1,3-DIPOLAR CYCLOADDITION REACTIONS OF PYRAZOLO[1,5-a]PYRIMIDINES WITH NITRILE OXIDE

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Abstract: An example of 1,3-dipolar cycloaddition reactions of arylnitrile oxide to pyrazolo[1,5-a]pyrimidines was described. The nitrile oxide reacts with the C3 –C4 double bond of pyrazolo[1,5-a]pyrimidine to give the corresponding pyrazolo[1,5-a]pyrimidine -isoxazolidines in moderate yields. The mechanism was discussed and the structure of all compounds was studied by IR and NMR Spectroscopy (^{1}H, ^{13}C, ^{19}F). Compound **4e** was characterized by HRMS.

Keywords: 3,5-diaminopyrazole, pyrazolo[1,5-a]pyrimidine, 1,3-dipolar cycloaddition and arylnitrile oxide .

INTRODUCTION

The cycloaddition of 1,3-dipolar (13DC) species to an alkene for the synthesis of five-membered rings is a classical reaction in organic chemistry[1],[2]. The (13DC) reaction between an arylnitrile oxide and an alkene gives the isoxazolidine skeleton, which is of great importance for the preparation of natural products[3],[4] and pharmaceuticals[5]. Isoxazolines have exhibited a wide range of biological activities including antiviral[6], antiapoptotic[7], antiparasitic[8] and anticancer[9] properties.

The method oftently employed generally to prepare isoxazole derivatives is the 1,3-dipolar cycloaddition of alkenes with nitrile oxides (from the dehydrohalogenation of hydroximoyl chlorides in the presence of triethylamine). It's quintessential to order that the reaction of pyrazolo[1,5-a]pyrimidine **3** with arylnitrile oxides has not been previously reported.

We revealed the synthesis of some new pyrazolo[1,5-a]pyrimidines[10]-[13] **3** and **4** from 3,5-diaminopyrazole[14a,b] (**1a-d**) (**Scheme 1**) which involves the condensation of (**1a-d**) with bifunctional electrophiles such as 1,3-diketones (**2a-c).**

Results and discussion

1. Synthesis of pyrazolo[1,5-a]pyrimidine

The reaction of aminopyrazole (**1a-d**) with symmetrical β-diketones (**2a)** or with unsymmetrical 1,3-diketones (**2b,c**) under similar conditions, we successfully demonstrated the formation of pyrazolo[1,5-a]pyrimidine **3** or **4** as the sole product with good yields. Spectral characteristics are also discussed (**Table 1**).

The pyrazolo [1,5-a] pyrimidines **3** or **4** were formed when refluxing equimolar amounts of (**2a-c**) with (**1a-d**) in absolute ethanol with drops of glacial acetic acid for an extended reaction time of 48h (**Scheme 1**).

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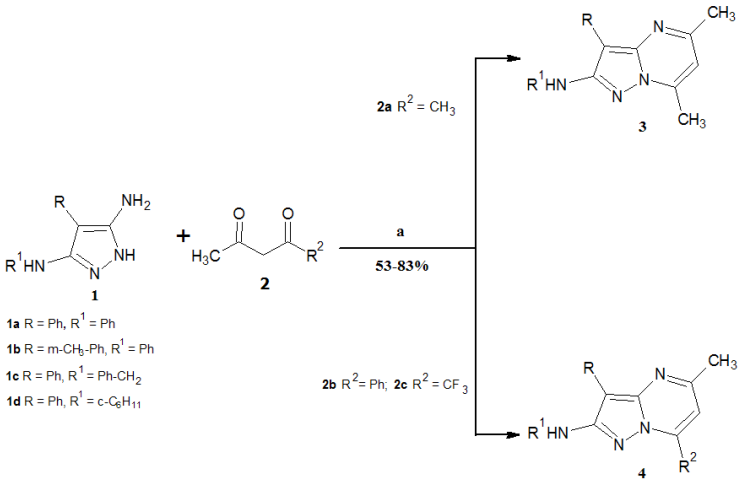


Scheme 1: Synthesis of pyrazolo[1,5-a]pyrimidine **3** or **4.**
Reagents and conditions: (a) Absolute Ethanol, acetic acid glacial, reflux, 48 h

TABLE 1: Yields of Compounds Synthesized

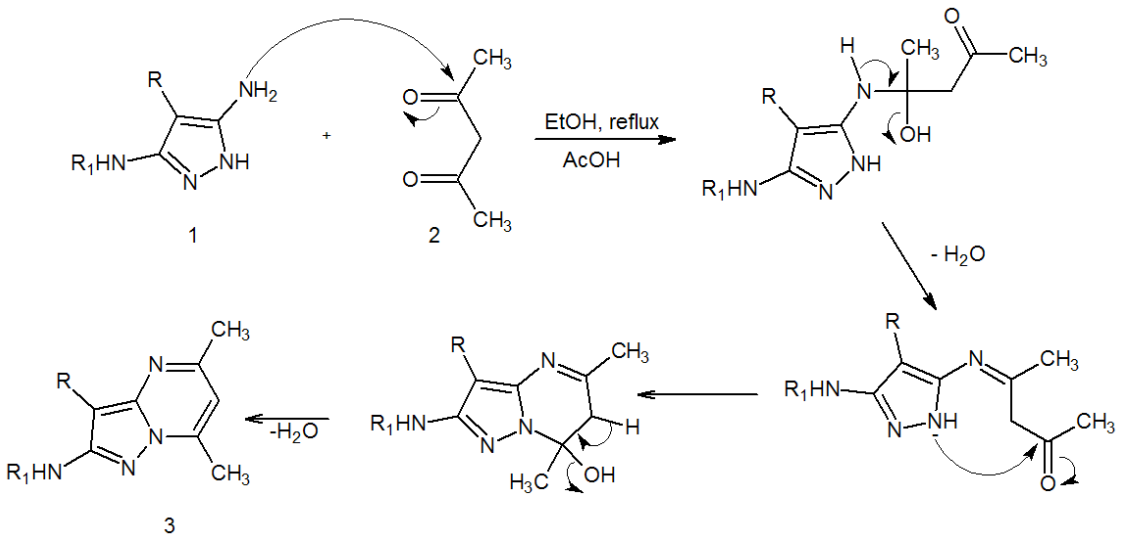
	R	R^1	R^2	Yield, (%)
3a	Ph	Ph	Me	62
3b	m-CH_3-Ph	Ph	Me	85
3c	Ph	Ph-CH_2	Me	70
3d	Ph	c-C_6H_{11}	Me	65
4e	Ph	Ph	Ph	62
4f	Ph	Ph	CF_3	62
4g	m-CH_3-Ph	Ph	Ph	64
4h	m-CH_3-Ph	Ph	CF_3	60
4i	Ph	Ph-CH_2	Ph	70
4j	Ph	Ph-CH_2	CF_3	61

The structures of all the products were confirmed on the basis of their NMR and IR spectra. The NMR spectra of the compounds were in a good agreement with their structures. Furthermore, the mass spectrum (EI) of the product (**4e**) showed a molecular ion peak at m/z = 376.11 (100%), the IR spectra of compounds **3** or **4** displayed an absorption at 1544 cm^{-1} corresponding to C=N and C=C stretching vibrations and at 3211-3278 cm^{-1} for the NH group and no NH_2 absorption at 3300-3600 cm^{-1} was observed.

The reaction of compounds (**1a-d**) with acetylacetone in refluxing ethanol provided the products (**3a-d**). The ^1H NMR spectrum of these compounds revealed a singlet at 2.7 (s, 3H) and 2,4 (s, 3H) assigned for the CH_3 group in addition to other signals attributable to the aromatic compounds.

Moreover, the reaction of compounds (**1a-c**) with appropriate unsymmetrical 1,3-diketones such as benzoylacetylacetone and 1,1,1-trifluoro-2,4-pentanedione under similar reaction conditions yielded the products (**4e-j**).

The first step of the mechanism involves the condensation of the NH_2 group of the pyrazole ring with the carbonyl group, followed by dehydration, subsequent cyclization, with loss of water (**Scheme 2**).

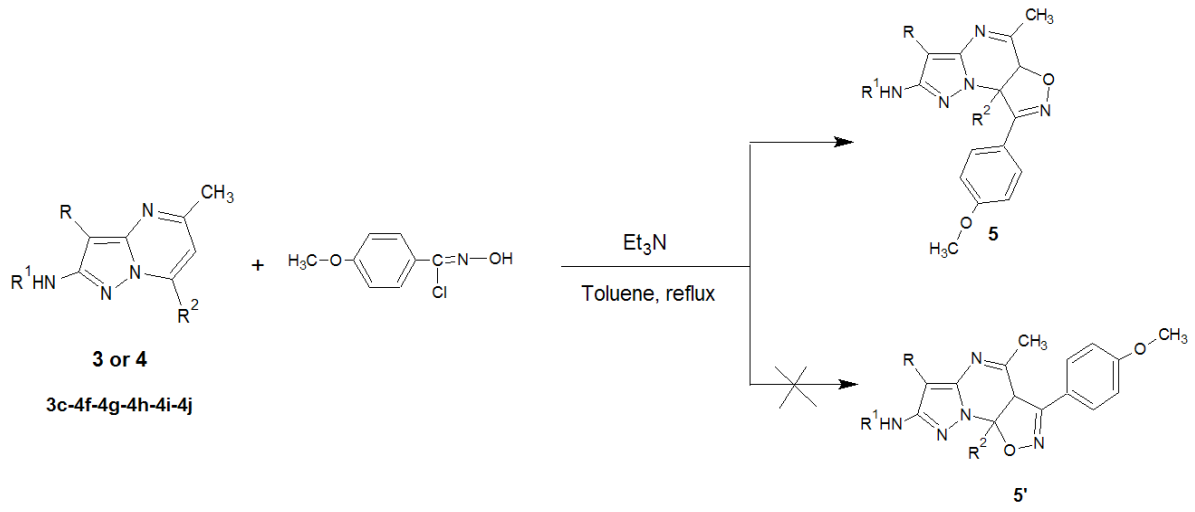


Scheme 2.

All compounds of pyrazolo[1,5-a]pyrimidines have been described.

2. Reactions of 1,3-diploar cycloaddition

In order to investigate the reaction of aminopyrazoles with bifunctional electrophiles, we studied the 1,3-dipolar cycloaddition of highly energetic nitrile oxide to alkenes. As a reaction model, the cycloaddition of dipolarophiles **3c, 4f-j** with the arylnitrile oxides (72h at reflux in toluene) was carried out according to Scheme **3** and gave **5** in good yields (table **2)**.



Scheme 3: Synthesis of isoxazoline

TABLE 2: Yields of Synthesized Compounds

	R	R^1	R^2	Yield, (%)
5c	Ph	Ph-CH_2	Me	59
5f	Ph	Ph	CF_3	35
5g	m-CH_3-Ph	Ph	Ph	53
5h	m-CH_3-Ph	Ph	CF_3	43
5i	Ph	Ph-CH_2	Ph	59
5j	Ph	Ph-CH_2	CF_3	37

The [3+2] cycloaddition reaction led to single adducts in each case, as evidenced by TLC and ^{1}H NMR examination of the crude reaction mixture. The reaction yielded regioselectively (100%) the isoxazolines **5**. The regiochemistry of the reaction was similar to that observed in an olefin activated by an electron-withdrawing group[15]-[18]. The structure of each product **5** has been confirmed by spectroscopic data. The ^{1}H NMR spectra revealed a triplet for the methoxy protons at 3.82 ppm and a singlet for the H-1 proton at 6.52 ppm besides other signals assigned to aromatics. ^{19}F NMR spectrum of the product **5f** showed a singlet peak at – 69.32 ppm. The ^{13}C NMR data also confirmed this result, showing a signal for the C=N group at 134 ppm and a quadruplet for the methoxy group. The structures of the obtained compounds **5c** and **5f** were unambiguously established by HMBC experiments; we have observed the absence of correlation between H_3 and $C_{3'}$. As a result, the cycloaddition product **5** is the only regioisomer.

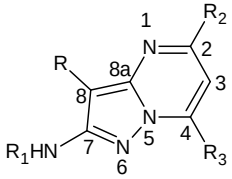
Conclusion

Efficient syntheses of novel isoxazolines have been demonstrated by the (100%) regio- and stereoselective reaction of pyrazolo[1,5-a]pyrimidines with nitrile oxides . The regiochemistry of the studied cycloaddition reaction is independent of the electronic nature of the substituent on the arylidene ring of the dipolarophile.

Experimental

The melting point was determined by Bûchi. Infrared spectra were recorded by using Shimadzu FTIR 8400S. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded at 300, 75 and 282.37 MHz respectively on a Bruker AC-300 with TMS as internal reference (for ^{1}H and ^{13}C). Materials: thin-layer chromatography (TLC): TLC plates (Merck, silica gel 60 F254 0.2 mm 200×200 nm); substances were detected using UV light at 254 nm. Mass spectra were accomplished with an HP 5889A quadripolar spectrometer by electronic impact EI (70 eV) or chemical ionization CI (500 eV) with NH_3 gas. High-Resolution Mass Spectrometry (HRMS) analyses were performed at the "Centre Commun de Spectrométrie de Masse" in Lyon (France), on a Micro-TOFOII Thermofischer Scientific for electro-spray ionization (ESI) measurements.

General procedure for the preparation of pyrazolo[1,5-a]pyrimidine



A mixture of aminopyrazole **1** (1 mmol), 1,3-diketone **2** (2 mmol), and Acetic acid glacial (0.5 mL) was heated under reflux in absolute ethanol (10mL) for 48 h, the solvent was removed under reduced pressure, the residue was treated with petroleum ether. Formed precipitate was filtrated and the residue obtained was recrystallized with ether and petroleum ether.

2,4-Dimethyl-8-phenyl-7-phenylamino-pyrazolo[1,5-a]pyrimidine 3a. mp=146°C ; ^{1}H NMR spectrum ($CDCl_3$, δppm) : 2.69 (H_3C-C=N) ; 2.35 (H_3C-C=C) ; 6.4 (HN-C_6H_5) ; 6.7-7.8 (H_{arom}); IR spectrum ($CHCl_3$, ν cm^{-1}): CH_3= 1390.40; -C=C,C=N (pyrazole ring) = 1544.18; -C=C (C_6H_5) = 1605.19; NH = 3277.96. ^{13}C NMR spectrum ($CDCl_3$, δppm): 24.75 (H_3C-C=N); 17.04 (H_3C-C=C); 159 (C_2); 106.91 (C_3); 152.93 (C_4); 145.93 (C_7); 116.91 (C_8); 120.63-144.6 (C_6H_5).

2,4-Dimethyl-8-m-tolyl-7-phenylamino-pyrazolo[1,5-a]pyrimidine 3b. mp=150°C; ^{1}H NMR spectrum ($CDCl_3$, δppm): 2.73 (H_3C-C=N) ; 2.34 (m-H_3C-C_6H_4) ; 2.65 (H_3C-C=C) ; 6.34 (HN-C_6H_5) ; 6.6-7.7 (H_{arom}) ; ^{13}C NMR spectrum ($CDCl_3$, δppm) : 23.74 (H_3C-C=N); 20.62 (m-H_3C-C_6H_4); 16.03 (H_3C-C=C); 166.67 (C_2); 105.8 (C_3); 144.58 (C_4); 151.99 (C_7); 115.91 (C_8); 115.91-143.55 (C_6H_5).

7-Benzylamino-2,4-dimethyl-8-phenyl-pyrazolo[1,5-a]pyrimidine 3c. mp=120°C; ^{1}H NMR spectrum ($CDCl_3$, δppm): 2.5 (H_3C-C=C); 2.73 (H_3C-C=N); 6.39 (HN-); 4.35 (H_2C-); 7.06-7.52 (H_{arom}) ; IR spectrum ($CHCl_3$, ν cm^{-1}): -C=C,C=N (pyrazole ring) = 1545.79; -C=C (C_6H_5) = 1617.48; NH = 3442.82. ^{13}C NMR

spectrum ($CDCl_3$, δppm) : 24.6 (H_3C-C=N); 17.6 (H_3C-C=C); 164.8 (C_2); 108.8 (C_3); 145.6 (C_4); 151.4 (C_7); 126.7-139.9 (C_6H_5).

7-Cyclohexylamino-2,4-dimethyl-8-phenyl- pyrazolo[1,5-a]pyrimidine 3d. mp= 184 °C; ^{1}H NMR spectrum ($CDCl_3$, δppm): 1.11-2.57 ($H_{cyclohexyl}$) ; 2.39 (H_3C-C=N) ; 2.65 (H_3C-C=) ; 6.5 (HN-C_6H_{11}) ; 6.7-7.4 (H_{arom}) ; IR spectrum ($CHCl_3$, ν cm^{-1}): -C=C,C=N (pyrazole ring) = 1509.82; -C=C (C_6H_5) = 1557.7; NH = 3311.96. ^{13}C NMR spectrum ($CDCl_3$, δppm) : 22.3 (H_3C-C=N); 17.2 (H_3C-C=C); 156.4 (C_2); 121.4 (C_3); 140.6 (C_4); 133.4 (C_7); 128.7-136.9 (C_6H_5).

4,8-Diphenyl-2-methyl-7-phenylamino-pyrazolo[1,5-a]pyrimidine 4e. mp=180° ; ^{1}H NMR spectrum ($CDCl_3$, δppm): 2.56 (H_3C-C=N) ; 6.5 (HN-C_6H_5) ; 6.6-8.1 (H_{arom}) ; IR spectrum ($CHCl_3$, ν cm^{-1}): C=N, C=C (pyrazole ring) = 1557.4 ; C=C (C_6H_5) = 1604.61 ; NH = 3448.32. ^{13}C NMR spectrum ($CDCl_3$, δppm): 24,84 (H_3C-C=N); 159,33 (C_2); 106.63 (C_3); 145.18 (C_4); 153.07 (C_7); 141.86 (C_7); 120,63-146,39 (C_6H_5).

2-Methyl-8-phenyl-2-phenylamino-4-(trifluoromethyl)-pyrazolo[1,5-*a*]pyrimidine 4f. mp= 156 °C; ^{1}H NMR spectrum ($CDCl_3$, δppm): 2.7 (H_3C-C=N); 6.6 (HN-C_6H_5) ; 6.7-7.7 (H_{arom}) ; IR spectrum ($CHCl_3$, ν cm^{-1}): C=C (C_6H_5) = 1609.53; C=N, C=C (pyrazole ring) = 1551.84 ; NH = 3360.83. ^{13}C NMR spectrum ($CDCl_3$, δppm): 24,6 (H_3C-C=N); CF_3 (118,9) ;165.5 (C_2); 109.7 (C_3); 138.89 (C_4); 155.5 (C_7); 117,8-140,9 (C_6H_5).

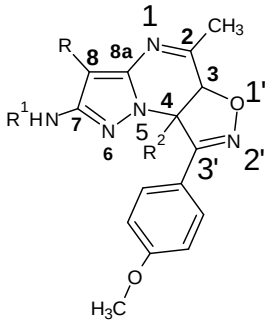
2-Methyl-8-m-tolyl-4-phenyl-7-phenylamino-pyrazolo[1,5-a]pyrimidine 4g. mp= 166 °C; ^{1}H NMR spectrum ($CDCl_3$, δppm): 2.49 (H_3C-C=N) ; 2.62 (m-H_3C-C_6H_4) ; 6.5 (HN-C_6H_5) ; 6.7-8.1 (H_{arom}) ; ^{13}C NMR spectrum ($CDCl_3$, δppm) : 24,68 (H_3C-C=N); 21,67 (m-H_3C-C_6H_4) ;159.28 (C_2); 106.55 (C_3); 146.47 (C_4); 153,11 (C_7); 120,76-145,08 (C_6H_5).

2-Methyl-8-m-tolyl-7-phenylamino-4-(trifluoromethyl)-pyrazolo[1,5-*a*]pyrimidine 4h. mp=240 °C; ^{1}H NMR spectrum ($CDCl_3$, δppm): 2.64 (H_3C-C=N); 2.42 (m-H_3C-C_6H_4) ; 6.6 (HN-C_6H_5) ; 6.7-7.7 (H_{arom}) ; ^{13}C NMR spectrum ($CDCl_3$, δppm) : 25.07 (H_3C-C=N) ; 21.62 (m-H_3C-C_6H_4); 117,78 (CF_3); 158.85 (C_2); 104.5 (C_3); 132.74 (C_4); 146.83 (C_7); 121,15-146,83 (C_6H_5).

7-Benzylamino-4,8-diphenyl-2-méthyl-pyrazolo[1,5-a]pyrimidine 4i. mp= 140 °C; ^{1}H NMR spectrum ($CDCl_3$, δppm): 2.33 (H_3C-C=N); 4 (HN-); 4.35 (H_2C-); 7.08-7.52 (H_{arom}) ; IR spectrum ($CHCl_3$, ν cm^{-1}): -C=C, C=N (pyrazole ring) = 1548.71; -C=C (C_6H_5) = 1613; NH = 3343.49. ^{13}C NMR spectrum ($CDCl_3$, δppm) : 24,6 (H_3C-C=N); 42,9 (H_2C-); 151.4 (C_2); 111.9 (C_3); 146.4 (C_4); 151.4 (C_7); 126,15-139,9 (C_6H_5).

7-Benzylamino-2-methyl-8-phenyl-4-(trifluoromethyl)-pyrazolo[1,5-*a*]pyrimidine 4j. mp= 262 °C; ^{1}H NMR spectrum ($CDCl_3$, δppm): 2.5 (H_3C-C=); 2.73 (H_3C-C=N); 4 (HN-); 4.35 (-H_2C);7.23-7.52 (H_{arom}); IR spectrum ($CHCl_3$, ν cm^{-1}): -C=C,C=N (pyrazole ring) = 1565.01; -C=C (C_6H_5) = 1622.1; NH = 3369.56. ^{13}C NMR spectrum ($CDCl_3$, δppm) : 24,6 (H_3C-C=N); 42,9 (H_2C-); 151,4 (C_2); 111,9 (C_3); 149,4 (C_4); 150,6 (C_7); 126,5-139,9 (C_6H_5).

General procedure for the preparation of the cycloadducts 5



Reactions were carried out under an atmosphere of dry N_2. Solvents were purified by standard methods and freshly distilled under nitrogen and dried before use. To a magnetically stirred solution of dipolarophiles **3** or **4** (0.5 mmol) and the appropriate precursor (0.5 mmol) of arylnitrile oxides in dry toluene, was refluxed under nitrogen for 15 min. Et_3N (0,5 mL) was then added and the mixture was stirred and refluxed for 72 h. After filtration of triethylamine hydrochloride, the solvent was evaporated under reduced pressure and the residue recrystallised from ethanol to give the product **5** respectively.

3'- (p-Methoxyphenyl) - 7- benzylamino – 2,4- dimethyl -8- phenyl - 3,4 - dihydroisoxazolo [3,4-d] pyrazolo [1,5-a] pyrimidine 5c. mp= 52°C
^{1}H NMR spectrum ($CDCl_3$, δppm): 2.5 (H_3C-C=C); 2.73 (H_3C-C=N); 3.8 (CH_3-O); 6.39 (HN); 4.35 (H_2C-); 6.3 (H_3); 7.06-7.52 (H_{arom}). ^{13}C NMR spectrum ($CDCl_3$, δppm): 24.6 (H_3C-C=N); 17.6 (H_3C-C=C); 55 (CH_3-O); 164.8 (C_2); 108.8 (C_3); 145.6 (C_4); 151.4 (C_7); 126.7-139.9 (C_6H_5).
3'- (p-Methoxyphenyl) - 2- methyl - 8 -phenyl - 7- phenylamino - 4- (trifluoromethyl)- 3,4 - dihydroisoxazolo [3,4-d] pyrazolo [1,5-a] pyrimidine 5f. mp= 131°C
^{1}H NMR spectrum ($CDCl_3$, δppm): 2.7 (H_3C-C=N); 6.6 (HN-C_6H_5) ; 3.7 (CH_3-O); 6.7-7.7 (H_{arom}) ; 6.5 (H_3); ; ^{13}C NMR spectrum ($CDCl_3$, δppm): 24,6 (H_3C-C=N); CF_3 (118,9) ;165.5 (C_2); 109.7 (C_3); 138.89 (C_4); 155.5 (C_7); 54.5 (CH_3-O); 117,8-140,9 (C_6H_5).
3'- (p-Methoxyphenyl) - 2- methyl -8- m-tolyl -4- phenyl -7- phenylamino – 3,4 - dihydroisoxazolo [3,4-d] pyrazolo [1,5-a] pyrimidine 5g. mp= 133°C
^{1}H NMR spectrum ($CDCl_3$, δppm): 2.49 (H_3C-C=N) ; 2.62 (m-H_3C-C_6H_4) ; 3.75 (CH_3-O); 6.5 (HN-C_6H_5) ; 6.5 (H_3); 6.7-8.1 (H_{arom}) ; ^{13}C NMR spectrum ($CDCl_3$, δppm) : 24,68 (H_3C-C=N); 21,67 (m-H_3C-C_6H_4) ;159.28 (C_2); 106.55 (C_3); 146.47 (C_4); 153,11 (C_7); 55.54 (CH_3-O); 120,76-145,08 (C_6H_5).
3'- (p-Methoxyphenyl) - 2- methyl - 8- m-tolyl -7- phenylamino -4 - (trifluoromethyl)-3,4-dihydroisoxazolo [3,4-d] pyrazolo [1,5-a] pyrimidine 5h. mp= 220°C
^{1}H NMR spectrum ($CDCl_3$, δppm): 2.64 (H_3C-C=N); 2.42 (m-H_3C-C_6H_4) ; 6.6 (HN-C_6H_5) ; 3.8 (CH_3-O); 5.3 (H_3); 6.7-7.7 (H_{arom}) ; ^{13}C NMR spectrum ($CDCl_3$, δppm) : 25.07 (H_3C-C=N) ; 21.62 (m-H_3C-C_6H_4); 117,78 (CF_3); 158.85 (C_2); 104.5 (C_3); 132.74 (C_4); 146.83 (C_7); 55.53 (CH_3-O)**;** 121,15-146,83 (C_6H_5).
3'- (p-Methoxyphenyl) - 7- benzylamino -4,8- diphenyl - 2 - methyl – 3,4 - dihydroisoxazolo [3,4-d] pyrazolo [1,5-a] pyrimidine 5i. mp= 137°C
^{1}H NMR spectrum ($CDCl_3$, δppm): 2.33 (H_3C-C=N); 4 (HN-); 4.35 (H_2C-); 3.8 (CH_3-O); 6.6 (H_3); 7.08-7.52 (H_{arom}) ; IR spectrum ($CHCl_3$, ν cm^{-1}): -C=C, C=N (pyrazole ring) = 1548.71; -C=C (C_6H_5) = 1613; NH = 3343.49. ^{13}C NMR spectrum ($CDCl_3$, δppm) : 24,6 (H_3C-C=N); 42,9 (H_2C-); 151.4 (C_2); 111.9 (C_3); 146.4 (C_4); 151.4 (C_7); 55.37 (CH_3-O)**;** 126,15-139,9 (C_6H_5).
3'- (p-Methoxyphenyl) - 7- benzylamino – 2 - methyl -8- phenyl – 4- (trifluoromethyl) – 3,4 - dihydroisoxazolo [3,4-d] pyrazolo [1,5-a] pyrimidine 5j. mp= 50°C
^{1}H NMR spectrum ($CDCl_3$, δppm): 2.5 (H_3C-C=); 2.73 (H_3C-C=N); 4 (HN-); 4.35 (-H_2C); 3.82 (CH_3-O); 6.8 (H_3); 7.23-7.52 (H_{arom}); IR spectrum ($CHCl_3$, ν cm^{-1}): -C=C,C=N (pyrazole ring) = 1565.01; -C=C (C_6H_5) = 1622.1; NH = 3369.56. ^{13}C NMR spectrum ($CDCl_3$, δppm) : 24,6 (H_3C-C=N); 42,9 (H_2C-); 151,4 (C_2); 111,9 (C_3); 149,4 (C_4); 150,6 (C_7); 55.54 (CH_3-O)**;**

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