Synthesis of new pyrazole-1,2,3-triazole dyads

Joana P.A. Ferreira, Vera L.M. Silva, José Elguero, Artur M.S. Silva

PII: S0040-4039(13)01288-4
DOI: http://dx.doi.org/10.1016/j.tetlet.2013.07.120
Reference: TETL 43318

To appear in: *Tetrahedron Letters*

Received Date: 6 June 2013
Revised Date: 19 July 2013
Accepted Date: 23 July 2013

Please cite this article as: Ferreira, J.P.A., Silva, V.L.M., Elguero, J., Silva, A.M.S., Synthesis of new pyrazole-1,2,3-triazole dyads, *Tetrahedron Letters* (2013), doi: http://dx.doi.org/10.1016/j.tetlet.2013.07.120

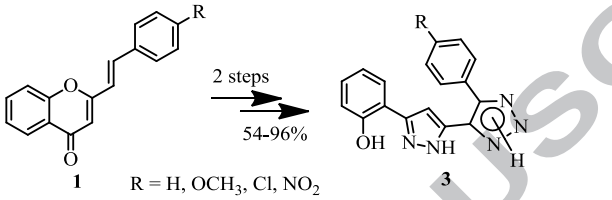
Graphical Abstract

Synthesis of new pyrazole-1,2,3-triazole dyads

Leave this area blank for abstract info.

Joana P. A. Ferreira,[a] Vera L. M. Silva,[a,*] José Elguero[b] and Artur M. S. Silva[a,*]

[a]*Department of Chemistry & QOPNA, University of Aveiro, 3810-193 Aveiro, Portugal;* [b]*Instituto de Química Médica, C/ Juan de la Cierva 3, 28006 Madrid, Spain*



1 R = H, OCH_3, Cl, NO_2 **3**

Tetrahedron Letters
journal homepage: www.elsevier.com

Synthesis of new pyrazole-1,2,3-triazole dyads

Joana P. A. Ferreira,[a] Vera L. M. Silva,[a,*] José Elguero[b] and Artur M. S. Silva[a,*]

[a]*Department of Chemistry & QOPNA, University of Aveiro, 3810-193 Aveiro, Portugal*
[b]*Instituto de Química Médica, C/ Juan de la Cierva 3, 28006 Madrid, Spain*

**Corresponding author. Tel.: +351-234-370714; fax: +351-234-370084; e-mail: artur.silva@ua.pt and verasilva@ua.pt*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Pyrazoles
1,2,3-Triazoles
(*E*)-2-Styryl-4*H*-chromen-4-ones
Hydrazine hydrate

ABSTRACT

An efficient two steps synthetic methodology of new 5(4)-aryl-4(5)-[3(5)-(2-hydroxyphenyl)-1*H*-pyrazol-5(3)-yl]-1*H*-1,2,3-triazole dyads was established. The reaction of (*E*)-2-styryl-4*H*-chromen-4-ones, used as building blocks, with sodium azide, gave 4(5)-aryl-5(4)-(chromon-2-yl)-1*H*-1,2,3-triazoles bearing either electron-donating or electron-withdrawing substituents in their styryl moiety which upon reaction with hydrazine hydrate afforded the expected pyrazoles in moderate to very good yields.

1. Introduction

1,2,3-Triazoles are five-membered nitrogen heterocyclic compounds, which display a wide spectrum of pharmacological properties.[1,4] They are also used as intermediates in the synthesis of antibiotics (e.g. Tazobactum),[4,5] and applied as agrochemicals, mainly as fungicides,[6] insecticides,[7] and plant growth regulators.[8,9] They have practical use in industrial applications as dyes, corrosion inhibitors (of copper and copper alloys), photostabilizers and in photographic materials.[10] Likewise, pyrazole derivatives are highly recognized because of their significant biological activities, mainly as antimicrobial, analgesic, anti-inflammatory (Celecoxib and Pirazolac), and anticancer agents.[11,12] In particular, certain *C*- and/or *N*-(2-hydroxyphenyl)pyrazoles are used as ultraviolet stabilizers,[13,14] analytical reagents in the complexation of transition metal ions,[15] analgesic agents, platelet aggregation inhibitors,[16] and also potent inhibitors of Hsp90 ATP-ase activity.[17-19] Similarly to 1,2,3-triazoles, pyrazoles have also widespread application in the fields of agriculture and in industry.[11,12,20-22]

Fused pyrazole-1,2,3-triazoles, such as pyrazole[3,4-*d*]-1,2,3-triazoles are known to exhibit antiproliferative properties and ability to cleave DNA upon activation by light.[23] Moreover 1,2,4-triazole-containing diarylpyrazolylcarboxamides, are potent receptor antagonists for the CB_1 cannabinoid-type receptors with effect in the treatment of obesity animal models.[24] Some diarylpyrazoles with cannabinomimetic activity present an amide bond that seems to be very important for their activity. 1,2,3-Triazoles are units that can act as mimics of the position of atoms and chemical properties of the amide bond, with no significant susceptibility to hydrolysis.[25]

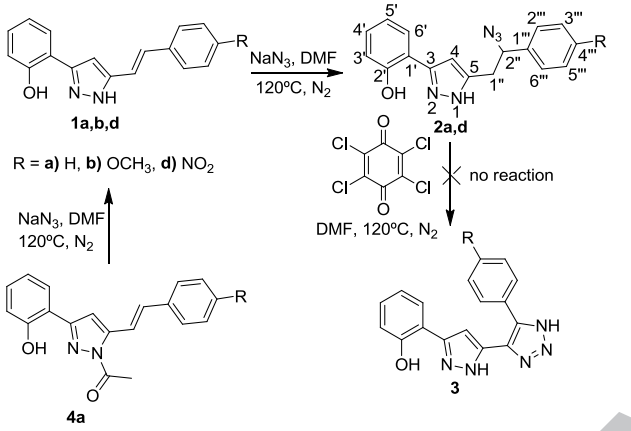
Considering the referred important applications and in continuation of our previous work to find new biologically active heterocyclic compounds, including cannabinoid-type compounds, based on the 3(5)-(2-hydroxyphenyl)-5(3)-styryl-1*H*-pyrazole scaffold,[26-28] now we are describing the synthesis of novel 3(5)-(2-hydroxyphenyl)pyrazole-1,2,3-triazole dyads.

2. Results and discussion

Our first approach to obtain pyrazole-1,2,3-triazole dyads involved the 1,3-dipolar cycloaddition reaction of 3(5)-(2-hydroxyphenyl)-5(3)-styryl-1*H*-pyrazole **1a**[27] with sodium azide (Scheme 1), accordingly to the procedure reported by Silva *et al.* for the synthesis of 4(5)-aryl-5(4)-(chromon-2-yl)-1*H*-1,2,3-triazoles.[28] An excess of sodium azide (5 molar equiv) was added to a solution of pyrazole **1a** in DMF being the mixture refluxed and after 6 hours the formation of a new product was observed by TLC. The NMR spectra of the isolated compound revealed the formation of 5(3)-(2-azido-2-phenylethyl)-3(5)-(2-hydroxyphenyl)-1*H*-pyrazole **2a** (20% yield),[29] which results from the nucleophilic attack of the azide anion to the *β*-position of the styryl double bond (Scheme 1). The analysis of the ^{1}H NMR spectra of compound **2a** confirms the absence of the signals typical of the vinylic protons H-α and H-β of compound **1a**, and the presence of two signals in the aliphatic region of the spectra: i) a doublet at δ_H 3.13 ppm due to the resonance of H-1'' and a triplet at δ_H 5.03 ppm due to the resonance of H-2''. The ^{13}C NMR spectra of **2a** also presents two signals in the aliphatic region due to C-1'' at δ_C 34.9 ppm and C-2'' at δ_C 73.7 ppm, the latter more deshielded due to the presence of the azide group.

Aiming to promote the dehydrogenation and intramolecular cyclization of the azide **2a**, it was treated with chloranil (1 molar equiv) in DMF and the mixture was refluxed for 24 hours, but unfortunately, under these conditions only degradation of the starting material was observed.

In order to evaluate the electronic effect of the substituent on the *para*-position of the styryl group on the reactivity of the vinylic double bond, we tried the reaction of (*E*)-3(5)-(2-hydroxyphenyl)-5(3)-(4-methoxystyryl)-1*H*-pyrazole **1b** and (*E*)-3(5)-(2-hydroxyphenyl)-5(3)-(4-nitrostyryl)-1*H*-pyrazole **1d** with sodium azide under the conditions previously described (a big excess of sodium azide in refluxing DMF for more than 72 hours). In the case of **1b** only the starting material was recovered (90%) after 5 days of reaction time, while in the case of **1d** azidopyrazole **2d** was obtained (37% yield) after 14 hours of reaction. These results indicates that the *β*-addition of the azide anion is favoured by the presence of an electron withdrawing substituent on the *para*-position of the styryl group.



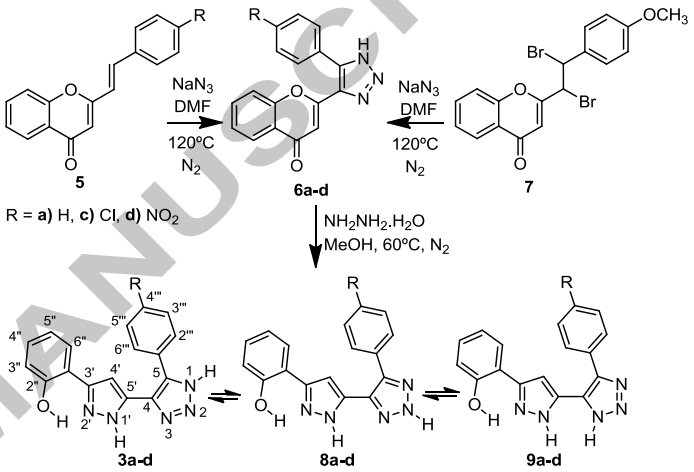
Scheme 1. Reaction of (*E*)-3(5)-(2-hydroxyphenyl)-5(3)-styryl-1*H*-pyrazoles **1a,b,d** and **4a** with sodium azide.

Our second approach towards the synthesis of pyrazole-1,2,3-triazole dyads involved the protection of the NH of the pyrazole with acetyl chloride in pyridine at room temperature. Acetyl was selected as an electron withdrawing, in order to make the vinylic double bond more electron deficient, and easily removable protecting group. The reaction of 1-acetyl-3(5)-(2-hydroxy-phenyl)-5(3)-styryl-1*H*-pyrazole **4a** with 5 molar equiv of sodium azide in refluxing DMF afforded pyrazole **1a** (87% yield), due to the cleavage of the acetyl group after 24 hours at reflux.

Since our strategies were not succeeded we had to develop another synthetic method in order to prepare the pyrazole-1,2,3-triazole dyads in good yields. Following our previous work on the synthesis of 4(5)-aryl-5(4)-(chromon-2-yl)-1*H*-1,2,3-triazoles,[28] we prepared 4(5)-aryl-5(4)-(chromon-2-yl)-1*H*-1,2,3-triazoles **6a,c,d** (76-89%) from the reaction of (*E*)-2-styryl-4*H*-chromen-4-ones **5a,c,d** with sodium azide, whereas **6b** was obtained (34%) from the reaction of 2-[1,2-dibromo-2-(4-methoxyphenyl)ethyl]-4*H*-chromen-4-one **7** with sodium azide, both reactions in DMF at 120ºC. Then, we performed the reaction of compounds **6a-d** with an excess of hydrazine hydrate (5 molar equiv) in methanol at 60ºC and we obtained the 5(4)-aryl-4(5)-[3(5)-(2-hydroxyphenyl)-1*H*-pyrazol-5(3)-yl]-1*H*-1,2,3-triazoles **3a-d/8a-d/9a-d** in moderate to very good yields depending on the substituent in the phenyl ring (Scheme 2, Table 1).[30-32] For compound **3a,b/8a,b/9a,b** better yields were obtained with a second addition of hydrazine hydrate (Table 1). The reaction mechanism involves a nucleophilic attack at C-2 of the 4*H*-chromen-4-one nucleus and consequent ring opening, followed by the intramolecular reaction between hydrazine and the carbonyl group with consequent formation of the pyrazole ring.[33-35] Compound **3a-d/8a-d/9a-d** has six tautomers, two of the pyrazole ring and three of the 1,2,3-triazole ring. That of the pyrazole is suggested as represented due to the O–H···N hydrogen bond between the OH and the N2' lone pair.[27,33,34,36,37] The tautomerism of 1,2,3-triazoles generally involves the three tautomers, N(1)H, N(2)H and N(3)H[38] and was not determined in the present work.

3. Conclusions

(*E*)-2-styryl-4*H*-chromen-4-ones were used as building blocks in the synthesis of 5(4)-aryl-4(5)-[3(5)-(2-hydroxyphenyl)-1*H*-pyrazol-5(3)-yl]-1*H*-1,2,3-triazoles. This methodology of preparing pyrazole-1,2,3-triazole dyads is very expeditious since the synthesis involves only two steps and compounds were obtained in very good yields especially for (*E*)-2-styryl-4*H*-chromen-4-ones bearing electron-withdrawing substituents in their styryl moiety.



Scheme 2. Synthesis of 5(4)-aryl-4(5)-[3(5)-(2-hydroxyphenyl)-1*H*-pyrazol-5(3)-yl]-1*H*-1,2,3-triazoles **3a-d/8a-d/9a-d** starting from 4(5)-aryl-5(4)-(chromon-2-yl)-1*H*-1,2,3-triazoles **6a-d**.

Table 1. Reaction conditions and yields obtained in the synthesis of 5(4)-aryl-4(5)-[3(5)-(2-hydroxyphenyl)-1*H*-pyrazol-5(3)-yl]-1*H*-1,2,3-triazoles **3a-d/ 8a-d/ 9a-d**.

Compound	$NH_2NH_2.H_2O$ (molar equiv)	Reaction time (h)	Temperature (ºC)	Yield of **3** (%)
6a, R = H	5	24	r.t	50
6a, R = H	5+5	48+27	r.t then 60	86
	5	24	60	86
6b, R = OCH_3	5	48	60	54
6b, R = OCH_3	5+5	48+24	60	67
6c, R = Cl	5	72	60	96
6d, R = NO_2	5	72	60	90

Acknowledgments

Thanks are due to the University of Aveiro, "Fundação para a Ciência e a Tecnologia", European Union, QREN, FEDER and COMPETE for funding the Organic Chemistry Research Unit (project PEst-C/QUI/UI0062/2011) and the Portuguese National NMR network. One of us Joana P. A. Ferreira is also grateful to "Fundação para a Ciência e a Tecnologia" and FSE for a PhD grant (SFRH/BD/45107/2008).

References and notes

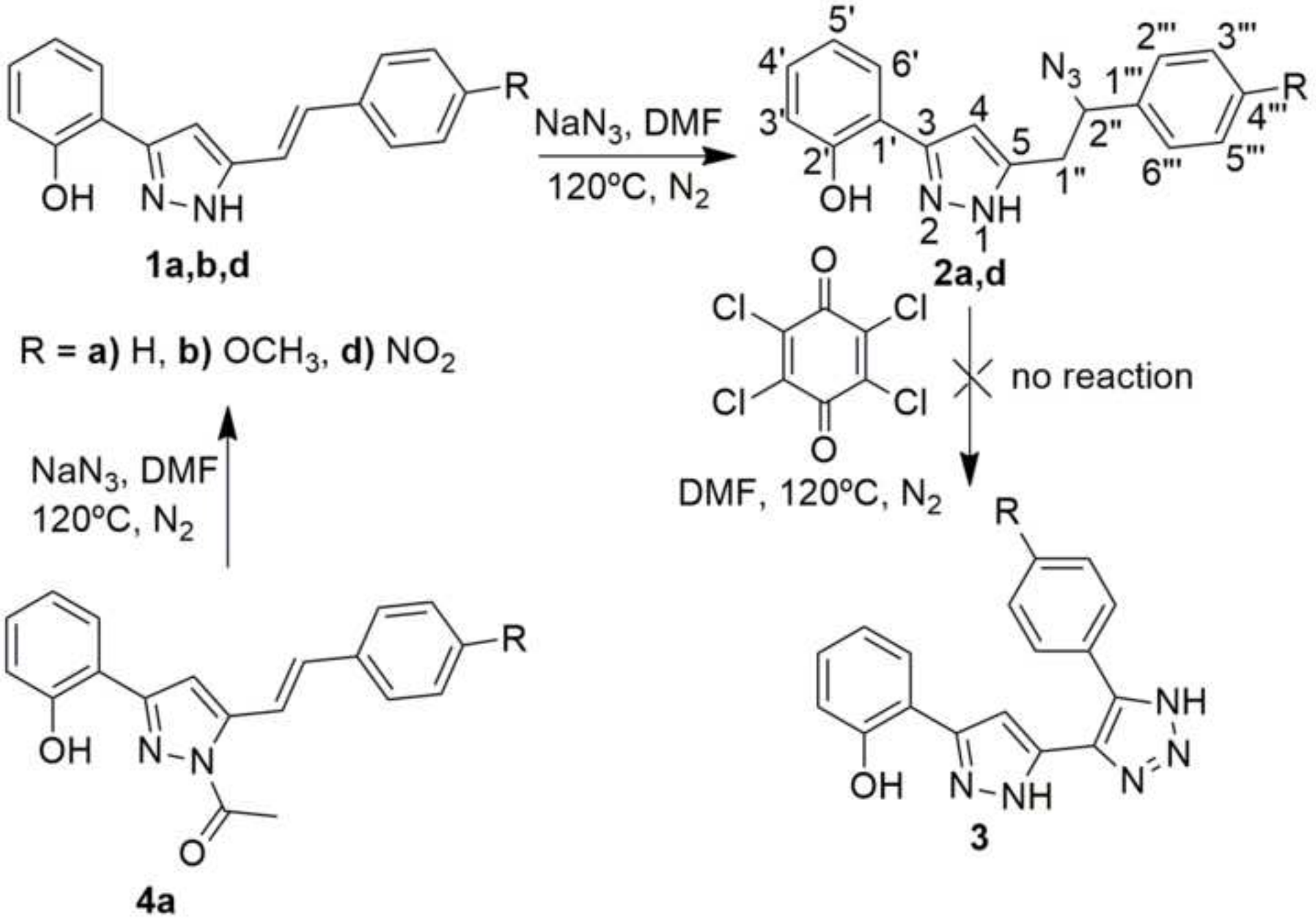
1. Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952-3015.
2. Melo, J. O. F.; Donnici, C. L.; Augusti R.; Ferreira, V. F.; Souza, C. B. V.; Ferreira, M. L. G.;Cunha, A. C. *Quim. Nova* **2006**, *29*, 569-579.

3. Shafran, E. A.; Bakulev, V. A.; Rozin, Y. A.; Shafran, Y. M. *Chem. Heterocycl. Compd.* **2008**, *44*, 1040-1069.
4. Agalave, S. G.; Maujan, S. R.; Pore, V. S. *Chem. Asian J.* **2011**, *6*, 2696-2718.
5. Aufort, M.; Herscovici, J.; Bouhours, P.; Moreau, N.; Girard, C. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 1195-1198.
6. Buechel, K. H.; Gold, H.; Frohberger, P. E.; Kaspers, H., German Patent 2407305, **1975**; *Chem. Abstr*. **1975**, *83*, 206290.
7. Boddy, I. K.; Briggs, G. G.; Harrison, R. P.; Jones, T. H.; O'Mahony, M. J.; Marlow, I. D.; Roberts, B. G.; Willis, R. J.; Bardsley, R.; Reid, J. *Pestic. Sci*. **1996**, *48* 189-196.
8. Reisser, F. British Patent 8101239, **1981**; *Chem. Abstr*. **1981**, *96*, 69006.
9. Krueger, H. R.; Schroeer, U.; Baumert, D.; Joppien, H. German Patent 2936951, **1981**; *Chem. Abstr*. **1981**, *96*, 52509.
10. Fan, W.-Q.; Katritzky, A. R. in: Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. (Eds.), *Comprehensive Heterocyclic Chemistry* II, Elsevier Science, Oxford, **1996**; Vol.4, pp. 1-126.
11. Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. In *Pyrazoles as Drugs: Facts and Fantasies in Targets in Heterocyclic Systems—Chemistry and Properties*, Attanasi, O. A.; Spinelli, D. Eds., Italian Society of Chemistry, Camerino, Italy, **2002**, vol 6., pp 52-98.
12. Fustero S.; Roselló M.-S.; Barrio, P.; Simón-Fuentes A. *Chem. Rev*. **2011**, *111*, 6984-7034.
13. Catalán, J.; Fabero, F.; Claramunt, R. M.; Santa María, M. D.; Foces-Foces, M. C.; Cano, F. H.; Martínez-Ripoll, M.; Elguero, J.; Sastre, R. *J. Am. Chem. Soc.* **1992**, *114*, 5039-5048.
14. Catalán, J.; Fabero, F.; Guijano, M. S.; Claramunt, R. M.; Santa María, M. D.; Foces-Foces, M.C.; Cano, F. H.; Elguero, J.; Sastre, R. *J. Am. Chem. Soc.* **1990**, *112*, 747-759.
15. Ahmad, R.; Ahmad, N.; Zia-Ul-Haq, M. *J. Chem. Soc. Pak*. **1996**, *18*, 38-41.
16. Dymock, B. W.; Barril, X.; Brough, P. A.; Cansfield, J. E.; Massey, A.; McDonald, E.; Hubbard, R. E.; Surgenor, A.; Roughley, S. D.; Webb, P.; Workman, P.; Wright, L.; Drysdale, M. J. *J. Med. Chem.* **2005**, *48*, 4212-4215.
17. Barril, X.; Beswick, M.; Collier, A.; Drysdale, M. J.; Dymock, B. W.; Fink, A.; Grant, K.; Howes, R.; Jordan, A. M.; Massey, A; Surgenor, A.; Wayne, J.; Workman, P.; Wright, L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2543-2548.
18. Howes, R; Barril, X.; Dymock, B. W.; Grant, K.; Northfield, C. J.; Robertson, A. G. S.; Surgenor, A. ; Wayne, J.; Wright, L.; James, K.; Matthews, T.; Cheung, K.-M.; McDonald, E.; Workman, P.; Drysdale, M. J. *Anal. Biochem.* **2006**, *350*, 202-213.
19. Cheung, K.-M. J.; Matthews, T. P.; James, K.; Rowlands, M. G.; Boxall, K. J.; Sharp, S. Y.; Maloney, A.; Roe, S. M.; Prodromou, C.; Pearl, L. H.; Aherne, G. W.; McDonald, E.; Workman, P. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 3338-3343.
20. Elguero, J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky A. R.; Rees, C. W.; Scriven, E. F. Eds Pergamon Press: Oxford, **1996**, Vol.3, pp 1-75.
21. Elguero, J. In: *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W. Eds Pergamon, Oxford, **1984**, Vol. 5, pp 167.
22. Stanovnik, B.; Svete, J. Chapter 12.1: *Pyrazoles*. In: Neier, R. (ed) Science of Synthesis, vol 12. Georg Thieme, Stuttgart, **2002**, Vol. 12, pp 15.
23. Manfredini, S.; Vicentini, C. B.; Manfrini. M.; Bianchi, N.; Rutigliano, C.; Mischiati, C.; Gambari, R. *Bioorg. Med. Chem.* **2000**, *8*, 2343-2346.
24. Seo, H. J.; Kim, M. J.; Lee, S. H.; Lee, S.-H.; Jung, M. E.; Kim, M.-S.; Ahn, K.; Kim, J.; Lee, J. *Bioorg. Med. Chem.* **2010**, *18*, 1149-1162.
25. Pedersen, D. S.; Abell, A. *Eur. J. Org. Chem.* **2011**, *2399-2411*.
26. Silva, V. L. M.; Silva, A. M. S.; Pinto, D. C. G. A.; Rodriguez, P.; Gómez, M.; Jagerovic, N.; Callado, L. F.; Cavaleiro, J. A. S.; Elguero, J.; Fernando-Ruiz, J. *Arkivoc* **2010**, (x), 226-247.
27. Silva, V. L. M.; Silva, A. M. S.; Pinto, D. C. G. A.: Cavaleiro, J. A. S.; Elguero, J. *Eur. J. Org. Chem.*, **2004**, 4348-4356.
28. Silva, A. M. S.; Vieira, J. S.; Brito, C. M.; Cavaleiro, J A. S.; Patonay, T.; Lévai, A.; Elguero, J. *Monatsth. Chem*. **2004**, *135*, 293-308.
29. *5(3)-(2-Azido-2-phenylethyl)-3(5)-(2-hydroxyphenyl)-1H-pyrazole* **2a**: Orange solid; Mp 251-252 ºC. ^{1}H NMR (DMSO-d_6+TFA, 300.13 MHz): δ_H 3.13 (d, 2H, *J* = 6.2 Hz, H-1''), 5.03 (t, 1H, *J* = 6.2 Hz, H-2''), 6.42 (s, 1H, H-4), 6.89 (dt, 1H, *J* = 7.8, 1.1 Hz, H-5'), 7.01 (dd, 1H, *J* = 7.8, 1.1 Hz, H-3'), 7.20 (dt, 1H, *J* = 7.8, 1.6 Hz, H-4'), 7.35-7.39 (m, 5H, H-2''',3''',4''',5''',6'''), 7.51 (dd, 1H, *J* = 7.8, 1.6 Hz, H-6'), 13.00 (s, 1H, 2'-O*H*) ppm; ^{13}C NMR (DMSO-d_6+TFA, 125.77 MHz): δ_C 34.9 (C-1''), 73.7 (C-2''), 101.5 (C-4), 116.9 (C-1'), 117.1 (C-3'), 119.3 (C-5'), 125.8 (C-3''',5'''), 126.5 (C-6'), 128.5 (C-4'''), 129.0 (C-2''',6'''), 129.2 (C-4'), 141.3 (C-5), 143.1 (C-1'''), 151.9 (C-3), 156.1 (C-2') ppm. ESI(+) MS m/z (int. rel.) 306 ([M+H)$^+$, 76), 328 ([M+Na]$^+$, 10); HR-ESI(+) MS *m/z* calcd. for ($C_{17}H_{15}N_5O$+H)$^+$: 306.1277; found 306.1276.
30. *General procedure for the synthesis of 5(4)-aryl-4(5)-[3(5)-(2-hydroxyphenyl)-1H-pyrazol-5(3)-yl]-1H-1,2,3-triazoles* **3a-d**. To a solution of 4(5)-aryl-5(4)-(chromon-2-yl)-1*H*-1,2,3-triazoles **6a–d** (0.52 mmol) in methanol (10 mL) were added an excess of hydrazine monohydrate (see Table 1) and the mixture was heated at 60ºC (for reaction time see Table 1) under nitrogen atmosphere. After this period the mixture was poured into acidified water (pH = 5) and the aqueous layer was extracted with chloroform and dried over anhydrous sodium sulfate. The solvent was evaporated to dryness and the solid residue was purified by thin layer chromatography using a 3:1 mixture of ethyl acetate: light petroleum as eluent. After several elutions, the main fraction was collected and after solvent evaporation the residue was recrystallized from ethanol to give compounds **3a-d** in moderate to very good yields (**3a**, 86%, 135.64 mg; **3b**, 67%, 116.14 mg; **3c**, 96%, 168.61 mg; **3d**, 90%, 163.01 mg).
31. 4(5)-[3(5)-(2-Hydroxyphenyl)-1*H*-pyrazol-5(3)-yl]-5(4)-phenyl-1*H*-1,2,3-triazole **3a**. White solid, M.p. 246-247 ºC.; ^{1}H NMR (DMSO-d_6+TFA, 300.13 MHz) δ_H 6.86 (dt, 1H, *J* = 7.8, 0.9 Hz, H-5''), 6.95 (dd, 1H, *J* = 7.8, 0.9 Hz, H-3"), 6.97 (s, 1H, H-4'), 7.16 (dt, 1H, *J* = 7.8, 1.5 Hz, H-4"), 7.41-7.48 (m, 3H, H-2''',6''',4'''), 7.66 (dd, 1H, *J* = 7.8, 1.5 Hz, H-6"), 7.80 (dd, 2H, *J* = 8.2, 1.4 Hz, H-3''',5'''), 13.00 (s, 2''-O*H*) ppm; ^{13}C NMR (DMSO-d_6+TFA, 75.47 MHz): δ_C 103.8 (C-4'), 116.1 (C-1"), 116.7 (C-3"), 119.6 (C-5"), 127.5 (C-6"), 128.2 (C-3''',5'''), 128.7 (C-2''',6'''), 129.6 (C-4'''), 130.0 (C-4"), 130.1 (C-4), 133.7 (C-5), 139.0 (C-5'), 141.4 (C-1'''), 144.6 (C-3'), 154.4 (C-2") ppm. ESI(+)MS m/z (int. rel.) 304 ([M+H)$^+$, 100), 326 ([M+Na]$^+$, 30); HR-ESI(+) MS m/z calcd. for ($C_{17}H_{13}N_5O$+H)$^+$: 304.1120; found 304.1118.
32. 5(4)-(4-Chlorophenyl)-4(5)-[3(5)-(2-hydroxyphenyl)-1*H*-pyrazol-5(3)-yl]-1*H*-1,2,3-triazole **3c**. Yellow solid; Mp 295-297 ºC. ^{1}H NMR (DMSO-d_6+TFA, 300.13 MHz): δ_H 6.89 (t, 1H, *J* = 8.0 Hz, H-5"), 6.96 (dd, 1H, *J* = 8.0, 1.0 Hz, H-3"), 6.97 (s, 1H, H-4'), 7.20 (t, 1H, *J* = 8.0 Hz, H-4"), 7.40 (d, 2H, *J* = 8.0 Hz, H-2''',6'''), 7.70 (d, 1H, *J* = 8.0 Hz, H-6"), 7.74 (d, 2H, *J* = 8.0 Hz, H-3''',5'''), 12.90 (s, 2"-OH); ^{13}C NMR (75.47, MHz): δ_C 102.6 (C-4'), 116.1 (C-1"), 116.5 (C-3"), 119.5 (C-5"), 127.5 (C-6"), 128.8 (C-3''',5'''), 130.1 (C-4,4"), 131.9 (C-2''',6'''), 133.8 (C-5), 139.2 (C-5'), 144.7 (C-3'), 145.0 (C-4'''), 147.6 (C-1'''), 154.2 (C-2") ppm. ESI(+) MS m/z (int. rel.) 339 ([M+H)$^+$, ^{35}Cl, 100), 341 [(M+H)$^+$, ^{37}Cl, 21)], 360 ([M+Na]$^+$, ^{35}Cl, 24); 362 [(M+Na)$^+$, ^{37}Cl, 24]; HR-ESI(+)MS *m/z* calcd. for ($C_{17}H_{12}{}^{35}ClN_5O$+H)$^+$: 338.0730; found 338.0729; m/z calcd. for ($C_{17}H_{12}{}^{37}ClN_5O$+H)$^+$: 340.0740; found 340.0739.
33. Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S.; Foces-Foces, M. C.; Llamas-Saiz, A. L.; Jagerovic, N.; Elguero, J. *Tetrahedron* **1999**, *55*, 10187-10200.
34. Silva,V. L. M.; Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro, J. A. S., Elguero, J. *Monatsh. Chem.* **2009**, *140*, 87-95.
35. Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S. *J. Heterocycl. Chem.* **2000**, *37*, 1629-1643.
36. Pinto, D. C. G. A.; Silva, A. M. S.; Almeida, L. M. P. M., Cavaleiro, J. A. S.; Elguero, J. *Eur. J. Org. Chem.* **2002**, 3807-3815.
37. Silva, V. L. M.; Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro, J. A. S.; Elguero, j. *Tetrahedron Lett.* **2007**, *48*, 3859-3862.
38. Minkin, V. I.; Garnovskii, A. D.; Elguero, J.; Katritzky, A. R.; Denisko, O. V. *Adv. Heterocycl. Chem.* **2000**, *76*, 157–323.

Scheme graphical abstract

1 R = H, OCH_3, Cl, NO_2 3

Scheme 1



Scheme 2