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Anticancer Properties of some Novel 2-Hetaryl-3-(5-Arylfuran-2-yl)-Acrylonitriles

Yuliia Matiichuk [1], Taras Chaban [1], Vasyl Matiychuk [2,*]

[1] Danylo Halytsky Lviv National Medical University, Pekarska 69, Zip Code: 79010, Lviv, Ukraine; yu_matiichuk@ukr.net;
[2] Ivan Franko National University of Lviv, 6 Kyryla and Mefodia, Zip Code: 79005, Lviv, Ukraine; v_matiychuk@ukr.net;
* Correspondence: v_matiychuk@ukr.net;

Scopus Author ID 6506975895

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Abstract: In our present work, we displayed an effective synthesis and anticancer activity assessment of some novel 2-hetaryl-3-(5-arylfuran-2-yl)-acrylonitriles. The structures of synthesized substances were determined by ^{1}H NMR spectroscopy and elemental analysis. *In vitro* anticancer activity assessment on the full panel of about 60 human cancer cell lines showed that received compounds displayed a weak and moderate kind of activity.

Keywords: organic synthesis; 2-hetaryl-3-(5-arylfuran-2-yl)-acrylonitriles; analytical and spectral methods, anticancer activity.

1. Introduction

Oncological diseases are currently one of the most serious problems of modern medicine, which requires the development of new drugs and treatment methods. The current state of cancer therapy is such that the development of new treatment approaches occurs without revolutionary breakthroughs. Despite the existence of more than 100 antitumor drugs in clinical practice, the effectiveness of most of them is not sufficient. The spectrum of oncological diseases sensitive to chemotherapy is limited. Most of the compounds obtained do not find clinical use due to their high toxicity, poor aqueous solubility, indiscriminate action, and several other side effects. Therefore, the issue of developing new, more active drugs remains relevant.

Furane is one of the most important scaffolds in medicinal chemistry. It is widely found in diverse pharmacologically active substances and naturally-occurring compounds. Among furane derivatives, arylfuranes also play an important role in drug design and discovery. These compounds exhibit antiviral [1], antimicrobial [1, 2], anticancer [3], and antimalarial [4] activities. They are inhibitors of farnesyltransferase [5], aldose reductase [6], Tyrosine Phosphatase [7], signal-regulating kinase 1 [8], and other ferments. Some compounds of this class are already used as medicines (Nitrofurazone, Dantrolene, Clodanolene, Azimilide, etc.).

The present work is devoted to the synthesis of a series of novel arylfuranes for further pharmacological *in vitro* antitumor activity assay based on the results obtained *via in silico* drug-likeness evaluation.

2. Materials and Methods

2.1. Materials.

The reagents used in the synthesis were commercially available and of analytical grade. All solvents and reagents were used without further purification.

2.2. Chemistry.

All melting points were determined in an open capillary. ^{1}H- spectra were recorded on a Varian Mercury 400 (400 MHz for ^{1}H) instrument with TMS or deuterated solvent as an internal reference. Chemical shifts are reported as δ (ppm). Elemental analysis was performed on a Vario MICRO cube automatic CHNS analyzer. This experimental analysis data on contents of Carbon, Hydrogen, and Nitrogen were within ±0.3% of the theoretical values.

General procedure for the synthesis of 2-hetaryl-3-(5-arylfuran-2-yl)-acrylonitriles as possible anticancer agents (10-12): The 0.01 mol of 5-arylfurfural 3a-e and 0.01 mol of heterylacetonitrile 7a,b, 8 or 9 was dissolved in 20 ml of ethanol in the presence of 2 drops of piperidine. The flask was refluxed for 1 h. The precipitate formed was filtered off, washed with alcohol, and the product was purified by recrystallization from a mixture of ethanol–DMF.

2-Benzothiazol-2-yl-3-[5-(4-bromophenyl)-furan-2-yl]-acrylonitrile (10). Yield 74%, mp > 193-194°C. ^{1}H NMR (400 MHz, DMSO) δ 8.21 (s, 1H, ArH), 8.14 (d, *J* = 8.0 Hz, 1H, ArH), 8.03 (d, *J* = 8.0 Hz, 1H, ArH), 7.86 (d, *J* = 8.5 Hz, 2H, C_6H_4), 7.73 (d, *J* = 8.5 Hz, 2H, C_6H_4), 7.56 (t, *J* = 7.3 Hz, 1H, ArH), 7.51-7.46 (m, 2H, ArH), 7.42 (d, *J* = 3.7 Hz, 1H, CH). Anal. Calcd. for $C_{20}H_{11}BrN_2OS$: C, 58.98; H, 2.72; N, 6.88. Found: C, 59.07; H, 2.75; N, 6.79.

3-[5-(2-Chlorophenyl)-furan-2-yl]-2-[4-(4-fluorophenyl)-thiazol-2-yl]acrylonitrile (11a). Yield 78%, mp 180-181°C. ^{1}H NMR (400 MHz, DMSO) δ 8.23 (d, *J* = 7.5 Hz, 2H, ArH+thiazole), 8.12-8.05 (m, 3H, ArH), 7.64-7.62 (m, 1H, ArH), 7.55-7.45 (m, 4H, ArH+CH), 7.32 (t, *J* = 8.8 Hz, 2H, ArH). Anal. Calcd. for $C_{22}H_{12}ClFN_2OS$: C, 64.95; H, 2.97; N, 6.89. Found: C, 65.06; H, 3.03; N, 6.82.

3-[5-(4-Bromophenyl)-furan-2-yl]-2-(4-phenyl-thiazol-2-yl)acrylonitrile (11b). Yield 79%, mp 162-163°C. ^{1}H NMR (400 MHz, DMSO) δ 8.23 (s, 1H, thiazole), 8.17 (s, 1H, ArH), 8.03 (d, *J* = 8.1 Hz, 2H, ArH), 7.84 (d, *J* = 8.4 Hz, 2H, C_6H_4), 7.72 (d, *J* = 8.1 Hz, 2H, C_6H_4), 7.50-7.37 (m, 5H, ArH+CH). Anal. Calcd. for $C_{22}H_{13}BrN_2OS$: C, 60.98; H, 3.02; N, 6.46. Found: C, 61.08; H, 3.08; N, 6.51.

2-[4-(4-Fluorophenyl)-thiazol-2-yl]-3-[5-(3-trifluoromethylphenyl)-furan-2-yl]-acrylonitrile (11c). Yield 84%, mp 206-2207°C. ^{1}H NMR (400 MHz, DMSO) δ 8.27-8.20 (m, 4H, ArH+thiazole), 8.09-8.05 (m, 2H, ArH), 7.78-7.75 (m, 2H, ArH), 7.57 (d, *J* = 3.7 Hz, 1H, ArH), 7.46 (d, *J* = 3.7 Hz, 1H, CH), 7.32 (t, *J* = 8.8 Hz, 2H, ArH). Anal. Calcd. for $C_{23}H_{12}F_4N_2OS$: C, 62.73; H, 2.75; N, 6.36. Found: C, 62.60; H, 2.82; N, 6.41.

3-[5-(2,6-Dichloro-phenyl)-furan-2-yl]-2-(4-phenyl-thiazol-2-yl)-acrylonitrile (11d). Yield 81%, mp 185-186°C. ^{1}H NMR (400 MHz, DMSO) δ 8.21 (d, *J* = 13.3 Hz, 2H, ArH+thiazole), 8.12 (s, 1H, ArH), 8.01 (d, *J* = 7.6 Hz, 2H, ArH), 7.61 (d, *J* = 8.5 Hz, 1H, ArH), 7.55 (d, *J* = 3.7 Hz, 1H, ArH), 7.50-7.37 (m, 5H, ArH+CH). Anal. Calcd. for $C_{22}H_{12}Cl_2N_2OS$: C, 62.42; H, 2.86; N, 6.62. Found: C, 62.50; H, 2.74; N, 6.55.

3-[5-(2-Fluorophenyl)-furan-2-yl]-2-(4-oxo-3,4-dihydroquinazolin-2-yl)-acrylonitrile (12a). Yield 71%, mp >260°C. ^{1}H NMR (400 MHz, DMSO) δ 12.45 (s, 1H, NH), 8.37 (s, 1H, ArH), 8.12 (d, *J* = 7.8 Hz, 1H, ArH), 8.03 (t, *J* = 7.7 Hz, 1H, ArH), 7.82 (t, *J* = 7.2 Hz, 1H,

ArH), 7.72 (d, *J* = 8.0 Hz, 1H, ArH), 7.55-7.37 (m, 5H, ArH+CH), 7.19-7.17 (m, 1H, ArH). Anal. Calcd. for $C_{21}H_{12}FN_3O_2$: C, 70.59; H, 3.38; N, 11.76. Found: C, 71.00; H, 3.41; N, 11.84.

3-[5-(2-Chloro-phenyl)furan-2-yl]-2-(4-oxo-3,4-dihydroquinazolin-2-yl)-acrylonitrile (12b). Yield 79%, mp >260°C. ^{1}H NMR (400 MHz, DMSO) δ 12.46 (s, 1H, NH), 8.36 (s, 1H, ArH), 8.19 (s, 1H, ArH), 8.14 (d, *J* = 7.7 Hz, 1H, ArH), 7.91-7.81 (m, 3H, ArH), 7.72 (d, *J* = 8.0 Hz, 1H, ArH), 7.57-7.53 (m, 2H, ArH), 7.42 (d, *J* = 3.8 Hz, 1H, CH). Anal. Calcd. for $C_{21}H_{12}ClN_3O_2$: C, 67.48; H, 3.24; N, 11.24. Found: C, 67.19; H, 3.22; N, 11.30.

3-[5-(4-Bromophenyl)furan-2-yl]-2-(4-oxo-3,4-dihydroquinazolin-2-yl)-acrylonitrile (12c). Yield 77%, mp >260°C. ^{1}H NMR (400 MHz, DMSO) δ 12.46 (s, 1H, NH), 8.34 (s, 1H, ArH), 8.13 (d, *J* = 7.8 Hz, 1H, ArH), 7.88-7.80 (m, 3H, ArH), 7.75-7.70 (m, 3H, ArH), 7.71 (t, *J* = 7.3 Hz, 1H, ArH),), 7.43-7.42 (m, 2H, ArH+CH). Anal. Calcd. for $C_{21}H_{12}BrN_3O_2$: C, 60.31; H, 2.89; N, 10.05. Found: C, 59.89; H, 2.76; N, 10.11.

2-(4-Oxo-3,4-dihydroquinazolin-2-yl)-3-[5-(3-trifluoromethylphenyl)-furan-2-yl]-acrylonitrile (12d). Yield 80%, mp >260°C. ^{1}H NMR (400 MHz, DMSO) δ 12.51 (s, 1H, NH), 8.38 (s, 1H, ArH), 8.29 (s, 1H, ArH), 8.22-8.20 (m, 1H, ArH), 8.12 (dd, *J* = 7.9 Hz, 1H, ArH), 7.86-7.51 (m, 4H, ArH), 7.60 (d, *J* = 3.8 Hz, 1H, ArH), 7.55-7.52 (m, 1H, ArH), 7.45 (d, *J* = 3.8 Hz, 1H, CH). Anal. Calcd. for $C_{22}H_{12}F_3N_3O_2$: C, 64.87; H, 2.97; N, 10.32. Found: C, 64.76; H, 2.89; N, 10.35.

3-[5-(2,6-Dichlorophenyl)-furan-2-yl]-2-(4-oxo-3,4-dihydroquinazolin-2-yl)-acrylonitrile (12e). Yield 78%, mp >260°C. ^{1}H NMR (400 MHz, DMSO) δ 12.50 (s, 1H, NH), 8.40 (s, 1H, ArH), 8.13 (d, *J* = 7.6 Hz, 2H, ArH), 7.83 (t, *J* = 7.4 Hz, 1H, ArH), 7.70 (d, *J* = 8.1 Hz, 1H, ArH), 7.63 (d, *J* = 8.6 Hz, 1H, ArH), 7.59-7.49 (m, 3H, ArH), 7.45 (d, *J* = 3.8 Hz, 1H, CH). Anal. Calcd. for $C_{21}H_{11}Cl_2N_3O_2$: C, 61.79; H, 2.72; N, 10.29. Found: C, 61.72; H, 2.69; N, 10.33.

2.3. Pharmacology.

The tested substances were added to the culture at a concentration (10^{-5}M), and the cultures were incubated for 48 h. Endpoint definition was carried out with a protein-binding dye, sulforhodamine B (SRB). Results for every tested compound were reported as the percent growth of the processed cells when compared to the untreated control cells. The percent growth was evaluated spectrophotometrically versus not processed controls. The cytotoxic and/or growth inhibitory effects of the most active substances were tested *in vitro* contrary to the full panel of about 60 human cancer cell lines at 10-fold dilutions of five concentrations ranging from 10^{-4} to 10^{-8}M. The 48-h continuous drug exposure protocol was followed, and an SRB protein assay was used to estimate cell viability or growth. Using the seven absorbance measurements [time zero, (Tz), control growth in the lack of drug, (C), and test growth in the presence of drug at the five concentration levels (Ti)], the percentage growth was calculated at each of the drug concentrations levels. Percentage growth inhibition was calculated as:

$[(Ti - Tz)/(C - Tz)] \times 100$, for concentrations for which $Ti \geq Tz$;

$[(Ti - Tz)/Tz] \times 100$, for concentrations for which $Ti < Tz$.

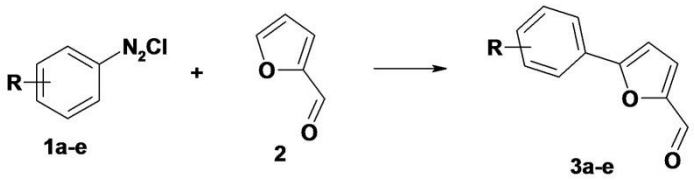
Three dose-response parameters were calculated for every compound. Growth inhibition of 50% (GI50) was calculated of $[(Ti - Tz)/(C - Tz)] \times 100 - 50$, which is the drug concentration resulting in a 50% below net protein magnification in the treated cells (measured by SRB staining) as compared to the net protein increase seen in the control cells. The drug concentration resulting in total growth inhibition (TGI) was calculated from Ti = Tz. The LC50 (concentration of drug resulting in a 50% contraction in the measured protein at the end of the

drug treatment as compared to that at the starting) indicating a net loss of cells next treatment was calculated from [(Ti − Tz)/Tz] × 100 = -50. Significance was calculated for each of these three parameters if the level of activity was reached; however, if the effect was not reached or was exceeded, the value for that parameter was pronounced as more or less than the maximum or minimum concentration was tested.

3. Results and Discussion

3.1.Synthesis of some 2-hetaryl-3-(5-arylfuran-2-yl)-acrylonitriles.

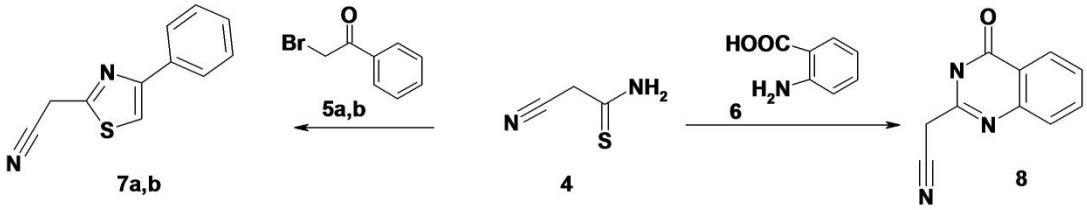
As an extension of our study on the design of biologically active heterocycles [9-51], we report herein the synthesis of different 2-hetaryl-3-(5-arylfuran-2-yl)-acrylonitriles and their anticancer activities. The key reagents –5-aylfurfurals were prepared by reaction of arendiazonium salts with furfural in Meerwein reaction conditions [52] according to the procedure [53] (Scheme 1).



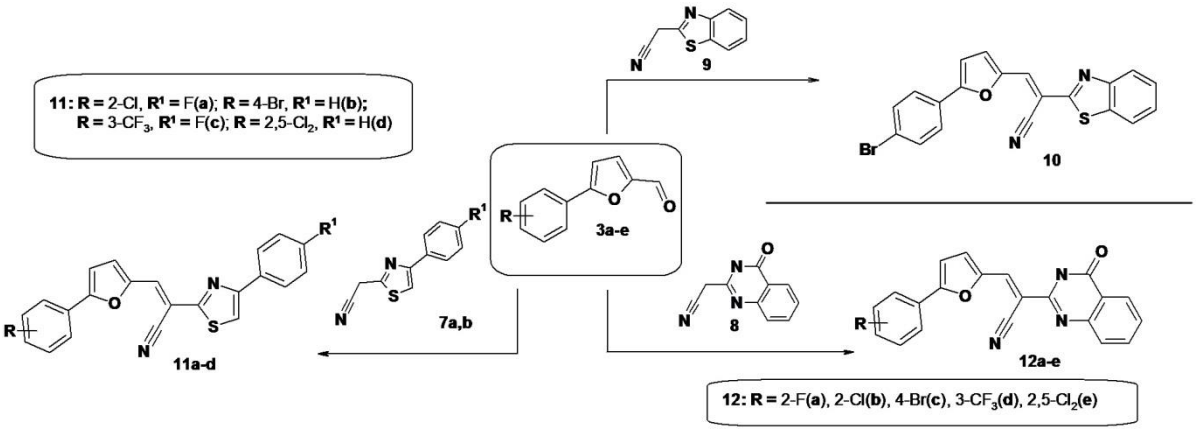
1,3: R = 2-F(**a**), 2-Cl(**b**), 2,5-Cl_2(**c**), 4-Br(**d**) 3-CF_3(**e**), 2-Cl-5-CF_3(**e**)

Scheme 1. Synthesis of 5-aryl-furan-2-carbaldehydes (3a-e).

Anthranilic acid and bromoacetophenones were using as another started reagents. They were transformed into hetarylacetonitriles by the reaction with cyanothioacetamide according to the procedure described in [54] (Scheme 2).



Scheme 2. Synthesis of hetarylacetonitriles (7a,b, 8).



Scheme 3. Synthesis of 2-hetaryl-3-(5-arylfuran-2-yl)-acrylonitriles (10-12).

The key step involves Knoevenagel condensation of synthesized 7a,b, 8, and commercially available benzothiazol-2-yl-acetonitrile 9 with 5-arylfurfyrals 3a-e. In this

nucleophilic step addition of active hydrogen from acetonitrile part with the carbonyl group of substituted aldehydes followed by water elimination to form 2-hetaryl-3-(5-arylfuran-2-yl)-acrylonitriles as final compounds. In this step, weak base piperidine is used in a catalytic amount. A similar reaction was described in the works [55-57] (Scheme 3).

The structures of the obtained compounds were confirmed by ^{1}H NMR spectroscopy and elemental analysis. The spectroscopic data of all compounds correspond to the proposed structures.

3.2. In silico drug-likeness evaluation.

Lipinski's and Veber rules are commonly used by pharmaceutical chemists in drug design to predict the oral bioavailability of organic molecules. According to Lipinski's ''rule of five'', a candidate molecule will likely to be orally active, if: i) the molecular weight is under 500, ii) the calculated octanol/water partition coefficient (Log P)<5, iii) there were fewer than 5 hydrogen bond donors (OH and NH groups) and, iv) there are less than ten hydrogen bond acceptors (notably N and O) [58].

Partition coefficient (LogP) is a significant parameter used in drug design to determine molecular hydrophobicity or lipophilicity. Log P effect the adsorption, bioavailability, drug-receptor interaction, metabolism, and toxicity of compounds. Only for compounds 12a-d log P values were found to be less than 5. For compounds 10, 11a-d, and 12e it is more than 5. But according to the Lipinski rule, violation of one parameter is still acceptable. This implies that these compounds will have good permeability across the cell membrane., The molecular weight of all synthesized compounds, was found to be less than 500 (table 1).

According to Veber et al. [59], good bioavailability is more likely for compounds with ≤10 rotatable bonds and TPSA of ≤140 A^2. Topological polar surface area (TPSA) is closely linked to the hydrogen bonding potential of a molecule and is a very good predictor of drug transport properties like intestinal absorption and blood-brain barrier penetration. TPSA of all the synthesized compounds was found to be in the range of and it below the 140 limits. None of the synthesized compounds was found to be rigid, as all of them had one or more than one rotatable bond.

The synthesized compounds had less than 10 hydrogen bond acceptors (HBA), and the number of hydrogen bond donors (HBD) is less than 5 (table 1).

Table 1. *In silico* drug-likeness evaluation.

Compound	Violation of Lipinski rules	Based on Lipinski rule				Based on Veber rule	
		HBA	***HBD***	***clog P***	***MW***	N_{ROTB}	***TPSA***
10	1	3	0	5.76	407.29	3	49.82
11a	1	3	0	5.91	406.87	4	49.82
11b	1	3	0	5.93	433.33	4	49.82
11c	1	3	0	6.15	440.42	5	49.82
11d	1	3	0	6.40	423.32	4	49.82
12a	0	5	1	4.05	357.34	3	82.69
12b	0	5	1	4.56	373.80	3	82.69
12c	0	5	1	4.74	418.2	3	82.69
12d	0	5	1	4.80	407.35	4	82.69
12e	1	5	1	5.22	408.24	3	82.69

HBA hydrogen bond acceptors, ***HBD*** hydrogen bond donors, ***clog P*** calculated logP, ***MW*** Molecular Weight, ***NROTB*** number of rotatable bonds, ***PSA*** polar surface area

It can be predicted that all the synthesized compounds are likely to be orally active.

3.3. Pharmacology.

The synthesized compounds were selected by the National Cancer Institute (NCI) Developmental Therapeutics Program (www.dtp.nci.nih.gov) for the *in vitro* cell line screening to investigate their anticancer activity. The primary anticancer assay was performed at approximately sixty human tumor cell lines panel derived from nine neoplastic diseases, following the protocol of the Drug Evaluation Branch, National Cancer Institute, Bethesda [60-64].

Results for each tested compound were reported as the percentage of growth of the treated cells when compared to the untreated control cells. The percentage of growth was evaluated spectrophotometrically versus controls not treated with test agents (table 2).

Table 2. Cytotoxic activity of the tested compounds in the concentration 10^{-5} M against 60 cancer cell lines.

Test compounds	Range of growth, %	Most sensitive cell line (cancer line/type) GP, %
10	61.32 - 175.89	MCF7 (Breast Cancer) 61.32 EKVX (Non-Small Cell Lung Cancer) 63.62 SNB-75(CNS Cancer) 67.39
11a	68.97 - 192.92	UO-31 (Renal Cancer) 68.97 EKVX (Non-Small Cell Lung Cancer) 76.70
11b	59.43 - 196.66	MCF7 (Breast Cancer) 59.43 T-47D (Breast Cancer) 64.62
11c	36.77- 199.81	MCF7 (Breast Cancer) 36.77 T-47D (Breast Cancer) 64.36 EKVX (Non-Small Cell Lung Cancer) 80.17
11d	69.86 - 193.34	UO-31 (Renal Cancer) 69.86 EKVX (Non-Small Cell Lung Cancer) 78.38
12a	84.54 - 122.21	MCF7 (Breast Cancer) 84.54
12b	77.40 - 133.41	UO-31 (Renal Cancer) 77.40
12c	84.21 - 140.10	MCF7 (Breast Cancer) 84.21
12d	76.40 - 119.40	MCF7 (Breast Cancer) 76.40 RPMI-8226 (Leukemia) 77.36
12e	67.16 - 174.05	UO-31 (Renal Cancer) 67.16 EKVX (Non-Small Cell Lung Cancer) 83.16

The screening results are shown in Table 2. As the experiment showed, all compounds showed low activity against most malignant tumor cells. But in the case of compounds 11a-d against several cancer cell lines, moderate activities were observed. A feature of such compounds is the presence of a thiazole nucleus in the molecule. About the biological potential of thiazole containing compounds, we reported previously [11, 40-48]. The most sensitive was the MCF7 Breast Cancer cell line to the compounds 11b and 11c with GP = 59.43 and 36.77%. It should also be noted that compounds 12a-e and especially 11a-d stimulate growing of the TK-10 Renal Cancer Cell line.

4. Conclusions

In conclusion, we have displayed that the suggested synthetic protocols provided the opportunity to design of series of new 2-hetaryl-3-(5-arylfuran-2-yl)-acrylonitriles. The structures of purpose substances were reaffirmed by using ^{1}H NMR spectroscopy and elemental analysis. The synthesized compounds were chosen by the National Cancer Institute (NCI) Developmental Therapeutics Program for the *in vitro* cell line screening to explore their anticancer activity. The tested compounds showed weak and moderate anticancer activity. Further optimization of the structure to improve pharmacological activity is at the present time in progress.

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Conflicts of Interest

The authors declare no conflict of interest.

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