New Convenient Five-Component One-Pot Synthesis of 3-Alkyl-6-amino-1,4-dihydro-4-{[(1,2,3-triazol-4-yl)methoxy]phenyl}pyrano[2,3-*c*]pyrazole-5-carbonitrile Derivatives

by **Minoo Dabiri***[a]), **Peyman Salehi***[b]), **Mahsa Fakharian**[a]), **Siyavash Kazemi Movahed**[a]), and **David I. MaGee**[c])

[a]) Department of Chemistry, Faculty of Science, Shahid Beheshti University, G. C., Evin, Tehran 1983963113, Iran (e-mail: m-dabiri@sbu.ac.ir)

[b]) Department of Phytochemistry, Medicinal Plants and Drugs Research Institute, Shahid Beheshti University, G. C., Evin, Tehran 1983963113, Iran (e-mail: p-salehi@sbu.ac.ir)

[c]) Department of Chemistry, University of New Brunswick, Fredericton, NB E3B 5A3, Canada

3-Alkyl-6-amino-1,4-dihydro-4-{[(1,2,3-triazol-4-yl)methoxy]phenyl}pyrano[2,3-*c*]pyrazole-5-carbonitrile derivatives were synthesized through a one-pot five-component condensation reaction.

Introduction. – Multicomponent reactions (MCRs) offer important benefits over linear-type syntheses due to their flexibility to accumulate three or more reactants converting them to higher-molecular-weight compounds in one-pot, and their high atom economy [1]. In recent years, by improving methods for MCRs and the combinatorial synthesis of heterocyclic compounds, these reaction techniques have emerged as valuable tools in chemical research [2].

Heterocyclic compounds bearing a 4*H*-pyran unit attracted much attention in medicinal chemistry [3]. For example, a 4*H*-pyran derivative, ethyl 2-amino-6-bromo-α-cyano-3-(ethoxycarbonyl)-4*H*-1-benzopyran-4-acetate (HA14-1), has been found to bind Bcl-2 protein and induce apoptosis of tumor cells [4]. Pyrano[2,3-*c*]pyrazoles are heterocycles that exhibit important biological features, *e.g.*, analgesic [5], antitumor, anticancer [4], and anti-inflammatory activities [6], and they also serve as potential inhibitors of human Chk1 kinase (*e.g.*, 4-(6-amino-2,4-dihydro-3,5-dimethylpyrano[2,3-*c*]pyrazol-4-yl)benzene-1,2-diol [7]). Also, spiro[3′*H*-indol-3′,4(4*H*)-pyrano[2,3-*c*]pyrazoles] have attracted attention as potential antimicrobial [8] and herbicidal [9] agents. Several synthetic approaches have been developed for the synthesis of 4-alkyl/aryl-6-amino-2,4-dihydro-3-methylpyrano[2,3-*c*]pyrazole-5-carbonitriles employing Et_3N [10][11], piperazine [12], piperidine [13], L-proline [14], γ-Al_2O_3 [15], and Mg/Al hydrotalcites [16] as catalysts.

Triazoles have attracted attention in medicinal chemistry since the introduction of the Cu^I-catalyzed 1,3-dipolar alkyne–azide coupling reaction by *Kolb* and *Sharpless* [17]. 1,2,3-Triazoles are more than just passive linkers, and possess properties such as moderate dipole character, H-bonding capability, rigidity, and stability under *in vivo* conditions [17]. 1,2,3-Triazoles display diverse biological properties including anti-HIV [18], antiallergic [19], antifungal [20], antimicrobial [21], antiasthmatic [22], and

antiviral activities [23]. Furthermore, they are used as optical brighteners, light stabilizers, and corrosion-retarding agents [24].

Several reports on improving anticancer activities of heterocyclic molecules through binding them to the 1,2,3-triazole ring have been published, *e.g.*, binding to isatin (in **A**) [25], β-lactam-chalcone (in **B**) [26], podophyllotoxins (in **C**) [27], and 2′,3′-dideoxy-2′,3′-diethane thionucleosides (in **D**) [28] (*Fig. 1*).

In conjunction with our research aimed at the development of methods for the synthesis of heterocyclic compounds and their linkage to 1,2,3-triazoles through 1,3-dipolar cycloaddition [29], herein we report a very simple and highly efficient one-pot five-component reaction for the synthesis of 3-alkyl-6-amino-1,4-dihydro-4-{[(1,2,3-triazol-4-yl)methoxy]phenyl}pyrano[2,3-*c*]pyrazole-5-carbonitrile derivatives as new compounds for combinatorial libraries.

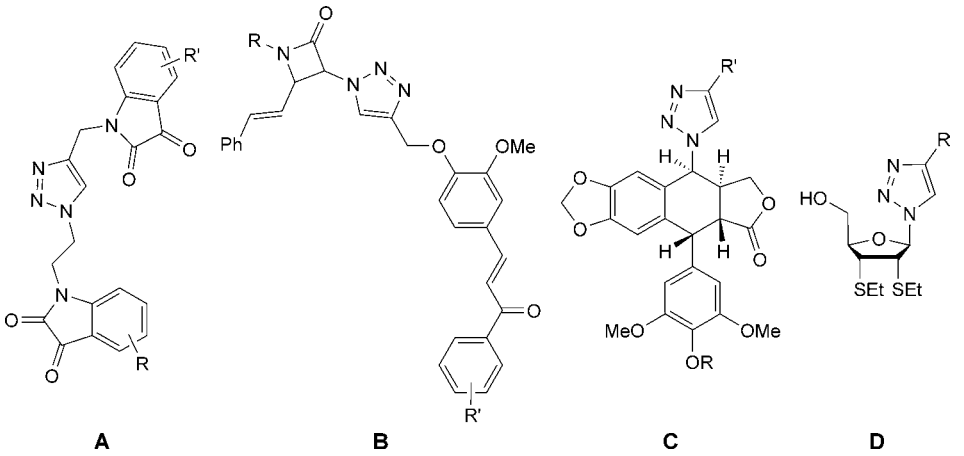
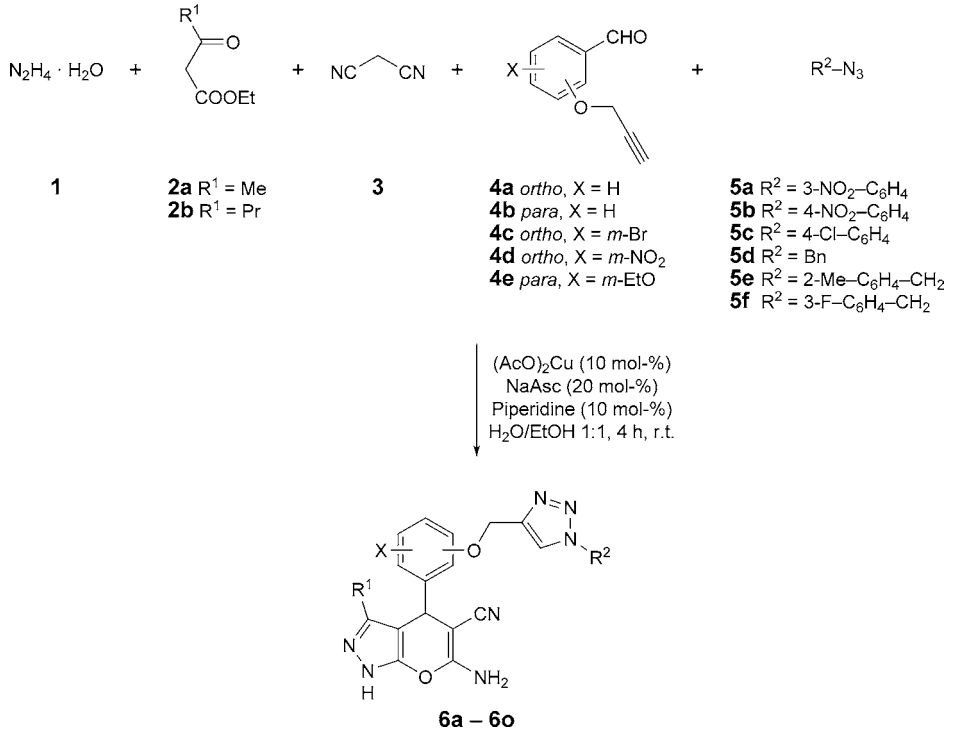


Figure. *Some important 1,2,3-triazoles with anticancer activities*

Results and Discussion. – A one-pot, five-component reaction of $N_2H_4 \cdot H_2O$ (**1**), active methylene compounds, such as β-keto esters **2a** and **2b**, malononitrile (propared,3-dinitrile; **3**), various aromatic propargyloxy ((prop-2-ynxyl)oxy) aldehydes, **4a**–**4e**, and azides, **5a**–**5f**, was designed, using piperidine (10 mol-%) and $(AcO)_2Cu$ (10 mol-%)/sodium ascorbate (NaAsc; 20 mol-%) as catalysts. The reactions were performed in H_2O/EtOH 1:1 at room temperature to furnish the target compounds, **6a**–**6o** (*Scheme 1*).

The reaction of $N_2H_4 \cdot H_2O$ (**1**) with ethyl acetoacetate (**2a**), **3**, 4-(prop-2-yn-1-yloxy)benzaldehyde (**4b**), and 4-azido-1-nitrobenzene (**5b**) was selected as model reaction for the optimization of various parameters, such as amount of the catalyst, reaction temperature, and solvent (*Table 1*). It is worth mentioning, that in the absence of piperidine in H_2O at different temperatures, the target compound **6h** was not formed (*Table 1*, *Entries 1*–*3*). Therefore, we investigated the reaction in different solvents, such as H_2O, EtOH, 1-methyl-1*H*-imidazolium trifluoroacetate ([Hmim]TFA), ^{t}BuOH, and H_2O/EtOH. In the presence of piperidine in H_2O at room temperature,

Scheme 1. *One-Pot Synthesis of 3-Alkyl-6-amino-4-{[(1,2,3-triazol-4-yl)methoxy]phenyl} pyrano[2,3-c]pyrazole-5-carbonitrile Derivatives*



the reaction was very slow, and **6h** was obtained in 58% yield (*Table 1*, *Entry 4*), but under reflux the desired compound was not obtained at all (*Table 1*, *Entry 5*). In another attempt, we used [Hmim]TFA as solvent at different temperatures, but no product was formed (*Table 1*, *Entries 6* and *7*). We also used EtOH and ^{t}BuOH as solvents in the presence of piperidine, and only in case of EtOH, **6h** was isolated in 47% yield (*Table 1*, *Entries 8* and *9*). In the presence of different Cu sources such as CuI and Cu_2O, **6h** was obtained in low yields (*Table 1*, *Entries 10–12*). After several attempts, $(AcO)_2Cu$ was selected as the best source and, in case of the reaction in H_2O/EtOH 1:1 at room temperature, the desired product, **6h**, was isolated in 78% yield (*Table 1*, *Entry 13*).

Under the optimized conditions, substituted active methylene compounds **2a** and **2b**, aromatic propargyloxy aldehydes **4a**–**4e**, and azides **5a**–**5f** were reacted in the presence of piperidine (10 mol-%) and $(AcO)_2Cu$ (10 mol-%)/NaAsc (20 mol-%) as catalysts in H_2O/EtOH 1:1 as solvent at room temperature for 4 h to afford the corresponding 1,4-dihydropyrano[2,3-*c*]pyrazoles **6a**–**6o** in good yields. The results are compiled in *Table 2*.

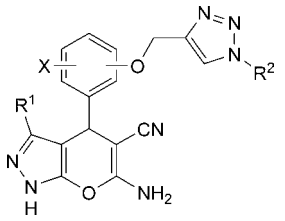
Generally, the results presented in *Table 2* show the diversity of the reactants for obtaining combinatorial libraries. Fortunately, we found that this transformation is applicable to a wide range of propargylated benzaldehydes, 1,3-dicarbonyl compounds,

Table 1. *Optimization of Reaction Conditions for the Synthesis of* **6h**[a])

Entry	Catalyst	Solvent	Temp. [°]	Yield [%][b])
1	$(AcO)_2Cu$/NaAsc	H_2O	r.t.	0
2	$(AcO)_2Cu$/NaAsc	H_2O	70	0
3	$(AcO)_2Cu$/NaAsc	H_2O	Reflux	0
4[c])	$(AcO)_2Cu$/NaAsc/piperidine	H_2O	r.t.	58
5[c])	$(AcO)_2Cu$/NaAsc/piperidine	H_2O	Reflux	0
6[d])	$(AcO)_2Cu$/NaAsc	[Hmim]TFA	r.t.	0
7[d])	$(AcO)_2Cu$/NaAsc	[Hmim]TFA	100	0
8[c])	$(AcO)_2Cu$/NaAsc/piperidine	EtOH	Reflux	47
9[c])	$(AcO)_2Cu$/NaAsc/piperidine	*t*BuOH	Reflux	0
10[e])	CuI/piperidine	H_2O	r.t.	23
11[e])	Cu_2O/piperidine	H_2O	r.t.	0
12[e])	Cu_2O/piperidine	H_2O	Reflux	0
13[c])	$(AcO)_2Cu$/NaAsc/piperidine	H_2O/EtOH	r.t.	78

[a]) Reagents and conditions: $N_2H_4 \cdot H_2O$ (0.05 ml, 1 mmol), ethyl acetoacetate (0.13 ml, 1 mmol), malononitrile (0.65 g, 1 mmol), 4-(prop-2-yn-1-yloxy)benzaldehyde (0.16 g, 1 mmol), and 1-azido-4-nitrobenzene (0.16 g, 1 mmol), $(AcO)_2Cu$ (0.02 g, 10 mol-%), NaAsc (0.04 g, 20 mol-%), solvent (10 ml), 4 h. [b]) Yields of the isolated products. [c]) Piperidine (10 mol-%). [d]) 1-Methyl-1*H*-imidazolium trifluoroacetate ([Hmim]TFA; 10 mol-%), under solvent-free conditions. [e]) Cu Sources (10 mol-%).

Table 2. *One-Pot Five-Component Synthesis of 3-Alkyl-6-amino-1,4-dihydro-4-{[(1,2,3-triazol-4-yl)-methoxy]phenyl}pyrano[2,3-c]pyrazole-5-carbonitriles* **6a**–**6o**



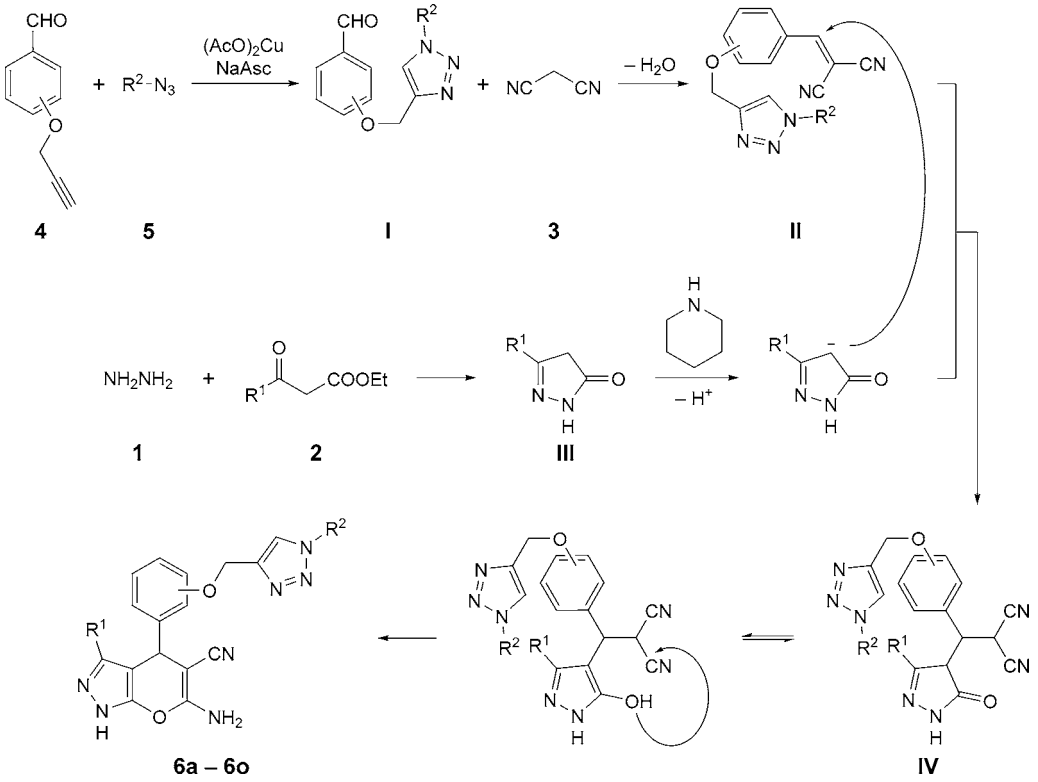
Compound	R^1	X	RO Position	R^2	Yield [%][a])
6a	Me	H	*ortho*	4-NO_2–C_6H_4	87
6b	Me	H	*ortho*	Bn	74
6c	Pr	H	*ortho*	Bn	78
6d	Pr	H	*ortho*	2-Me–C_6H_4–CH_2	74
6e	Pr	H	*ortho*	3-F–C_6H_4–CH_2	90
6f	Me	H	*para*	3-NO_2–C_6H_4	86
6g	Pr	H	*para*	3-NO_2–C_6H_4	82
6h	Me	H	*para*	4-NO_2–C_6H_4	85
6i	Pr	H	*para*	4-NO_2–C_6H_4	80
6j	Me	H	*para*	4-Cl–C_6H_4	81
6k	Pr	H	*para*	4-Cl–C_6H_4	79
6l	Me	H	*para*	Bn	80
6m	Me	3-Br	*ortho*	Bn	75
6n	Me	3-NO_2	*ortho*	4-NO_2–C_6H_4	77
6o	Pr	3-EtO	*para*	Bn	65

[a]) Yields of the isolated products.

and azides, providing an easy access to densely substituted 1,2,3-triazole-linked 1,4-dihydropyrano[2,3-*c*]pyrazoles **6a**–**6o** in good-to-high yields (65–90%).

Mechanistically, we assume that this reaction proceeds *via* the following key steps: *i*) *Huisgen* 1,3-dipolar cycloaddition between propargylated benzaldehyde **4** and azide **5**, leading to triazole derivative **I** as intermediate (formation of **I** was confirmed by comparison with an authentic sample on TLC), *ii*) formation of intermediate **II** *via Knoevenagel* condensation of **I** and **3**, *iii*) addition of intermediate **III** (formed *in situ* by reaction of **1** with **2**) to give intermediate **IV**, followed by cyclization to afford the product, compound **6** (*Scheme 2*).

Scheme 2. *Proposed Mechanism for the Synthesis of* **6a**–**6o**



In conclusion, a highly efficient and novel method for the synthesis of 3-alkyl-6-amino-1,4-dihydro-4-{[(1,2,3-triazol-4-yl)methoxy]phenyl}pyrano[2,3-*c*]pyrazole-5-carbonitrile derivatives through a five-component condensation of active-methylene compounds, $N_2H_4 \cdot H_2O$, malononitrile, various aromatic propargyloxy aldehydes, and azides in high yield and excellent atomic economy is reported. The method is mild, simple, efficient, and environmentally benign using H_2O/EtOH as solvent.

We gratefully acknowledge financial support from the *Research Council of Shahid Beheshti University.*

Experimental Part

General. The chemicals were obtained from *Fluka* and *Merck*, and used without further purification. M.p.: *Electrothermal 9100* apparatus; uncorrected. IR Spectra: *BOMEM MB* series FT-IR apparatus; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker DRX-300 Avance* (300.1 and 75.5 MHz, resp.) or *Varian Unity 400* spectrometer (399.9 and 100.6 MHz, resp.); in (D_6)DMSO; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. EI-MS: *Shimadzu GCMS-QP1100EX* mass spectrometer (70 eV); in *m*/*z*. Elemental analyses: *Elementar Analysensysteme GmbH VarioEL* CHNS elemental analyzer; in %.

General Procedure for the Preparation of **6a**–**6o**. $N_2H_4 \cdot H_2O$ (**1**; 1 mmol), β-keto esters (**2a** and **2b**; 1 mmol), malononitrile (**3**; 1 mmol), various aromatic propargyloxy aldehydes (**4a**–**4e**; 1 mmol), and azides (**5a**–**5f**; 1 mmol) in the presence of $(AcO)_2Cu$ (10 mol-%), NaAsc (20 mol-%), and piperidine (10 mol-%) in H_2O/EtOH 1:1 (2 ml) as solvent were mixed thoroughly, and then the mixture was stirred for 4 h at r.t. After cooling, conc. NH_3 (2 ml) and H_2O (5 ml) were added, and stirring was continued for 30 min. The solid was filtered and washed with hot EtOH to give the corresponding pure products.

*6-Amino-1,4-dihydro-3-methyl-4-(2-{[1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}phenyl)pyrano[2,3-*c*]pyrazole-5-carbonitrile* (**6a**). Yield: 409 mg (87%). M.p. 240–242°. IR (KBr): 3359, 3308, 2199, 1520, 1339. ^1H-NMR: 1.77 (*s*, Me); 5.05 (*s*, CH); 5.30 (*s*, CH_2); 6.81–7.25 (*m*, 4 arom. H, NH_2); 8.25 (*d*, *J* = 8.5, 2 arom. H); 8.46 (*d*, *J* = 8.5, 2 arom. H); 9.02 (*s*, 1 arom. H); 12.01 (*s*, NH). ^{13}C-NMR: 10.0; 56.9; 62.2; 98.3; 113.2; 121.3; 121.4; 122.0; 123.3; 126.0; 128.4; 129.6; 132.9; 135.7; 135.8; 141.3; 145.2; 147.2; 155.4; 155.5; 161.8. Anal. calc. for $C_{23}H_{18}N_8O_4$ (470.15): C 58.72, H 3.86, N 23.82; found: C 58.76, H 3.88, N 23.79.

*6-Amino-4-{2-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]phenyl}-1,4-dihydro-3-methylpyrano[2,3-*c*]pyrazole-5-carbonitrile* (**6b**). Yield: 325 mg (74%). M.p. 180° (dec.). IR (KBr): 3468, 3282, 3116, 2176. ^1H-NMR: 1.70 (*s*, Me); 4.97 (*s*, CH); 5.17 (*s*, CH_2); 5.61 (*s*, CH_2); 6.81–7.34 (*m*, 9 arom. H, NH_2); 8.23 (*s*, 1 arom. H); 11.99 (*s*, NH). ^{13}C-NMR: 10.0; 53.3; 56.6; 62.4; 95.8; 113.1; 121.3; 121.8; 124.9; 128.3; 128.7; 129.1; 129.2; 129.4; 132.9; 133.7; 136.5; 140.9; 155.4; 155.5; 159.2; 161.9. Anal. calc. for $C_{24}H_{21}N_7O_2$ (439.18): C 65.59, H 4.82, N 22.31; found: C 65.65, H 4.83, N 22.32.

*6-Amino-4-{2-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]phenyl}-1,4-dihydro-3-propylpyrano[2,3-*c*]pyrazole-5-carbonitrile* (**6c**). Yield: 364 mg (78%). M.p. 178–180°. IR (KBr): 3468, 3340, 3180, 2181. ^1H-NMR: 0.61 (*t*, *J* = 6.87, Me); 1.12–1.24 (*m*, CH_2); 2.01–2.16 (*m*, CH_2); 4.54 (*s*, CH); 5.09 (*s*, CH_2); 5.60 (*s*, CH_2); 6.83–7.35 (*m*, 9 arom. H, NH_2); 8.28 (*s*, 1 arom. H); 12.10 (*s*, NH). ^{13}C-NMR: 13.8; 21.4; 26.7; 36.1; 53.3; 58.2; 61.5; 98.0; 114.4; 121.3; 125.1; 128.2; 128.4; 128.6; 128.9; 129.0; 129.2; 136.5; 137.7; 140.2; 143.5; 155.1; 157.3; 161.0. Anal. calc. for $C_{26}H_{25}N_7O_2$ (467.21): C 66.79, H 5.39, N 20.97; found: C 66.84, H 5.41, N 20.95.

*6-Amino-4-(2-{[1-(2-methylbenzyl)-1*H*-1,2,3-triazol-4-yl]methoxy}phenyl)-1,4-dihydro-3-propylpyrano[2,3-*c*]pyrazole-5-carbonitrile* (**6d**). Yield: 356 mg (74%). M.p. 140–142°. IR (KBr): 3468, 3340, 3180, 2181. ^1H-NMR: 0.47 (*t*, *J* = 7.2, Me); 0.98–1.11 (*m*, CH_2); 2.02–2.11 (*m*, CH_2); 2.31 (*s*, Me); 4.99 (*s*, CH); 5.15 (*s*, CH_2); 5.62 (*s*, CH_2); 6.76–7.24 (*m*, 8 arom. H, NH_2); 8.10 (*s*, 1 arom. H); 11.98 (*s*, NH). ^{13}C-NMR: 13.6; 19.1; 21.5; 26.4; 51.4; 55.4; 57.1; 62.5; 98.1; 113.1; 121.4; 121.9; 124.80; 126.7; 128.3; 128.7; 129.0; 129.6; 130.6; 133.43; 134.6; 136.7; 139.9; 143.6; 155.3; 155.5; 161.7. Anal. calc. for $C_{27}H_{27}N_7O_2$ (481.22): C 67.34, H 5.65, N 20.36; found: C 67.38, H 5.66, N 20.34.

*6-Amino-4-(2-{[1-(3-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl]methoxy}phenyl)-1,4-dihydro-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile* (**6e**). Yield: 437 mg (90%). M.p. 160–162°. IR (KBr): 3470, 3279, 3135, 2184, 755. ^1H-NMR: 0.46 (*t*, *J* = 7.25, Me); 0.99–1.11 (*m*, CH_2); 2.02–2.49 (*m*, CH_2); 5.01 (*s*, CH); 5.18 (*s*, CH_2); 5.65 (*s*, CH_2); 6.81–7.42 (*m*, 8 arom. H, NH_2); 8.25 (*s*, 1 arom. H); 12.01 (*s*, NH). ^{13}C-NMR: 13.5; 21.5; 26.4; 52.6; 52.6; 57.1; 62.5; 98.1; 113.1; 115.1; 115.3; 115.3; 115.5; 121.4; 121.8; 124.4 (*d*, *J* = 2.8); 124.9; 128.3; 129.6; 131.3 (*d*, *J* = 4.0); 133.5; 139.1; 139.9; 143.8; 155.3 (*d*, *J* = 22.1); 161.7; 162.7 (*d*, *J* = 244.4). Anal. calc. for $C_{26}H_{24}FN_7O_2$ (485.20): C 64.32, H 4.98, N 20.19; found: C 64.38, H 5.00, N 20.15.

*6-Amino-1,4-dihydro-3-methyl-4-(4-{[1-(3-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}phenyl)pyrano[2,3-*c*]pyrazole-5-carbonitrile* (**6f**). Yield: 404 mg (86%). M.p. 208–210°. IR (KBr): 3396, 3311, 2188, 1536, 1350. ^{1}H-NMR: 1.77 (*s*, Me); 4.54 (*s*, CH); 5.22 (*s*, CH_2); 6.80–8.72 (*m*, 8 arom. H, NH_2); 9.15 (*s*, 1 arom. H); 12.05 (*s*, NH). ^{13}C-NMR: 10.2; 57.9; 61.4; 98.3; 115.0; 115.4; 115.7; 121.3; 123.7; 123.8; 126.7; 129.0; 132.0; 136.0; 137.5; 137.6; 144.9; 149.0; 155.2; 157.2; 161.2. Anal. calc. for $C_{23}H_{18}N_8O_4$ (470.15): C 58.72, H 3.86, N 23.82; found: C 58.74, H 3.87, N 23.81.

*6-Amino-1,4-dihydro-4-(4-{[1-(3-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}phenyl)-3-propylpyrano[2,3-*c*]pyrazole-5-carbonitrile* (**6g**). Yield: 408 mg (82%). M.p. 198–200°. IR (KBr): 3482, 3233, 2186, 1536, 1348. ^{1}H-NMR: 0.60 (*s*, Me); 1.15–1.19 (*m*, CH_2); 2.06–2.14 (*m*, CH_2); 4.55 (*s*, CH); 5.24 (*s*, CH_2); 6.85–7.11 (*m*, 4 arom. H, NH_2); 7.89–8.74 (*m*, 4 arom. H); 9.19 (*s*, 1 arom. H); 12.11 (*s*, NH). ^{13}C-NMR: 13.3; 20.9; 26.2; 35.6; 57.7; 61.0; 97.5; 114.6; 114.9; 120.8; 123.2; 123.3; 126.2; 128.6; 131.6; 137.1; 137.5; 139.7; 144.4; 148.5; 154.6; 156.7; 160.6. Anal. calc. for $C_{25}H_{22}N_8O_4$ (498.18): C 60.24, H 4.45, N 22.48; found: C 60.25, H 4.46, N 22.48.

*6-Amino-1,4-dihydro-3-methyl-4-(4-{[1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}phenyl)pyrano[2,3-*c*]pyrazole-5-carbonitrile* (**6h**). Yield: 400 mg (85%). M.p. 208–210°. IR (KBr): 3396, 3311, 2188, 1536, 1350. ^{1}H-NMR: 1.79 (*s*, Me); 4.56 (*s*, CH); 5.24 (*s*, CH_2); 6.85–7.13 (*m*, 4 arom. H, NH_2); 8.25 (*d*, $J = 8.8$, 2 arom. H); 8.46 (*d*, $J = 8.8$, 2 arom. H); 9.16 (*s*, 1 arom. H); 12.09 (*s*, NH). ^{13}C-NMR: 9.8; 55.6; 61.0; 97.8; 114.6; 115.2; 120.7; 120.8; 123.3; 125.6; 128.6; 129.9; 137.1; 140.8; 144.6; 146.8; 154.7; 156.7; 160.5. Anal. calc. for $C_{23}H_{18}N_8O_4$ (470.15): C 58.72, H 3.86, N 23.82; found: C 58.75, H 3.87, N 23.80.

*6-Amino-1,4-dihydro-4-(4-{[1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}phenyl)-3-propylpyrano[2,3-*c*]pyrazole-5-carbonitrile* (**6i**). Yield: 399 mg (80%). M.p. 192–194°. IR (KBr): 3470, 3252, 2183, 1530, 1341. ^{1}H-NMR: 0.59 (*s*, Me); 1.13–1.21 (*m*, CH_2); 2.04–2.14 (*m*, CH_2); 4.56 (*s*, CH); 5.24 (*s*, CH_2); 6.84–7.10 (*m*, 4 arom. H, NH_2); 8.23 (*d*, $J = 7.8$, 2 arom. H); 8.44 (*d*, $J = 7.8$, 2 arom. H); 9.15 (*s*, 1 arom. H); 12.10 (*s*, NH). ^{13}C-NMR: 13.2; 20.8; 26.1; 35.6; 57.8; 60.9; 97.4; 114.6; 120.6; 120.9; 123.1; 125.4; 128.5; 137.4; 139.8; 140.7; 144.5; 146.8; 154.6; 156.6; 160.5. Anal. calc. for $C_{25}H_{22}N_8O_4$ (498.18): C 60.24, H 4.45, N 22.48; found: C 60.26, H 4.46, N 22.47.

*6-Amino-4-(4-{[1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}phenyl)-1,4-dihydro-3-methylpyrano[2,3-*c*]pyrazole-5-carbonitrile* (**6j**). Yield: 372 mg (81%). M.p. 217–219°. IR (KBr): 3482, 3248, 2190, 798. ^{1}H-NMR: 1.78 (*s*, Me); 4.55 (*s*, CH); 5.20 (*s*, CH_2); 6.82–7.69 (*m*, 4 arom. H, NH_2); 7.95–7.97 (*m*, 4 arom. H); 8.97 (*s*, 1 arom. H); 12.07 (*s*, NH). ^{13}C-NMR: 9.8; 57.5; 61.0; 97.8; 114.6; 120.8; 121.9; 122.9; 128.6; 128.7; 129.9; 133.0; 135.4; 135.5; 137.0; 144.1; 154.7; 156.7; 160.7. Anal. calc. for $C_{23}H_{18}ClN_7O_2$ (459.12): C 60.07, H 3.95, N 21.32; found: C 60.09, H 3.97, N 21.30.

*6-Amino-4-(4-{[1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}phenyl)-1,4-dihydro-3-propylpyrano[2,3-*c*]pyrazole-5-carbonitrile* (**6k**). Yield: 385 mg (79%). M.p. 185° (dec.). IR (KBr): 3351, 3149, 2183, 828. ^{1}H-NMR: 0.60 (*s*, Me); 1.05–1.21 (*m*, CH_2); 2.06–2.13 (*m*, CH_2); 4.55 (*s*, CH); 5.21 (*s*, CH_2); 6.83–7.09 (*m*, 4 arom. H, NH_2); 7.67 (*d*, $J = 7.56$, 2 arom. H); 7.95 (*d*, $J = 7.56$, 2 arom. H); 8.97 (*s*, 1 arom. H); 12.10 (*s*, NH). ^{13}C-NMR: 13.3; 20.9; 26.2; 35.6; 57.7; 61.0; 97.5; 114.6; 120.8; 121.8; 122.9; 128.5; 128.6; 129.9; 133.0; 135.4; 137.4; 139.7; 144.1; 154.6; 156.7; 160.6. Anal. calc. for $C_{25}H_{22}ClN_7O_2$ (487.15): C 61.54, H 4.54, N 20.09; found: C 61.59, H 4.55, N 20.08.

*6-Amino-4-{4-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]phenyl}-1,4-dihydro-3-methylpyrano[2,3-*c*]pyrazole-5-carbonitrile* (**6l**). Yield: 591 mg (80%). M.p. 192–194°. IR (KBr): 3426, 3248, 3133, 2189. ^{1}H-NMR: 1.78 (*s*, Me); 4.55 (*s*, CH); 5.11 (*s*, CH_2); 5.61 (*s*, CH_2); 6.84–7.36 (*m*, 9 arom. H, NH_2); 8.27 (*s*, 1 arom. H); 12.09 (*s*, NH). ^{13}C-NMR: 9.8; 52.8; 57.6; 61.1; 97.9; 114.5; 120.9; 124.7; 128.0; 128.2; 128.5; 128.8; 135.6; 136.6; 136.0; 136.9; 143.1; 154.8; 156.8; 160.8. Anal. calc. for $C_{24}H_{21}N_7O_2$ (439.18): C 65.59, H 4.82, N 22.31; found: C 65.61, H 4.83, N 22.32.

*6-Amino-4-{2-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]-5-bromophenyl}-1,4-dihydro-3-methylpyrano[2,3-*c*]pyrazole-5-carbonitrile* (**6m**). Yield: 388 mg (75%). M.p. 175–177°. IR (KBr): 3376, 3317, 3164, 2182, 1591. ^{1}H-NMR: 1.72 (*s*, Me); 4.95 (*s*, CH); 5.18 (*s*, CH_2); 5.61 (*s*, CH_2); 6.92–8.35 (*m*, 8 arom. H, NH_2); 8.75 (*s*, 1 arom. H); 12.08 (*s*, NH). Anal. calc. for $C_{24}H_{20}BrN_7O_2$ (517.09): C 55.61, H 3.89, N 18.91; found: C 55.59, H 3.90, N 18.92. Due to the very low solubility, we could not record the ^{13}C-NMR spectrum of **6m**.

*6-Amino-1,4-dihydro-3-methyl-4-(5-nitro-2-{[1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}phenyl)pyrano[2,3-*c*]pyrazole-5-carbonitrile* (**6n**). Yield: 396 mg (77%). M.p. 240–242°. IR (KBr): 3258,

3117, 2186, 1594, 1343. ^{1}H-NMR: 1.79 (*s*, Me); 5.11 (*s*, CH); 5.49 (*s*, CH_2); 6.95–8.26 (*m*, 5 arom. H, NH_2); 8.46 (*d*, $J = 7.71$, 2 arom. H); 9.01 (*s*, 1 arom. H); 12.11 (*s*, NH). ^{13}C-NMR: 9.7; 55.5; 62.4; 97.5; 113.3; 120.9; 123.2; 124.3; 125.4; 126.3; 128.7; 133.6; 140.7; 141.3; 143.5; 146.9; 148.6; 152.9; 154.8; 156.7; 161.6. Anal. calc. for $C_{23}H_{17}N_9O_6$ (515.13): C 53.59, H 3.32, N 24.46; found: C 53.63, H 3.33, N 24.45.

*6-Amino-4-{4-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]-3-ethoxyphenyl}-1,4-dihydro-3-propyl pyrano[2,3-*c*]pyrazole-5-carbonitrile* (**6o**). Yield: 332 mg (65%). M.p. 177–179°. IR (KBr): 3470, 3321, 3228, 2199. ^{1}H-NMR: 0.62 (*t*, $J = 7.2$, Me); 1.17–1.31 (*m*, CH_2, Me); 2.05–2.12 (*m*, CH_2); 3.91 (*q*, $J = 6.8$, CH_2); 4.53 (*s*, CH); 5.08 (*s*, CH_2); 5.60 (*s*, CH_2); 6.66–7.36 (*m*, 8 arom. H, NH_2); 8.23 (*s*, 1 arom. H); 12.09 (*s*, NH). ^{13}C-NMR: 13.3; 14.6; 21.0; 26.2; 36.0; 52.8; 57.6; 62.0; 63.8; 97.3; 113.0; 114.3; 119.6; 124.7; 127.9; 127.9; 128.1; 128.7; 128.8; 136.0; 138.1; 139.8; 143.2; 148.1; 154.6; 160.6. Anal. calc. for $C_{28}H_{29}N_7O_3$ (511.23): C 65.74, H 5.71, N 19.17; found: C 65.81, H 5.73, N 19.14.

REFERENCES

[1] L. Weber, *Drug Discovery Today* **2002**, *7*, 143; A. Dömling, *Curr. Opin. Chem. Biol.* **2002**, *6*, 306.
[2] A. Nefzi, J. M. Ostresh, R. A. Houghten, *Chem. Rev. (Washington, DC, U.S.)* **1997**, *97*, 449; L. A. Thompson, *Curr. Opin. Chem. Biol.* **2000**, *4*, 324.
[3] M. N. Elinson, A. S. Dorofeev, S. K. Feducovich, S. V. Gorbunov, R. F. J. Nasybullin, N. O. Stepanov, G. I. Nikishin, *Tetrahedron Lett.* **2006**, *47*, 7629; J. P. Gesson, N. Fonteneau, M. Mondon, S. Charbit, H. Ficheux, F. Schutze, U.S. Pat. 6,965,039 B2, 2005.
[4] J.-L. Wang, D. Liu, Z.-J. Zhang, S. Shan, X. Han, S. M. Srinivasula, C. M. Croce, E. S. Alnemri, Z. Huang, *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 7124.
[5] S. C. Kuo, L. J. Huang, H. Nakamura, *J. Med. Chem.* **1984**, *27*, 539.
[6] M. E. A. Zaki, H. A. Soliman, O. A. Hiekal, A. E. Rashad, *Z. Naturforsch., C* **2006**, *61*, 1.
[7] N. Foloppe, L. M. Fisher, R. Howes, A. Potter, A. G. S. Robertson, A. E. Surgenor, *Bioorg. Med. Chem.* **2006**, *14*, 4792.
[8] A. H. Abdel-Rahman, E. M. Keshk, M. A. Hanna, S. M. El-Bady, *Bioorg. Med. Chem.* **2004**, *12*, 2483.
[9] K. C. Joshi, R. Jain, S. Arora, *J. Indian Chem. Soc.* **1988**, *65*, 277.
[10] H. Junek, H. Aigner, *Chem. Ber.* **1973**, *106*, 914.
[11] Y. A. Sharanin, L. G. Sharanina, V. V. Puzanova, *Zh. Org. Khim.* **1983**, *19*, 2609; Y. A. Sharanin, L. G. Sharanina, V. V. Puzanova, *J. Org. Chem. USSR (Engl. Transl.)* **1983**, *19*, 221; H. M. Al-Matar, K. D. Khalil, A. Y. Adam, M. H. Elnagdi, *Molecules* **2010**, *15*, 6619.
[12] Y. Peng, G. Song, R. Dou, *Green Chem.* **2006**, *8*, 573.
[13] G. Vasuki, K. Kumaravel, *Tetrahedron Lett.* **2008**, *49*, 5636.
[14] H. Mecadon, M. R. Rohman, I. Kharbangar, B. M. Laloo, I. Kharkongor, M. Rajbangshi, B. Myrboh, *Tetrahedron Lett.* **2011**, *52*, 3228.
[15] H. Mecadon, M. R. Rohman, M. Rajbangshi, B. Myrboh, *Tetrahedron Lett.* **2011**, *52*, 2523.
[16] S. W. Kshirsagar, N. R. Patil, S. D. Samant, *Synth. Commun.* **2011**, *41*, 1320.
[17] H. C. Kolb, K. B. Sharpless, *Drug Discovery Today* **2003**, *8*, 1128.
[18] R. Alvarez, S. Velazquez, A. San-Felix, S. Aquaro, E. De Clercq, C.-F. Perno, A. Karlsson, J. Balzarini, M. J. Camarasa, *J. Med. Chem.* **1994**, *37*, 4185.
[19] D. R. Buckle, C. J. M. Rockell, H. Smith, B. A. Spicer, *J. Med. Chem.* **1986**, *29*, 2262.
[20] C. B. Vicentini, V. Brandolini, M. Guarneri, P. Giori, *Farmaco* **1992**, *47*, 1021; J. C. Fung-Tomc, E. Huczko, B. Minassian, D. P. Bonner, *Antimicrob. Agents Chemother.* **1998**, *42*, 313.
[21] M. J. Genin, D. A. Allwine, D. J. Anderson, M. R. Barbachyn, D. E. Emmert, S. A. Garmon, D. R. Graber, K. C. Grega, J. B. Hester, D. K. Hutchinson, J. Morris, R. J. Reischer, C. W. Ford, G. E.Zurenko, J. C. Hamel, R. D. Schaadt, D. Stapert, B. H. Yagi, *J. Med. Chem.* **2000**, *43*, 953.
[22] Y. Naito, F. Akahoshi, S. Takeda, T. Okada, M. Kajii, H. Nishimura, M. Sugiura, C. Fukaya, Y. Kagitani, *J. Med. Chem.* **1996**, *39*, 3019.
[23] O. Makabe, H. Suzuki, S. Umezawa, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2689.
[24] N. Gouault, J.-F. Cupif, A. Sauleau, M. David, *Tetrahedron Lett.* **2000**, *41*, 7293.

[25] P. Singh, P. Sharma, A. Anand, P. M. S. Bedi, T. Kaur, A. K. Saxena, V. Kumar, *Eur. J. Med. Chem.* **2012**, *55*, 455.
[26] P. Singh, R. Raj, V. Kumar, M. P. Mahajan, P. M. S. Bedi, T. Kaur, A. K. Saxena, *Eur. J. Med. Chem.* **2012**, *47*, 594.
[27] D. M. Reddy, J. Srinivas, G. Chashoo, A. K. Saxena, H. M. S. Kumar, *Eur. J. Med. Chem.* **2011**, *46*, 1983.
[28] J.-L. Yu, Q.-P. Wu, Q.-S. Zhang, Y.-H. Liu, Y.-Z. Li, Z.-M. Zhou, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 240.
[29] M. Dabiri, P. Salehi, M. Bahramnejad, F. Sherafat, *J. Comb. Chem.* **2010**, *12*, 638; P. Salehi, M. Dabiri, M. Koohshari, S. K. Movahed, M. Bararjanian, *Mol. Diversity* **2011**, *15*, 833; P. Salehi, D. I. MaGee, M. Dabiri, L. Torkian, J. Donahue, *Mol. Diversity* **2012**, *16*, 231; D. I. MaGee, P. Salehi, M. Dabiri, M. Bahramnejad, *Synth. Commun.* **2013**, *43*, 486; L. Torkian, M. Dabiri, P. Salehi, M. Bararjanian, *Helv. Chim. Acta* **2011**, *94*, 1416.

Received July 27, 2014