O\underline{C}H_2Ar$), 115.1 (C-4), 119.5 (C-2'), 125.8 (C-2''), 126.1 (C-4'), 127.0 (C-4''), 127.2 (C-2'''), 128.4 (C-5''), 128.9 (C-3'), 129.5 (C-3'''), 130.1 (C-5), 132.1 (C-6''), 133.8 (C-3''), 133.9 (C-1''), 136.5 (C-4'''), 136.9 (C-1'), 139.8 (C-1'), 142.9 (C-3), 149.4 (C=N), 171.9 (C=O) ppm; **IR** (KBr): ν C=O 1670, ν C=N 1530, ν C-O 1270 and 1200, ν N-O 960 cm^{-1}; **MS** (m/z): 493 (MH+, 7%), 331 (5%), 77 (44%).

Anal. Calcd. for $C_{27}H_{22}N_3O_3F_3$: C, 65.65; H, 4.45; N, 8.51. Found: C, 65.63; H, 4.44; N, 8.53.

General procedure for mild hydrolysis of methylbenzoate derivatives (11) and (12)[24].

To a solution of 0.97 mmol of the methyl ester derivative (11) or (12) in 12 mL of acetone were added 7 mL of 1N aqueous LiOH solution. The resulting

mixture was stirred at room temperature for 3 hours then neutralized with 1N aqueous HCl (ca. 3 mL) until pH 4 and extracted with diethyl ether (3 X 30 mL). The organic extracts were jointed and submitted at usual work-up to give the respective acid derivative as described below;

[1-Phenyl-4-pyrazolyl(1-N-phenyl)] methylene]amino]oxi]-4-methylenebenzoic acid (2c).

This derivative was obtained in 77 % yield, as a dark yellow oil; **IR** (KBr): ν O-H 3420, ν C=O 1685, ν C=N 1610; ν C-O 1279, ν N-O 950 cm^{-1}; **MS** (m/z): 397 (MH+, 100%), 380 (10%), 262 (37%), 246 (11%), 232 (70%), 77 (50%).

Anal. Calcd. for $C_{25}H_{23}N_3O_3$: C, 72.55; H, 5.56; N, 10.15. Found: C, 72.53; H, 5.57; N, 10.16.

[1-(3-Trifluoromethyl)phenyl-4-pyrazolyl(1-N-phenyl)]methylene] amino]oxi]-4-methylenebenzoic acid (3c).

This derivative was obtained in 77% yield, as a dark yellow oil; **IR** (KBr): ν O-H 3429, ν C=O 1690, ν C=N 1606; δ C-O 1286, ν N-O 951; **MS** (m/z): 465 (MH+, 55%), 330 (9%), 315 (15%), 77 (36%).

Anal. Calcd. for $C_{26}H_{22}N_3O_3F_3$: C, 64.80; H, 4.57; N, 8.72. Found: C, 64.77; H, 4.56; N, 8.75.

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