ISSN 1070-3632, Russian Journal of General Chemistry, 2019, Vol. 89, No. 4, pp. 831–835. © Pleiades Publishing, Ltd., 2019.

Synthesis and Anticancer Activity of 1,2,3-Triazole Fused *N*-Arylpyrazole Derivatives

R. Lakkakula[a], A. Roy[a]*, K. Mukkanti[b], and G. Sridhar[c]

[a] *GVK Biosciences Private Limited, Medicinal Chemistry Division, 28A, Nacharam, IDA-Mallapur, Hyderabad, Telangana, 500076 India*
**e-mail: sridhar1org@gmail.com*

[b] *Department of Chemistry, Jawaharlal Nehru Technological University–Hyderabad, Kukatpally, Hyderabad, Telangana, 500085 India*

[c] *Organic and Biomolecular Chemistry Division, CSIR–Indian Institute of Chemical Technology, Hyderabad, 50010 India*

Received February 3, 2019; revised April 3, 2019; accepted April 9, 2019

Abstract—A novel series of triazole derivatives **11a**–**11j** is synthesized. **S**tructures of the products are confirmed by ^{1}H and ^{13}C NMR, and mass spectral data. The anticancer activities of compounds **11a**–**11j** are evaluated against three human cancer cell lines (MCF-7, A549, and A375) using the standard MTT assay in vitro, using doxorubicin as the positive control. All the compounds exhibit significant activity against cancer cell lines. The compounds **11a, 11d, 11e, 11g,** and **11j** demonstrate more potent activity than the positive control.

Keywords: celecoxib, rimonabant, pyrazole, 1,2,3-triazole and anticancer activity

DOI: 10.1134/S1070363219040315

INTRODUCTION

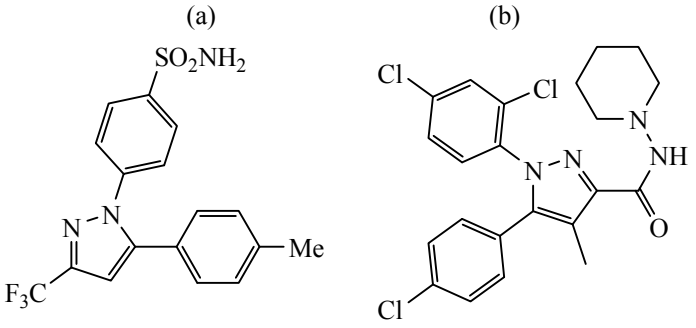
Pyrazole derivatives demonstrate a broad spectrum of biological activities, including anticancer [1], anti-inflammatory [2], anticonvulsant [3], antipyretic [4], and antimicrobial [5, 6]. Celecoxib **1** [7] and Rimonabant **2** [8] are pyrazole core containing drugs available on the market (see the figure).

1,2,3-Triazole derivatives also play an important role in pharmaceutical chemistry [9]. Generally, 1,2,3-triazoles are synthesized by the Huisgen 1,3-dipolar cycloaddition reaction catalyzed by Cu(I) [10].

In view of the above we have synthesized a novel series of 1,2,3-triazole derivatives combined with *N*-arylpyrazoles **11a**–**11j**. The synthesized compounds **11a**–**11j** were tested for their anticancer activity against different human cancer cell lines.

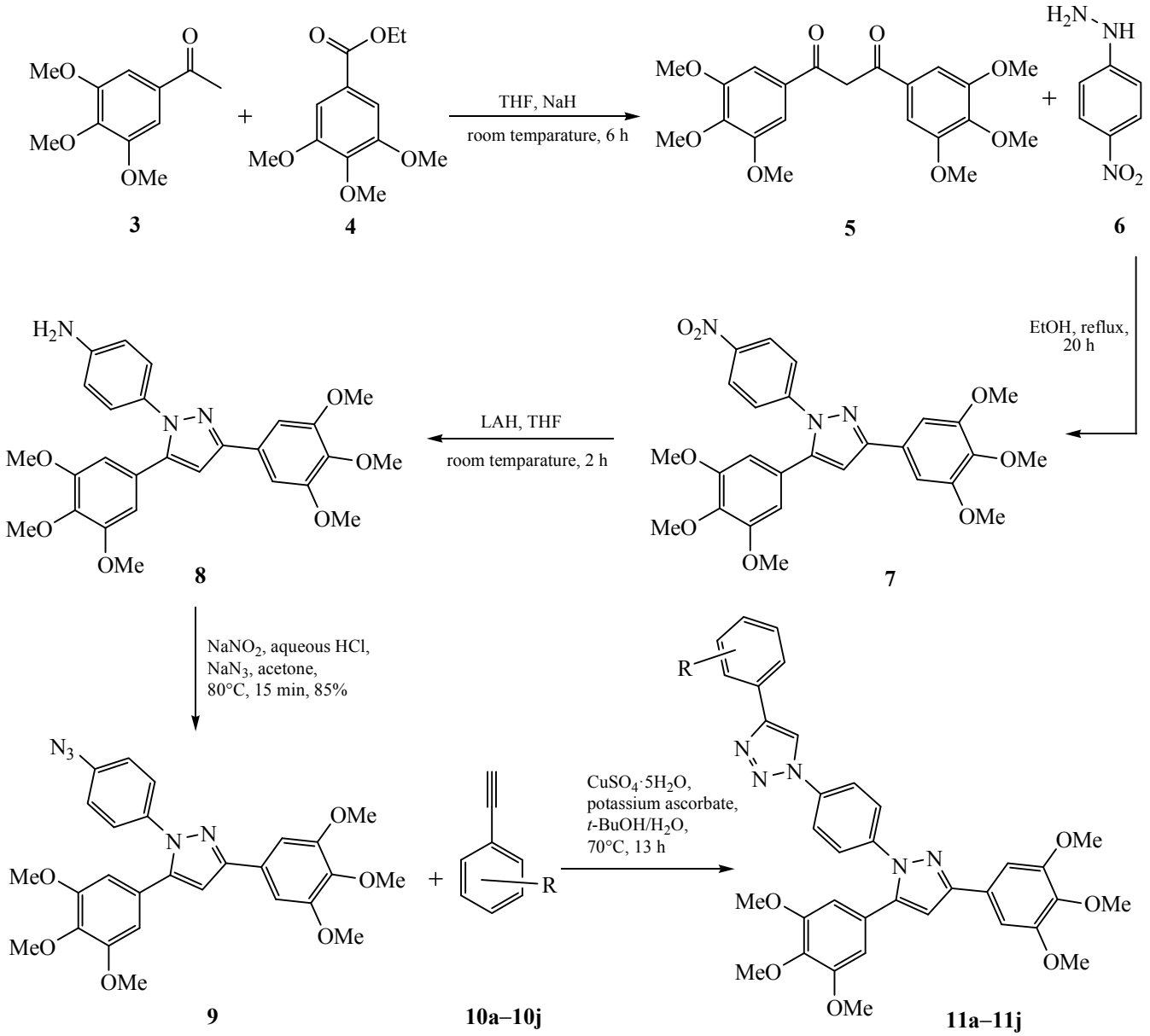
RESULTS AND DISCUSSION

Synthesis of the key intermediate 1-(4-azidophenyl)-3,5-bis(3,4,5-trimethoxyphenyl)-1*H*-pyrazole (**9**) (Scheme 1) started with the reaction of 1-(3,4,5-trimethoxyphenyl)ethanone (**3**) with ethyl 3,4,5-trimethoxybenzoate (**4**) which gave 1,3-bis(3,4,5-



Structures of compounds (a) **1** and (b) **2**.

Scheme 1.



R = H (**10a, 11a**), 3,4,5-trimethoxy (**10b, 11b**), 4-methoxy (**10c, 11c**), 4-bromo (**10d, 11d**), 4-trifluoro (**10e, 11e**), 3,5-ditrifluoro (**10f, 11f**), 3,5-difluoro (**10g, 11g**), 2,4,6-trimethyl (**10h, 11h**), 3,5-dimethoxy (**10i, 11i**), 4-nitro (**10j, 11j**).

trimethoxyphenyl)propane-1,3-dione (**5**). Its following reaction with 1-(4-nitrophenyl)hydrazine (**6**) led to pyrazole intermediate (**7**) with high yield. Reduction of compound **7** by $LiAlH_4$ in THF gave the amine intermediate **8**, diazotation of which followed by the Sand Mayer reaction afforded the azide **9**. The Huisgen 1,3-dipolar cycloaddition of intermediate **9** with substituted aromatic alkynes **10a**–**10j** upon prolonged heating at 70°C afforded the corresponding final compounds **11a**–**11j.**

In vitro cytotoxicity. The newly synthesized compounds were tested for their cytotoxicity against three human tumor cell lines: breast (MCF-7), lung (A-549), and melanoma (A-375) cells using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Here doxorubicin was used as a positive control (see the table). All tested compounds exhibited potent anticancer activity with IC_{50} values ranging from 0.13 to 9.34 μM. Activity of the compounds **11a, 11d, 11e, 11g,** and **11j** was higher than that of the positive control.

EXPERIMENTAL

All chemicals were obtained from Aldrich (Sigma–Aldrich, St. Louis, MO, USA), Lancaster (Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA) and used without further purification. Progress of the reactions was monitored by TLC, performed on silica gel glass plates containing 60 F-254, and visualized under UV light or by iodine indicator. ^{1}H and ^{13}C NMR spectra were measured on a Bruker UXNMR/XWIN-NMR (300 MHz) spectrometer using DMSO-d_6 as a solvent and TMS as an internal standard. ESI spectra were measured on a Micro mass, Quattro LC using ESI+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. Melting points were determined on an electrothermal melting point apparatus, and are uncorrected.

1,3-Di(3,4,5-trimethoxyphenyl)-1,3-propanedione (5). To a solution of 3,4,5-trimethoxyacetophenone **3** (30 g, 142.7 mmol) in dry THF (300 mL), NaH (6.8 g, 285.4 mmol) was added in portions under the atmosphere of N_2 maintaining temperature below –5°C. After stirring the mixture at this temperature for 30 min, ethyl 3,4,5-trimethoxybenzoate (**4**) (51.4 g, 214 mmol) was added, and the reaction mixture was stirred at room temperature for 6 h. After completion of reaction, the solvent was evaporated, and the residue was mixed with ice-water, acidified with HCl (1N) to pH 6 and extracted with ethyl acetate (3 ×100 mL). The combined organic layers were washed with water (50 mL) and dried over Na_2SO_4. The solvent was evaporated, the solid residue was washed with hexane and dried under high vacuum to provide a solid mass, which was re-dissolved in CH_2Cl_2 and dried under high vacuum to give diketone **5** as white solid, yield 94%. ^{1}H NMR spectrum, δ, ppm: 3.93 s (12H), 3.95 s (6H), 6.61 s (1H), 7.19 s (4H), 16.94 br.s (1H). MS (ESI): 405 $[M + H]^+$.

1-(4-Nitrophenyl)-3,5-di(3,4,5-trimethoxyphenyl)-1*H*-pyrazole (7). 4-Nitrophenylhydazine (**6**) (20.4 g, 133.6 mmol) was added upon stirring to a solution of diketone **5** (45 g, 111.3 mmol) in ethanol (100 mL). The reaction mixture was stirred upon refluxing for 20 h, then it was concentrated in vacuum. The residue was mixed with ethyl acetate, washed with water and dried over Na_2SO_4. The crude product was purified by column chromatography with ethyl acetate–hexane (6 : 4) to afford pure compound **7** (yield 85%). ^{1}H NMR spectrum, δ, ppm: 3.87 s (6H), 3.91 s (3H), 3.93 s (6H), 3.96 s (3H), 6.93 s (1H), 7.20 s (2H), 7.27 d (2H, J = 8.13 Hz), 7.30 s (2H), 7.57 d (2H, J = 8.13 Hz). MS (ESI): 522 $[M + H]^+$.

In vitro cytotoxicity data of target compounds **11a–11j**

Compound	IC_{50}, μM		
	MCF-7	A-549	A375
11a	1.78	2.90	0.23
11b	3.78	2.98	2.22
11c	3.67	5.60	Not active
11d	1.90	1.11	1.44
11e	0.10	0.13	1.20
11f	7.65	2.11	4.56
11g	0.22	2.44	0.33
11h	8.12	2.09	3.23
11i	9.34	Not active	Not active
11j	0.34	0.76	0.89
Doxorubicin	2.02	2.18	5.51

4-[3,5-Di(3,4,5-trimethoxyphenyl)-1*H*-1-pyrazolyl]-aniline (8). To a solution of 1-(4-nitrophenyl)-3,5-di-(3,4,5-trimethoxyphenyl)-1*H*-pyrazole **7** (46 g, 88.2 mmol) in dry THF (150 mL) was added $LiAlH_4$ (13.4 g, 353.1 mmol). The mixture was vigorously stirred at room temperature for 2 h. The mixture was then cooled down, quenched with aq Na_2SO_4, filtered on acelite pad, and concentrated under reduce pressure to remove THF. The aqueous layer was extracted with ethyl acetate (30 mL). The organic extracts were dried, and the solvent was evaporated to give a pure compound **8** (yield 96%). ^{1}H NMR spectrum, δ, ppm: 3.86 s (6H), 3.91 s (3H), 3.93 s (6H), 3.95 s (3H), 6.45 br.s (2H), 6.93 s (1H), 7.13 d (2H, J = 8.10 Hz), 7.19 s (2H), 7.28 s (2H), 7.54 d (2H, J = 8.10 Hz). MS (ESI): 492 $[M + H]^+$.

1-(4-Azidophenyl)-3,5-bis(3,4,5-trimethoxyphenyl)-1*H*-pyrazole (9). A solution of HCl (0.2 N, 50 mL) was added to a solution of 4-[3,5-di(3,4,5-trimethoxyphenyl)-1*H*-1-pyrazolyl]aniline **8** (39 g, 79.4 mmol) in acetone (100 mL) at 0°C. After 20 min of stirring, $NaNO_2$ (16.4 g, 238.2 mmol) was added to the mixture within 20 min followed by addition of NaN_3 (15.4 g, 238.2 mmol). After 15 min of stirring, the product was extracted by diethyl ether (100 mL), the combined extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography with ethyl acetate–hexane (2 : 8) to afford pure compound **9** (yield 79%). ^{1}H NMR spectrum, δ, ppm: 3.86

s (6H), 3.91 s (3H), 3.93 s (6H), 3.96 s (3H), 6.94 s (1H), 7.20 s (2H), 7.29 d (2H, J = 8.14 Hz), 7.36 s (2H), 7.56 d (2H, J = 8.14 Hz). MS (ESI): 518 $[M + H]^+$.

Synthesis of compounds 11a–11j. Compound **9** (500 mg, 9.67 mmol) and an ethynylbenzene **10a–10j** (9.67 mmol) were mixed in *n*-BuOH–H_2O (1 : 1, 10 mL) in a sealed tube in presence of $CuSO_4 \cdot 5H_2O$ (24 mg, 0.096 mmol) and potassium ascorbate (207 mg, 0.967 mmol). The reaction mixture was stirred at 70°C for 13 h. Upon cooling down, the reaction mixture was poured into H_2O (16 mL) at 0°C, and the precipitate was filtered off and washed with H_2O. The crude product was purified by column chromatography with ethyl acetate–hexane (3 : 7) to afford the corresponding pure compound **11a–11j**.

1-{4-[3,5-Bis(3,4,5-trimethoxyphenyl)-1*H*-pyrazol-1-yl]phenyl}-4-phenyl-1*H*-1,2,3-triazole (11a). Yield 69%, mp 310–312°C. ^{1}H NMR spectrum, δ, ppm: 3.87 s (6H), 3.91 s (3H), 3.93 s (6H), 3.95 s (3H), 6.95 s (1H), 7.21 s (2H), 7.36 s (2H), 7.40–7.47 m (3H), 7.52 d (2H, J = 8.10 Hz), 7.56 d (2H, J = 8.14 Hz), 8.12 d (2H, J = 8.14 Hz), 8.28 s (1H). ^{13}C NMR spectrum, δ, ppm: 57.4, 57.9, 61.6, 61.9, 106.5, 107.4, 108.3, 116.7, 125.6, 125.8, 126.2, 127.8, 128.3, 129.4, 129.6, 132.2, 137.4, 141.3, 142.6, 144.4, 147.5, 148.2, 151.6, 154.8, 155.6. MS (ESI): 620 $[M + H]^+$.

1-{4-[3,5-Bis(3,4,5-trimethoxyphenyl)-1*H*-pyrazol-1-yl]phenyl}-4-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazole (11b). Yield 65%, mp 321–323°C. ^{1}H NMR spectrum, δ, ppm: 3.87 s (6H), 3.89 s (6H), 3.91 s (3H), 3.93 s (6H), 3.95 s (3H), 3.96 s (3H), 6.95 s (1H), 7.20 s (2H), 7.35 s (2H), 7.41 s (2H), 7.55 d (2H, J = 8.13 Hz), 8.11 d (2H, J = 8.13 Hz), 8.27 s (1H). ^{13}C NMR spectrum, δ, ppm: 56.4, 57.6, 57.9, 60.3, 61.6, 61.9, 106.2, 106.7, 108.2, 111.4, 116.4, 125.7, 126.3, 127.4, 128.5, 129.1, 137.4, 141.6, 142.8, 144.3, 144.7, 147.4, 149.6, 151.4, 154.6, 154.8, 156.7. MS (ESI): 710 $[M + H]^+$.

1-{4-[3,5-Bis(3,4,5-trimethoxyphenyl)-1*H*-pyrazol-1-yl]phenyl}-4-(4-methoxyphenyl)-1*H*-1,2,3-triazole (11c). Yield 70%, mp 317–319°C. ^{1}H NMR spectrum, δ, ppm: 3.78 s (3H), 3.86 s (6H), 3.91 s (3H), 3.93 s (6H), 3.95 s (3H), 6.95 s (1H), 7.21 s (2H), 7.28 d (2H, J = 8.09 Hz), 7.34 s (2H), 7.54–7.65 m (4H), 8.10 d (2H, J = 8.13 Hz), 8.27 s (1H). ^{13}C NMR spectrum, δ, ppm: 55.5, 57.4, 57.6, 61.6, 61.7, 106.4, 107.7, 108.6, 115.6, 116.7, 124.4, 125.6, 125.9, 127.3, 128.6, 129.4, 137.5, 141.3, 142.7, 144.6, 147.6, 148.6, 151.3, 154.6, 155.6, 160.5. MS (ESI): 650 $[M + H]^+$.

1-{4-[3,5-Bis(3,4,5-trimethoxyphenyl)-1*H*-pyrazol-1-yl]phenyl}-4-(4-bromophenyl)-1*H*-1,2,3-triazole (11d). Yield 76%, mp 330–332°C. ^{1}H NMR spectrum, δ, ppm: 3.87 s (6H), 3.93 s (3H), 3.94 s (6H), 3.96 s (3H), 6.96 s (1H), 7.21 s (2H), 7.29–7.35 m (4H), 7.57 d (2H, J = 8.15 Hz), 7.62 d (2H, J = 8.13 Hz), 8.12 d (2H, J = 8.13 Hz), 8.28 s (1H). ^{13}C NMR spectrum, δ, ppm: 57.7, 57.8, 61.8, 61.9, 106.7, 107.6, 108.7, 116.7, 122.4, 125.6, 125.9, 127.3, 128.5, 129.5, 131.4, 132.6, 137.5, 141.4, 142.7, 144.5, 147.2, 147.8, 151.1, 154.2, 155.7. MS (ESI): 699 $[M + H]^+$.

1-{4-[3,5-Bis(3,4,5-trimethoxyphenyl)-1*H*-pyrazol-1-yl]phenyl}-4-[4-(trifluoromethyl)phenyl]-1*H*-1,2,3-triazole (11e). Yield 71%, mp 305–307°C. ^{1}H NMR spectrum, δ, ppm: 3.88 s (6H), 3.93 s (3H), 3.94 s (6H), 3.96 s (3H), 6.95 s (1H), 7.20 s (2H), 7.28 s (2H), 7.34 d (2H, J = 8.13 Hz), 7.56 d (2H, J = 8.16 Hz), 7.60 d (2H, J = 8.16 Hz), 8.11 d (2H, J = 8.13 Hz), 8.27 s (1H). ^{13}C NMR spectrum, δ, ppm: 57.8, 57.9, 61.7, 61.9, 106.5, 107.5, 108.7, 116.7, 121.5, 125.6, 125.8, 126.7, 127.5, 128.6, 129.3, 129.7, 133.5, 137.5, 141.4, 142.6, 144.3, 147.4, 147.9, 151.5, 154.6, 155.7. MS (ESI): 688 $[M + H]^+$.

1-{4-[3,5-Bis(3,4,5-trimethoxyphenyl)-1*H*-pyrazol-1-yl]phenyl}-4-[3,5-bis(trifluoromethyl)phenyl]-1*H*-1,2,3-triazole (11f). Yield 64%, mp 309–311°C. ^{1}H NMR spectrum, δ, ppm: 3.88 s (6H), 3.93 s (3H), 3.94 s (6H), 3.96 s (3H), 6.96 s (1H), 7.21 s (2H), 7.29 s (2H), 7.35 d (2H, J = 8.13 Hz), 7.39 s (1H), 7.42 s (2H), 8.11 d (2H, J = 8.13 Hz), 8.27 s (1H). ^{13}C NMR spectrum, δ, ppm: 57.6, 57.8, 61.6, 61.8, 106.8, 107.6, 108.6, 116.7, 119.6, 123.5, 125.6, 125.9, 127.4, 129.6, 130.6, 131.5, 134.6, 137.7, 141.3, 142.4, 144.7, 147.6, 150.5, 151.6, 154.8, 155.9. MS (ESI): 756 $[M + H]^+$.

1-{4-[3,5-Bis(3,4,5-trimethoxyphenyl)-1*H*-pyrazol-1-yl]phenyl}-4-(3,5-difluorophenyl)-1*H*-1,2,3-triazole (11g). Yield 66%, mp 290–292°C. ^{1}H NMR spectrum, δ, ppm: 3.86 s (6H), 3.92 s (3H), 3.94 s (6H), 3.95 s (3H), 6.96 s (1H), 7.20–7.27 m (3H), 7.30 s (2H), 7.34 s (2H), 7.39 d (2H, J = 8.10 Hz), 8.11 d (2H, J = 8.10 Hz), 8.27 s (1H). ^{13}C NMR spectrum, δ, ppm: 57.6, 57.8, 61.6, 61.8, 104.5, 106.4, 107.5, 108.7, 114.7, 116.8, 125.7, 125.9, 127.3, 129.5, 135.3, 136.4, 137.6, 141.3, 142.6, 144.5, 147.5, 151.3, 154.7, 155.8, 159.4. MS (ESI): 656 $[M + H]^+$.

1-{4-[3,5-Bis(3,4,5-trimethoxyphenyl)-1*H*-pyrazol-1-yl]phenyl}-4-mesityl-1*H*-1,2,3-triazole (11h). Yield 65%, mp 296–298°C. ^{1}H NMR spectrum, δ, ppm: 2.23 s (3H), 2.32 s (6H), 3.86 s (6H), 3.90 s (3H), 3.93 s

(6H), 3.94 s (3H), 6.94 s (1H), 7.20 s (2H), 7.24 s (2H), 7.29 s (2H), 7.34 d (2H, J = 8.09 Hz), 8.07 d (2H, J = 8.09 Hz), 8.26 s (1H). ^{13}C NMR spectrum, δ, ppm: 21.6, 22.7, 57.6, 57.8, 61.6, 61.8, 106.3, 107.4, 108.6, 116.5, 125.6, 125.9, 127.3, 129.5, 129.6, 130.8, 136.5, 137.6, 138.5, 141.3, 142.3, 144.7, 147.5, 148.6, 151.8, 154.3, 155.2. MS (ESI): 662 $[M + H]^+$.

1-{4-[3,5-Bis(3,4,5-trimethoxyphenyl)-1*H*-pyrazol-1-yl]phenyl}-4-(3,5-dimethoxyphenyl)-1*H*-1,2,3-triazole (11i). Yield 67%, mp 327–329°C. ^{1}H NMR spectrum, δ, ppm: 3.76 s (6H), 3.86 s (6H), 3.90 s (3H), 3.93 s (6H), 3.94 s (3H), 6.67 s (1H), 6.95 s (1H), 7.20 s (2H), 7.27 s (2H), 7.31 s (2H), 7.35 d (2H, J = 8.10 Hz), 8.08 d (2H, J = 8.10 Hz), 8.25 s (1H). ^{13}C NMR spectrum, δ, ppm: 54.3, 57.6, 57.8, 61.5, 61.7, 99.5, 106.5, 107.4, 108.4, 111.7, 116.7, 125.7, 125.9, 127.4, 129.6, 133.4, 137.6, 141.3, 142.7, 144.7, 147.4, 149.2, 151.3, 154.8, 155.9, 158.7. MS (ESI): 680 $[M + H]^+$.

1-{4-[3,5-Bis(3,4,5-trimethoxyphenyl)-1*H*-pyrazol-1-yl]phenyl}-4-(4-nitrophenyl)-1*H*-1,2,3-triazole (11j). Yield 78%, mp 337–339°C. ^{1}H NMR spectrum, δ, ppm: 3.87 s (6H), 3.92 s (3H), 3.93 s (6H), 3.95 s (3H), 6.95 s (1H), 7.21 s (2H), 7.28 s (2H), 7.32 d (2H, J = 8.16 Hz), 7.37 d (2H, J = 8.14 Hz), 8.12–8.17 m (4H), 8.27 s (1H). ^{13}C NMR spectrum, δ, ppm: 57.6, 57.8, 61.7, 61.9, 106.7, 107.8, 108.6, 116.8, 125.6, 125.8, 126.7, 127.8, 129.4, 131.4, 137.4, 138.3, 141.3, 142.5, 144.5, 147.2, 147.8, 148.1, 151.6, 154.6, 155.9. MS (ESI): 665 $[M + H]^+$.

MTT assay. Cytotoxic activity of the compounds **11a**–**11j** was determined using MTT assay. 1×10^4 cells/well were seeded in 200 mL DMEM, supplemented with 10% FBS in each well of 96-well microculture plates and incubated for 24 h at 37°C in a CO_2 incubator. Compounds, diluted to the desired concentrations in culture medium, were added to the wells with respective vehicle control. After 48 h of incubation, 10 mL of MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] (5 mg/mL) were added to each well and the plates were further incubated for 4 h. Then the supernatant from each well was carefully removed, formazan crystals were dissolved in 100 mL of DMSO and absorbance at 540 nm wavelength was recorded.

CONCLUSIONS

A series of 1,2,3-triazole containing *N*-arylpyrazole derivatives **11a**–**11j** is synthesized, and their structures are confirmed by ^{1}H and ^{13}C NMR, and mass spectra. All target compounds **11a**–**11j** are evaluated for their antitumor activity against MCF-7, A549 and A375 cancer cell lines by the MTT assay. Among these, com-pounds **11a, 11d, 11e, 11g**, and **11j** demonstrate more potent activity than the positive control doxorubicin.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

REFERENCES

1. Shi, J.B., Tang, W.J., Qi, X.B., Li, R., and Liu, X.H., *Eur. J. Med. Chem*., 2015, vol. 90, p. 889. doi 10.1016/j.ejmech.2014.12.013
2. Bekhit, A.A., Ashour, H.M., Bekhit, A.E.D.A., and Bekhit, S.A., *Med. Chem.,* 2009, vol. 5, p. 103. doi 10.2174/157340609787582936
3. Abdel-Aziz, M., Abuo-Rahma, G.E.D.A., and Hassan, A.A., *Eur. J. Med. Chem*., 2009, vol. 44, p. 3480. doi 10.1016/j.ejmech.2009.01.032
4. Carmo Malvar, D., Teixeira Ferreira, R., Castro, R.A., Castro, L.L., Carreira Freitas, A.C., Costa, E.A., and Souza, G.E.P., *Life Sci*., 2014, vol. 95, p. 81. doi 10.1016/j.lfs.2013.12.005
5. Song, M.X., Zheng, C.J., Deng, X.Q., Sun, L P., Wu, Y., and Piao, H.R., *Eur. J. Med. Chem*., 2013, vol. 60, p. 376. doi 10.1016/j.ejmech.2012.12.007
6. Gadakh, A.V., Pandit, C., Rindhe, S.S., and Karale, B.K., *Bioorg. Med. Chem. Lett*., 2010, vol. 20, p. 5572. doi 10.1016/j.bmcl.2010.07.019
7. Penning, T.D., Talley, J.J., Bertenshaw, S.R., Carter, J.S., Collins, P.W., Docter, S., Graneto, M.J., Lee, L.F., Malecha, J.W., Miyashiro, J.M., Rogers, R.S., Rogier, D.J., Yu, S.S., Anderson, G.D., Burton, E.G., Cogburn, J.N., Gregory, S.A., Koboldt, C.M., Perkins, W.E., Seibert, K., Veenhuizen, A.W., Zhang, Y.Y., and Isakson, P.C., *J. Med. Chem.* 1997, vol. 40, p. 1347. doi 10.1021/jm960803q
8. Elguero, J. and Rees, C.W., *Compr. Heterocycl. Chem. II*, 1996, vol. 3, p. 1.
9. (a) Nicolaou, K.C., Bulger, P.G., and Sarlah, D., *Angew Chem. Int. Ed*., 2005, vol. 44, p. 4442. doi 10.1002/anie.200500368; (b) Carey, J.S., Laffan, D., Thomson, C., and Williams, M.T., *Org. Biomol. Chem*., 2006, vol. 4, p. 2337. doi 10.1039/B602413K; (c) Floris, C., Thomas, B., and Florence, M., *Org. Biomol. Chem*., 2012, vol. 10, p. 4878. doi 10.1039/C2OB25554E; (d) Jeong, Y.Y. and Ryu, J.S., *J. Org. Chem*., 2010, 75, p. 4183. doi 10.1021/jo100618d
10. (a) Huisgen, R., Szeimies, G., and Möbius, L., *Chem. Ber*., 1967, vol. 100, p. 2494. doi 10.1002/cber.19671000806; (b) Huisgen, R., Knorr, R., Möbius, L., and Szeimies, G., *Chem. Ber*., 1965, vol. 98, p. 4014. doi 10.1002/cber.19650981228; (c) Huisgen, R., *Angew. Chem. Int. Ed.,* 1963, vol. 2, p. 633. doi 10.1002/anie.196306331;(d) Huisgen, R., *Angew. Chem. Int. Ed.,* 1963, vol. 2, p. 565. doi 10.1002/anie.196305651