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SYNTHESIS OF 7-β-(*N*,*N*-DIALKYLAMINO)ETHOXY DERIVATIVES OF NATURAL ISOFLAVONES AND 4-ARYL-3-[2-HYDROXY-4-β-(*N*,*N*-DIALKYLAMINO) ETHOXY]PHENYLPYRAZOLES BASED ON THEM

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*7-*O*-β-(*N,N-*dialkylamino)ethyl derivatives of formononetin, 2-methylformononetin, and cladrin were synthesized. Their recyclization through the action of hydrazine hydrate was studied. A series of 4-aryl-3-[2-hydroxy-4-*β-(*N,N-*dialkylamino)ethoxy]phenylpyrazoles was obtained.*

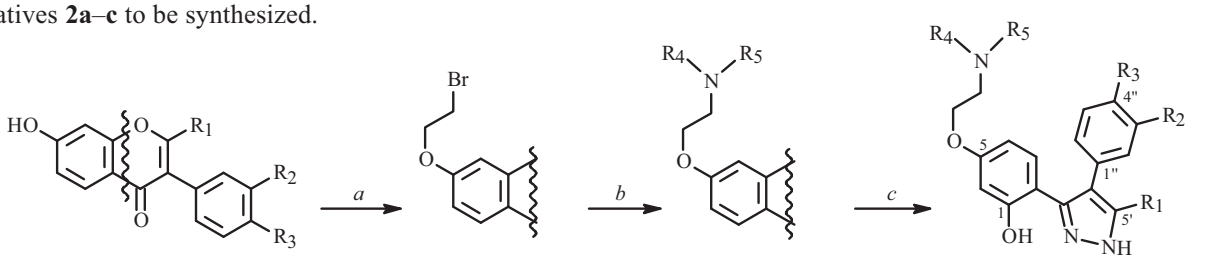
Keywords: formononetin, 2-methylformononetin, cladrin, ethanolamine, pyrazole.

Many effective modern drugs are analogs or derivatives of natural compounds. A significant fraction of new drugs are currently natural compounds (10%) and their derivatives (29%) [1].

The goal of the present work was to synthesize 7-*O*-β-(*N*,*N*-dialkylamino)ethyl derivatives of the natural isoflavones formononetin (**1a**), 2-methylformononetin (**1b**), and cladrin (**1c**) and also 3-[2-hydroxy-4-β-(*N*,*N*-dialkylamino)ethoxy]-phenyl-4-arylpyrazoles as their recyclization products.

Methods for synthesizing ω-(*N*,*N*-dialkylamino)alkoxy derivatives of flavonoids via the reaction of hydroxyflavones with ω-(*N*,*N*-dialkylamino)alkyl halides were described [2–4]. The reaction of amines with ω-haloalkoxyflavonoids [5–8] and with phenol glycidyl esters [9] were also used to prepare these compounds.

Alkylation by an excess of dibromoethane in DMF in the presence of potash was used to synthesize 7-*O*-β-(*N*,*N*-dialkylamino)ethyl derivatives of formononetin, 2-methylformononetin, and cladrin. This enabled 7-(2-bromoethoxy) derivatives **2a**–**c** to be synthesized.



1a - c **2a - c** **3a,b, 4c, 5a,b, 6c, 7a,b, 8a** **9a,b, 10c, 11a,b, 12c, 13a,b, 14a**

a: $R_1 = R_2 = H$, $R_3 = OCH_3$; **b:** $R_1 = CH_3$, $R_2 = H$, $R_3 = OCH_3$; **c:** $R_1 = H$, $R_2 = R_3 = OCH_3$

3,9: $R_4R_5 = CH_2CH_2CH_2CH_2CH_2$; **4,10:** $R_4R_5 = CH_2CH_2CH(CONH_2)CH_2CH_2$

5,11: $R_4R_5 = CH_2CH_2OCH_2CH_2$; **6,12:** $R_4R_5 = CH_2CH(CH_3)OCH(CH_3)CH_2$

7,13: $R_4R_5 = CH_2CH_2N(Ph)CH_2CH_2$; **8,14:** $R_4R_5 = CH_2CH_2N(C_6H_4\text{-F-}p)CH_2CH_2$

a. $BrCH_2CH_2Br$, K_2CO_3; *b*. HNR_4R_5, *i*-Pr_2NEt; *c*. N_2H_4

Alkylation of secondary amines by 7-(2-bromoethoxy)isoflavones **2a**–**c** in the presence of base was studied in order to prepare 7-β-(*N*,N-dialkylamino)ethoxy derivatives of the natural isoflavones. As it turned out, the reaction occurred in high yield if it was carried out in EtOH in the presence of *i*-Pr_2NEt. Thus, a series of derivatives of natural isoflavones **3**–**8** that contained piperidine, piperidinecarboxamide, morpholine, 2,6-dimethylmorpholine, and *N*-substituted piperazines bound through a linker to the chromone ring was synthesized.

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The structures of the synthesized 7-β-(*N*,*N*-dialkylamino)ethoxy derivatives of isoflavones **3**–**8** were confirmed by NMR spectroscopy. Thus, PMR spectra of these compounds contained proton resonances of the isoflavone group and the amine groups.

3,4-Diarylpyrazoles are known to be interesting compounds for biological studies because they exhibit high inhibitory activity of Hsp90 [10–13]. Furthermore, 3,4-diarylpyrazoles are inhibitors of catechol-*O*-methyltransferase (COMT) [14] in addition to cyclooxygenase-2 [15]. Considering this, the development of synthetic methods for the new compounds of this series was very timely.

Although several approaches to the synthesis of similar pyrazole derivatives were developed, the most convenient method for preparing 3,4-diarylpyrazoles was recyclization of the chromone ring through the action of hydrazine [10–18].

Recyclization of the synthesized 7-β-(*N*,*N*-dialkylamino)ethoxy isoflavone derivative **3**–**8** through the action of hydrazine was studied in order to prepare 4-aryl-3-[2-hydroxy-4-β-(*N*,*N*-dialkylamino)ethoxy]phenylpyrazoles. Electron-donating methoxyls in ring B of the natural isoflavone derivatives decreased markedly their reactivity toward dinucleophiles, especially for 2-methylsubstituted isoflavones **3b**, **5b**, and **7b**, recyclization of which through the action of hydrazine occurred in several hours.

The pyrazole structures of **9**–**14** were confirmed by PMR spectroscopy. Occurrence of the reaction with opening of the chromone ring was confirmed by a diamagnetic shift by 0.5–0.8 ppm of the resonances for phenol protons H-4 and H-6 of the pyrazole products compared with the position of the H-6 and H-8 proton resonances of the starting isoflavones. Furthermore, the resonance of the H-3(5) proton was observed as two broad singlets of total intensity 1H because of tautomerism of the pyrazole ring. Also, the exact positions of the pyrazole H-1 and phenol OH-1 substituents could not be located in most instances because of exchange processes.

Thus, a series of 7-β-(*N*,*N*-dialkylamino)ethoxy derivatives of natural isoflavones in addition to 4-aryl-3-[2-hydroxy-4-β-(*N*,*N*-dialkylamino)ethoxy]phenylpyrazoles as products of their recyclization were synthesized.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Sorbfil UV-254 (Russia) and Merck plates (Germany). The eluents were toluene:EtOH mixtures (9:1, 95:5). PMR spectra were measured in $CDCl_3$ or DMSO-d_6 relative to TMS (internal standard) on the δ-scale on a VXR-300 instrument (Varian, 300 MHz). Analytical data of all compounds agreed with those calculated.

General Method for Preparing 7-(2-Bromoethoxy)isoflavones 2a–c. A solution of 7-hydroxyisoflavone (**1a**–**c**, 10 mmol) in DMF (20 mL) was treated with potash (25 mmol) and dibromoethane (50 mmol). The mixture was stirred at 75–80°C for 2–5 h (end of reaction determined by TLC). The potash was filtered off. The DMF was evaporated in vacuo. The solid was crystallized from *i*-PrOH:DMF.

7-(2-Bromoethoxy)-3-(4-methoxyphenyl)-4*H*-chromen-4-one (2a). Yield 58%, $C_{18}H_{15}BrO_4$, mp 178–180°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.79 (3H, s, 4′-OCH_3), 3.84–3.91 (2H, m, CH_2Br), 4.47–4.54 (2H, m, CH_2O-7), 7.0 (2H, d, ^3J = 9.0, H-3′, 5′), 7.12 (1H, dd, ^3J = 8.9, ^4J = 2.5, H-6), 7.21 (1H, d, ^4J = 2.5, H-8), 7.53 (2H, d, ^3J = 9.0, H-2′, 6′), 8.05 (1H, d, ^3J = 8.9, H-5), 8.43 (1H, s, H-2).

7-(2-Bromoethoxy)-2-methyl-3-(4-methoxyphenyl)-4*H*-chromen-4-one (2b). Yield 64%, $C_{19}H_{17}BrO_4$, mp 165–167°C. PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.30 (3H, s, CH_3-2), 3.64–3.74 (2H, m, CH_2Br), 3.84 (3H, s, 4′-OCH_3), 4.33–4.43 (2H, m, CH_2O-7), 6.84 (1H, d, ^4J = 2.3, H-8), 6.92–7.0 (3H, m, H-6, H-3′, H-5′), 7.20 (2H, d, ^3J = 8.7, H-2′, H-6′), 8.14 (1H, d, ^3J = 8.6, H-5).

7-(2-Bromoethoxy)-3- (3,4-dimethoxyphenyl)-4*H*-chromen-4-one (2c). Yield 60%, $C_{19}H_{17}BrO_5$, mp 165–167°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.80 (6H, s, 3′-OCH_3 and 4′-OCH_3), 3.84–3.91 (2H, m, CH_2Br), 4.47–4.54 (2H, m, CH_2O-7), 7.00 (1H, d, ^3J = 8.2, H-5′), 7.07–7.27 (4H, m, H-6, H-8, H-2′, H-6′), 8.05 (1H, d, ^3J = 9.0, H-5), 8.43 (1H, s, H-2).

General Method for Preparing 7-β-(*N*,*N*-Dialkylamino)ethoxy Derivatives of Isoflavones 3a,b, 4c, 5a,b, 6c, 7a,b, 8a. A solution of the appropriate 7-(2-bromoethoxy)isoflavone **2a**–**c** (2 mmol) in EtOH (30 mL) was treated with secondary amine (2.4 mmol) and di-isopropylethylamine (3 mmol), refluxed for 4–8 h (end of reaction determined by TLC), cooled, and diluted with H_2O. The resulting precipitate was filtered off and crystallized from EtOH:H_2O.

3-(4-Methoxyphenyl)-7-(2-piperidin-1-ylethoxy)-4*H*-chromen-4-one (3a). Yield 70%, $C_{23}H_{25}NO_4$, mp 122–124°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.31–1.59, 2.38–2.48 (6H, m, 4H, m, piperidine protons), 2.63–2.78 (2H, m, $NC\underline{H}_2CH_2O$-7), 3.79 (3H, s, 4′-OCH_3), 4.18–4.26 (2H, m, $NCH_2C\underline{H}_2O$-7), 6.99 (2H, d, ^3J = 8.7, H-3′, H-5′), 7.07 (1H, dd, ^3J = 9.0, ^4J = 2.3, H-6), 7.17 (1H, d, ^4J = 2.3, H-8), 7.53 (2H, d, ^3J = 8.7, H-2′, H-6′), 8.02 (1H, d, ^3J = 9.0, H-5), 8.40 (1H, s, H-2).

2-Methyl-3-(4-methoxyphenyl)-7-(2-piperidin-1-ylethoxy)-4*H*-chromen-4-one (3b). Yield 67%, $C_{24}H_{27}NO_4$, mp 113–115°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.32–1.56, 2.39–2.48 (6H, m, 4H, m, piperidine protons), 2.26 (3H, c, CH_3-2), 2.65–2.72 (2H, m, $NC\underline{H}_2CH_2O$-7), 3.80 (3H, s, 4′-OCH_3), 4.17–4.24 (2H, m, $NCH_2C\underline{H}_2O$-7), 6.98 (2H, d, ^3J = 8.7, H-3′, H-5′), 7.03 (1H, dd, ^3J = 9.0, ^4J = 2.3, H-6), 7.13 (1H, d, ^4J = 2.3, H-8), 7.20 (2H, d, ^3J = 8.7, H-2′, H-6′), 7.92 (1H, d, ^3J = 9.0, H-5).

1-(2-{[3-(3,4-Dimethoxyphenyl)-4-oxo-4*H*-chromen-7-yl]oxy}ethyl)piperidine-4-carboxamide (4c). Yield 65%, $C_{25}H_{28}N_2O_6$, mp 207–209°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.45–1.73, 1.92–2.14, 2.89–3.06 (5H, m, 2H, m, 2H, m, piperidine protons), 2.66–2.79 (2H, m, $NC\underline{H}_2CH_2O$-7), 3.79 (6H, s, 3′-OCH_3, 4′-OCH_3), 4.19–4.27 (2H, m, $NCH_2C\underline{H}_2O$-7), 6.68–7.27 (7H, m, $CONH_2$, H-6, H-8, H-2′, H-5′, H-6′), 8.02 (1H, d, ^3J = 8.9, H-5), 8.50 (1H, s, H-2).

3-(4-Methoxyphenyl)-7-(2-morpholin-4-ylethoxy)-4*H*-chromen-4-one (5a). Yield 74%, $C_{22}H_{23}NO_5$, mp 156–158°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.45–2.53, 3.55–3.62 (4H, m, 4H, m, morpholine protons), 2.70–2.78 (2H, m, $NC\underline{H}_2CH_2O$-7), 3.79 (3H, s, 4′-OCH_3), 4.21–4.29 (2H, m, $NCH_2C\underline{H}_2O$-7), 6.99 (2H, d, ^3J = 8.7, H-3′, H-5′), 7.08 (1H, dd, ^3J = 9.0, ^4J = 2.3, H-6), 7.17 (1H, d, ^4J = 2.3, H-8), 7.53 (2H, d, ^3J = 8.7, H-2′, H-6′), 8.03 (1H, d, ^3J = 9.0, H-5), 8.40 (1H, s, H-2).

2-Methyl-3-(4-methoxyphenyl)-7-(2-morpholin-4-ylethoxy)-4*H*-chromen-4-one (5b). Yield 67%, $C_{23}H_{25}NO_5$, mp 112–114°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.29 (3H, c, CH_3-2), 2.44–2.56, 3.56–3.65 (4H, m, 4H, m, morpholine protons), 2.72–2.80 (2H, m, $NC\underline{H}_2CH_2O$-7), 3.82 (3H, s, 4′-OCH_3), 4.16–4.24 (2H, m, $NCH_2C\underline{H}_2O$-7), 6.93 (2H, d, ^3J = 8.7, H-3′, H-5′), 6.93 (1H, dd, ^3J = 9.0, ^4J = 2.3, H-6), 6.99 (1H, d, ^4J = 2.3, H-8), 7.14 (2H, d, ^3J = 8.7, H-2′, H-6′), 7.92 (1H, d, ^3J = 9.0, H-5).

7-[2-(2,6-Dimethylmorpholin-4-yl)ethoxy]-3-(3,4-dimethoxyphenyl)-4*H*-chromen-4-one (6c). Yield 73%, $C_{25}H_{29}NO_6$, mp 107–109°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.01–1.15, 1.68–1.80, 2.80–2.89, 3.50–3.64 (6H, 2H, 2H, 2H, 4 m, morpholine protons), 2.68–2.76 (2H, m, $NC\underline{H}_2CH_2O$-7), 3.80 (6H, s, 3′-OCH_3, 4′-OCH_3), 4.21–4.29 (2H, m, $NCH_2C\underline{H}_2O$-7), 6.96–7.24 (5H, m, H-6, H-8, H-2′, H-5′, H-6′), 8.03 (1H, d, ^3J = 9.0, H-5), 8.46 (1H, s, H-2).

3-(4-Methoxyphenyl)-7-[2-(4-phenylpiperazin-1-yl)ethoxy]-4*H*-chromen-4-one (7a). Yield 69%, $C_{28}H_{28}N_2O_4$, mp 160–162°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.60–2.70, 3.08–3.19 (4H, m, 4H, m, piperazine protons), 2.76–2.85 (2H, m, $NC\underline{H}_2CH_2O$-7), 3.79 (3H, s, 4′-OCH_3), 4.23–4.33 (2H, m, $NCH_2C\underline{H}_2O$-7), 6.73–6.96 (3H, m, H-2‴, H-4‴, H-6‴), 7.00 (2H, d, ^3J = 8.7, H-3′, H-5′), 7.10 (1H, dd, ^3J = 8.7, ^4J = 2.0, H-6), 7.17–7.25 (3H, m, H-8, H-3‴, H-5‴), 7.53 (2H, d, ^3J = 8.7, H-2′, H-6′), 8.04 (1H, d, ^3J = 8.7, H-5), 8.42 (1H, s, H-2).

2-Methyl-3-(4-methoxyphenyl)-7-[2-(4-phenylpiperazin-1-yl)ethoxy]-4*H*-chromen-4-one (7b). Yield 76%, $C_{29}H_{30}N_2O_4$, mp 150–152°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.27 (3H, c, CH_3-2), 2.61–2.90, 3.10–3.18 (4H, m, 4H, m, piperazine protons), 2.77–2.85 (2H, m, $NC\underline{H}_2CH_2O$-7), 3.80 (3H, s, 4′-OCH_3), 4.24–4.33 (2H, m, $NCH_2C\underline{H}_2O$-7), 6.72–6.96 (3H, m, H-2‴, H-4‴, H-6‴), 6.99 (2H, d, ^3J = 8.7, H-3′, H-5′), 7.06 (1H, dd, ^3J = 8.7, ^4J = 2.3, H-6), 7.15–7.26 (5H, m, H-8, H-2′, H-6′, H-3‴, H-5‴), 7.93 (1H, d, ^3J = 8.7, H-5).

3-(4-Methoxyphenyl)-7-{2-[4-(4-fluorophenyl)piperazin-1-yl]ethoxy}-4*H*-chromen-4-one (8a). Yield 70%, $C_{28}H_{27}FN_2O_4$, mp 170–172°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.61–2.70, 3.04–3.12 (4H, m, 4H, m, piperazine protons), 2.77–2.85 (2H, m, $NC\underline{H}_2CH_2O$-7), 3.79 (3H, s, 4′-OCH_3), 4.25–4.32 (2H, m, $NCH_2C\underline{H}_2O$-7), 6.89–7.07 (6H, m, H-3′, H-5′, N′-$C_6\underline{H}_4$-F-*p*), 7.10 (1H, dd, ^3J = 8.7, ^4J = 2.0, H-6), 7.20 (1H, d, ^4J = 2.0, H-8), 7.53 (2H, d, ^3J = 8.7, H-2′, H-6′), 8.03 (1H, d, ^3J = 8.7, H-5), 8.41 (1H, s, H-2).

General Method for Preparing 3-[2-Hydroxy-4-β-(*N*,*N*-dialkylamino)ethoxy]phenyl-4-arylpyrazoles 9a,b, 10c, 11a,b, 12c, 13a,b, 14a. A hot solution of the appropriate isoflavone **3**–**8** (4.5 mmol) in the minimal amount of EtOH was treated with hydrazine hydrate (2 mL, 60 mmol, 85%), refluxed for 0.1–2 h (end of reaction determined by TLC), and poured into H_2O (100–150 mL). The precipitate was filtered off and crystallized from MeOH.

2-[4-(4-Methoxyphenyl)-1*H*-pyrazol-3(5)-yl]-5-(2-piperidin-1-ylethoxy)phenol (9a). Yield 85%, $C_{23}H_{27}N_3O_3$, mp 80–82°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.30–1.59, 2.32–2.46 (6H, m, 4H, m, piperidine protons), 2.60–2.69 (2H, m, $NC\underline{H}_2CH_2O$-5), 3.79 (3H, s, 4″-OCH_3), 3.96–4.07 (2H, m, $NCH_2C\underline{H}_2O$-5), 6.36 (1H, dd, ^3J = 8.1, ^4J = 2.2,

H-4), 6.47 (1H, d, ^{4}J = 2.2, H-6), 6.85 (2H, d, ^{3}J = 8.9, H-3″, H-5″), 7.00 (1H, d, ^{3}J = 8.1, H-3), 7.20 (2H, d, ^{3}J = 8.9, H-2″, H-6″), 7.78 (1H, br.s, H-5′(3′)).

2-[5(3)-Methyl-4-(4-methoxyphenyl)-1*H*-pyrazol-3(5)-yl]-5-(2-piperidin-1-ylethoxy)phenol (9b). Yield 81%, $C_{24}H_{29}N_3O_3$, mp 192–194°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.29–1.55, 2.32–2.48 (6H, m, 4H, m, piperidine protons), 2.15 (3H, c, CH_3-5′(3′)), 2.55–2.42 (2H, m, NC$\underline{H}_2$$CH_2$O-5), 3.77 (3H, s, 4″-$OCH_3$), 3.93–4.03 (2H, m, NCH_2C$\underline{H}_2$O-5), 6.22 (1H, dd, ^{3}J = 8.6, ^{4}J = 2.4, H-4), 6.42 (1H, d, ^{4}J = 2.4, H-6), 6.94 (2H, d, ^{3}J = 8.4, H-3″, H-5″), 7.13 (2H, d, ^{3}J = 8.4, H-2″, H-6″), 7.13 (1H, d, ^{3}J = 8.6, H-3), 11.20 (1H, s, OH), 13.00 (1H, br.s, NH).

1-(2-{4-[4-(3,4-Dimethoxyphenyl)-1*H*-pyrazol-3(5)-yl]-3-hydroxyphenoxy}-ethyl)piperidine-4-carboxamide (10c). Yield 75%, $C_{25}H_{30}N_4O_5$, mp 104–106°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.44–1.73, 1.91–2.12, 2.86–2.99 (5H, 2H, 2H, 3m, piperidine protons), 2.58–2.70 (2H, m, NC$\underline{H}_2$$CH_2$O-5), 3.59, 3.72 (3H, 3H, 2s, 3″-OCH_3, 4″-OCH_3), 3.98–4.06 (2H, m, NCH_2C$\underline{H}_2$O-5), 6.22–7.27 (8H, m, $CONH_2$, H-3, H-4, H-6, H-2″, H-5″, H-6″), 7.73, 7.94 (1H, 2 br.s, H-5′(3′)).

2-[4-(4-Methoxyphenyl)-1*H*-pyrazol-3(5)-yl]-5-(2-morpholin-4-ylethoxy)phenol (11a). Yield 84%, $C_{22}H_{25}N_3O_4$, mp 63–65°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.40–2.56, 3.52–3.63 (4H, m, 4H, m, morpholine protons), 2.62–2.72 (2H, m, NC$\underline{H}_2$$CH_2$O-5), 3.79 (3H, s, 4″-$OCH_3$), 3.99–4.09 (2H, m, NCH_2C$\underline{H}_2$O-5), 6.37 (1H, dd, ^{3}J = 9.0, ^{4}J = 2.3, H-4), 6.48 (1H, d, ^{4}J = 2.3, H-6), 6.85 (2H, d, ^{3}J = 8.4, H-3″, H-5″), 7.01 (1H, d, ^{3}J = 9.0, H-3), 7.20 (2H, d, ^{3}J = 8.4, H-2″, H-6″), 7.78 (1H, br.s, H-5′(3′)).

5(3)-Methyl-2-[4-(4-methoxyphenyl)-1*H*-pyrazol-3(5)-yl]-5-(2-morpholin-4-ylethoxy)phenol (11b). Yield 80%, $C_{23}H_{27}N_3O_4$, mp 187–189°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.15 (3H, c, CH_3-5′(3′)), 2.40–2.47, 3.52–3.60 (4H, m, 4H, m, morpholine protons), 2.60–2.67 (2H, m, NC$\underline{H}_2$$CH_2$O-5), 3.77 (3H, s, 4″-$OCH_3$), 3.97–4.04 (2H, m, NCH_2C$\underline{H}_2$O-5), 6.22 (1H, dd, ^{3}J = 8.7, ^{4}J = 2.2, H-4), 6.43 (1H, d, ^{4}J = 2.2, H-6), 6.89 (1H, d, ^{3}J = 8.7, H-3), 6.92–7.19 (4H, m, $C_6\underline{H}_4$-OMe-*p*), 11.20 (1H, s, OH), 12.98 (1H, br.s, NH).

5-[2-(2,6-Dimethylmorpholin-4-yl)ethoxy]-2-[4-(3,4-dimethoxyphenyl)-1*H*-pyrazol-3(5)-yl]phenol (12c). Yield 76%, $C_{25}H_{31}N_3O_5$, mp 79–81°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.97–1.16, 1.65–1.77, 2.75–2.86, 3.49–3.64 (6H, 2H, 2H, 2H, 4 m, morpholine protons), 2.58–2.96 (2H, m, NC$\underline{H}_2$$CH_2$O-5), 3.72 (6H, s, 3″-$OCH_3$, 4″-$OCH_3$), 3.99–4.09 (2H, m, NCH_2C$\underline{H}_2$O-5), 6.27–6.58 (2H, m, H-4, H-6), 6.70–7.18 (4H, m, H-3, H-2″, H-5″, H-6″), 7.73, 7.94 (1H, 2 br.s, H-5′(3′)).

2-[4-(4-Methoxyphenyl)-1*H*-pyrazol-3(5)-yl]-5-[2-(4-phenylpiperazin-1-yl)ethoxy]phenol (13a). Yield 88%, $C_{28}H_{30}N_4O_3$, mp 92–94°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.58–2.67, 3.09–3.17 (4H, m, 4H, m, piperazine protons), 2.70–2.78 (2H, m, NC$\underline{H}_2$$CH_2$O-5), 3.72 (3H, s, 4″-$OCH_3$), 4.04–4.12 (2H, m, NCH_2C$\underline{H}_2$O-5), 6.28–6.57 (2H, m, H-4, H-6), 6.72–7.30 (10H, m, H-3, $C_6\underline{H}_4$-OMe-*p*, *N*′-$C_6\underline{H}_5$), 7.68, 7.92 (1H, 2 br.s, H-5′(3′)).

5(3)-Methyl-2-[4-(4-methoxyphenyl)-1*H*-pyrazol-3(5)-yl]-5-[2-(4-phenylpiperazin-1-yl)ethoxy]phenol (13b). Yield 85%, $C_{29}H_{32}N_4O_3$, mp 203–205°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.16 (3H, c, CH_3-5′(3′)), 2.58–2.65, 3.08–3.16 (4H, m, 4H, m, piperazine protons), 2.68–2.75 (2H, m, NC$\underline{H}_2$$CH_2$O-5), 3.78 (3H, s, 4″-$OCH_3$), 4.01–4.10 (2H, m, NCH_2C$\underline{H}_2$O-5), 6.26 (1H, dd, ^{3}J = 8.8, ^{4}J = 2.2, H-4), 6.46 (1H, d, ^{4}J = 2.2, H-6), 6.72–7.27 (10H, m, H-3, $C_6\underline{H}_4$-OMe-*p*, *N*′-$C_6\underline{H}_5$).

2-[4-(4-Methoxyphenyl)-1*H*-pyrazol-3(5)-yl]-5-{2-[4-(4-fluorophenyl)piperazin-1-yl]ethoxy}phenol (14a). Yield 88%, $C_{28}H_{29}FN_4O_3$, mp 171–173°C. PMR spectrum (300 MHz, DMSO-d_6, δ, ppm): 2.59–2.67, 3.03–3.13 (4H, m, 4H, m, piperazine protons), 2.70–2.79 (2H, m, NC$\underline{H}_2$$CH_2$O-5), 3.72 (3H, s, 4″-$OCH_3$), 4.04–4.12 (2H, m, NCH_2C$\underline{H}_2$O-5), 6.28–6.56 (2H, m, H-4, H-6), 6.74–7.26 (9H, m, H-3, $C_6\underline{H}_4$-OMe-*p*, *N*′-$C_6\underline{H}_4$-F-*p*), 7.68, 7.91 (1H, 2 br.s, H-5′(3′)).

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