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Reactions under increased pressure: The reactivity of functionally substituted 3-oxo-2-arylhydrazones toward active methylene reagents in Q-tube

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RESEARCH ARTICLE

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ABSTRACT

A one-pot two-component reaction of 3-oxo-2-arylhydrazones with active methylene nitriles under high pressure in a Q-tube safe reactor was reported. Comparison between conventional and Q-tube safe reactor-assisted synthesis of organic compounds was done by comparing total reaction time and percentage yield. The results show that the compound 5-cyano-6-oxo-1,4-diphenyl-1,6-dihydro-pyridazine-3-carboxylic acid ethyl ester (3) was synthesized within 2 h in a yield of 97%. In addition, the pyrazolo[3,4-c]pyridines 5b and 5c were obtained in yields of 93 and 95% within 1 h reaction time, respectively. The obtained results suggest that Q-tube safe reactor-assisted syntheses were led to higher product yields within very short reaction times.

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1. Introduction

Recently, our group was involved in consequently a program aimed at utilizing 3-oxo-2-arylhydrazones as precursors to heteroaromatics [1]. Several of which were patented for diverse utilities [2,3]. Our contribution in this area has been recently surveyed [4,5], and major results are outlined in Scheme 1 and 2.

Since 1997 [6], we have investigated extensively the utility of microwave to accelerate reaction rates. However, we recently realized that the microwave is just heating at a temperature higher than that of the media as the polar reactants are form hot spots and then release temperature to the reaction media [7]. The microwave technology is expensive to scale up [8] and no industrial example utilizing it exists accordingly there is a need for employing neoteric energy sources to increase energy efficiency. The pressure also allows reactions to proceed at temperatures higher than those of the media. It also increases the rate of reaction conditions and enhances the formation of transition state with negative activation volume [9]. As a result of this, we turned to utilize reactions in Q-tube (a safety device that enables conducting reactions in the laboratory), and successfully we could produce several articles whose results are outlined in Scheme 3 and 4 [10-12]. Our aim is to develop a novel and efficient protocol for the synthesis of cyclic derivatives with multi-component reaction (MCR) which includes a condensation reaction utilizing a Q-tube safe reactor in a short time with high yield.

2. Experimental

2.1. Instrumentation

Infrared spectra were recorded using dry KBr pellets and a Jasco vacuum FT-IR 6300 instrument and absorption bands are reported in cm^{-1}. ^1H- and ^{13}C-NMR spectra were determined by using a Bruker DPX instrument at 400 or 600 MHz for ^1H-NMR and 100 or 125 MHz for ^{13}C-NMR and either $CDCl_3$ or DMSO-d_6 solutions with TMS as internal standards. Chemical shifts are reported in ppm. Mass spectra and accurate mass measurements were made using a GC-MS DFS Thermo spectrometer with the EI (70 eV) mode. All reactions were monitored by using TLC with ethyl acetate: petroleum ether (1:1, *v:v*) as eluent and were carried out until starting materials were completely consumed.

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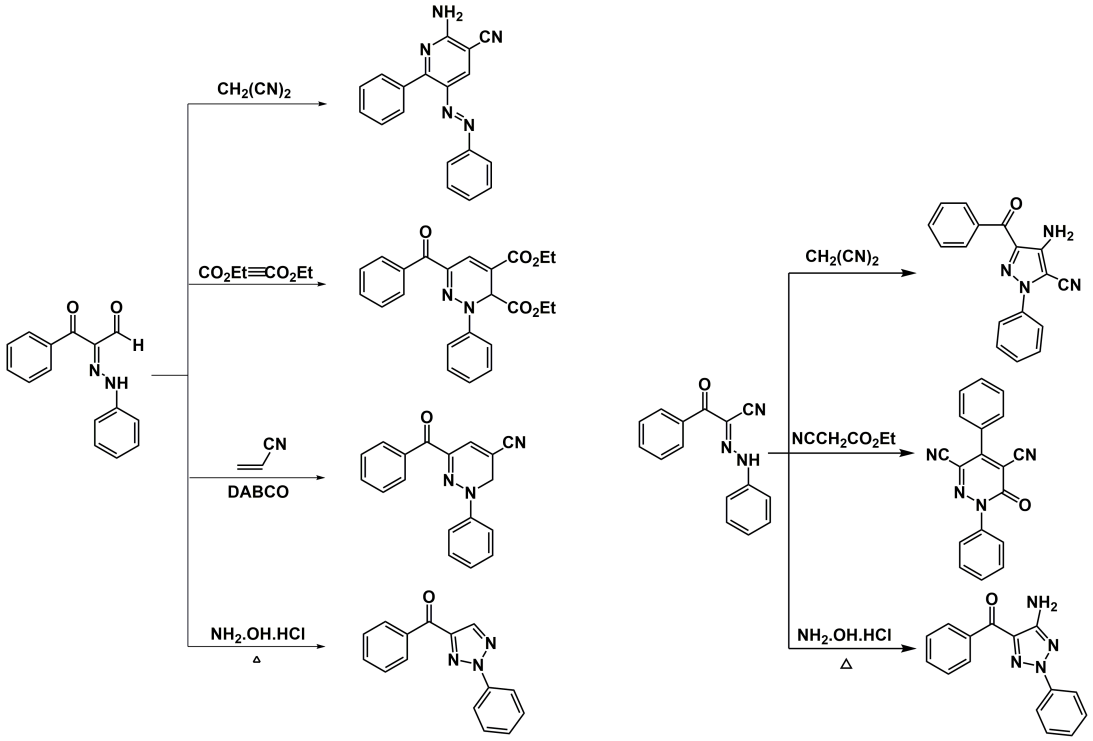
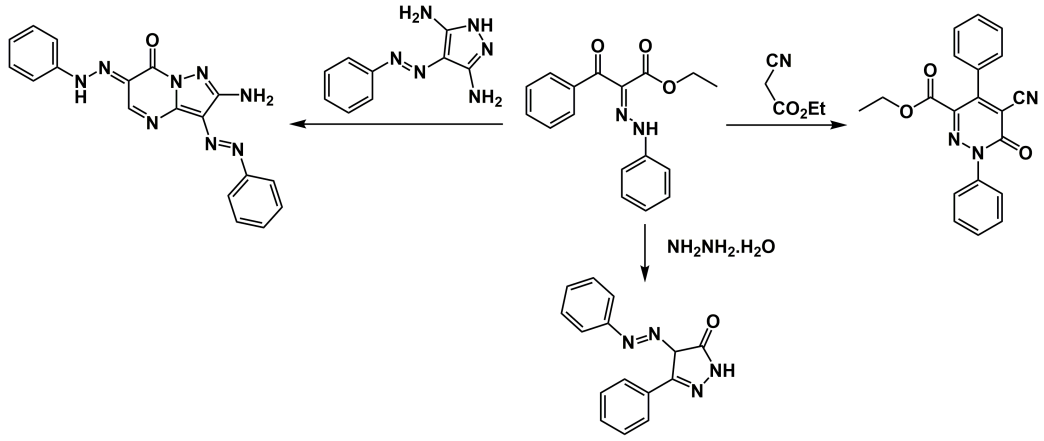


Scheme 1



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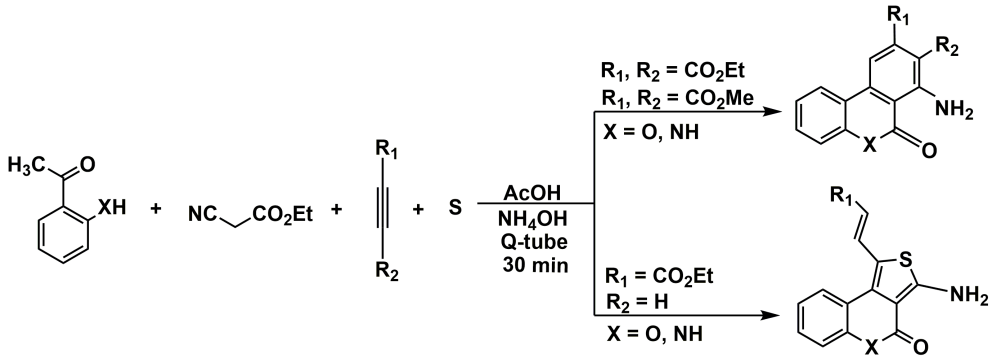

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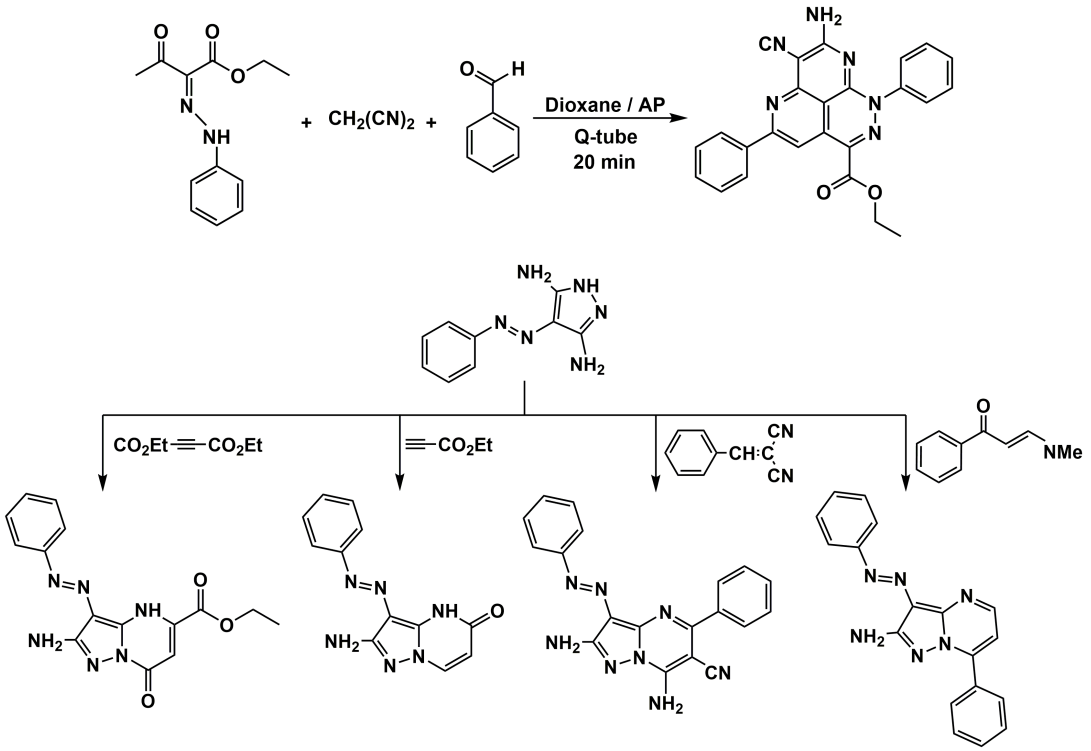
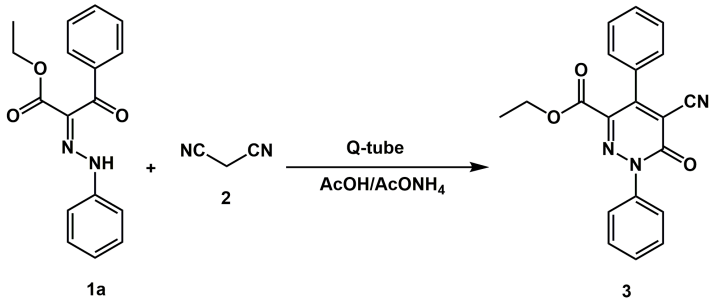


Scheme 4



Scheme 5

Sonication was performed in MKC6 Guyson ultrasonic bath (Model-MKC6, operating frequency 38 kHz +/- 10% and output power of 110 Watts) with a digital timer (6 sec. to 100 min.) and the heater allows solution heating to be set from 20 to 80 °C in 1 °C increment. The inside tank dimensions are 150 × 300 × 150 mm (length × width × depth) with a fluid capacity of 6 liters. Q-tube-assisted reactions were performed in a Q-tubeTM safe pressure reactor from Q Labtech, equipped with a cap/sleeve, pressure adapter (120 psi), needle adapter/needle, borosilicate glass tube, Teflon septum, and catch bottle.

2.2. Synthesis

2.2.1. Synthesis of compounds 1a-c

3-Oxo-3-phenyl-2-(phenyl-hydrazono)-propionic acid ethyl ester (**1a**), 3-oxo-3-phenyl-2-(2-(*p*-tolyl)hydrazono)propanal (**1b**) and 3-oxo-3-(4-chlorophenyl)-2-(2-phenylhydrazono) propanal (**1c**) were prepared according to previously published methods [11,13].

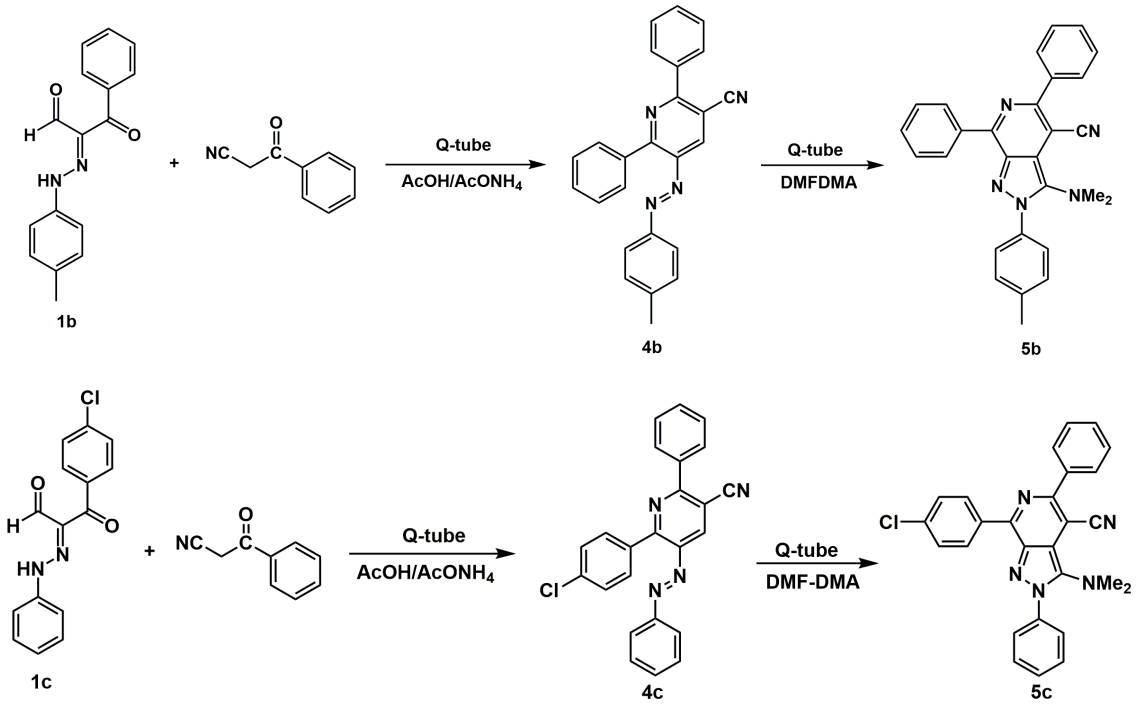
2.2.2. Synthesis of 5-cyano-6-oxo-1,4-diphenyl-1,6-dihydro-pyridazine-3-carboxylic acid ethyl ester (3)

Mixture of the 3-oxo-3-phenyl-2-(phenyl-hydrazono)-propionic acid ethyl ester (**1a**) (1.0 g, 3.0 mmol) and malononitrile (**2**) (0.3 g, 4.5 mmol) in acetic acid (10 mL), and ammonium acetate (1.0 g) sequentially added in a 35 mL Q-tube, furnished by Q Labtech. A Teflon septum was placed on the top of the tube, and an appropriate cap and pressure adapter were used. The mixture was heated in an oil bath at 130 °C. After about 2 h, the reaction mixture was monitored by TLC and GC/MS and stopped. The hot reaction mixture was filtrated and washed with ethanol. The separated solid products obtained on standing at room temperature were collected by filtration, washed with ethanol (Scheme 5).

5-Cyano-6-oxo-1, 4-diphenyl-1, 6-dihydro-pyridazine-3-carboxylic acid ethyl ester (**3**): Color: Yellow. Yield: 97%. M.p.: 80-82 °C. FT-IR (KBr, ν, cm^{-1}): 1731, 1666 (CO), 2223 (CN). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.26 (t, 3H, *J* = 6.6 Hz, OCH_2CH_3), 4.32 (q, 2H, *J* = 6.6 Hz, OCH_2CH_3), 7.05 (t, 1H, *J* = 7.2 Hz, Ar-H), 7.26-7.29 (m, 2H, Ar-H), 7.32 (t, 2H, *J* = 7.8 Hz, Ar-H), 7.54 (t, 2H, *J* = 7.2 Hz, Ar-H), 7.64-7.65 (m, 1H, Ar-H), 7.85-7.86 (m, 2H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 13.89, 61.06, 114.49, 123.76, 125.74, 129.06, 132.35, 137.34, 137.72, 140.22, 142.42, 149.96, 156.18, 161.59, 172.26, 188.88, 192.26, 206.49.

Table 1. The % yield products and reaction time.

Method	Product (3)		Product (5b)		Product (5c)	
	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)
Conventional	No product	No product	8	93	8	94
Q-tube	2	97	1	93	1	95



Scheme 6

MS (EI, *m/z* (%)): 346.1 (M^+, 19), 345.1 (M, 100), 77 (90). HRMS (EI, *m/z*) calcd. for $C_{20}H_{15}O_3N_3$, 345.1108; Found: 345.1107.

2.2.3. General procedure for the preparation of compounds 4b,c

Independent mixtures of 3-oxo-3-phenyl-2-(2-(*p*-tolyl) hydrazono)propanal (**1b**) and 3-oxo-3-(4-chlorophenyl)-2-(2-phenylhydrazono)propanal (**1c**) derivatives (5 mmol), benzoylacetonitrile (0.725 g, 5 mmol), and ammonium acetate (1 g) in acetic acid (10 mL) sequentially added in a 35 mL Q-tube pressure tube. The progress of the reactions was monitored by using TLC and 1:1 ethyl acetate/petroleum ether as eluent. A Teflon septum was placed on the top of the tube, and an appropriate cap and pressure adapter were used. The mixture was heated in an oil bath at 140 °C. After about 30 min, the mixtures were cooled to room temperature. The formed solids were collected by filtration and crystallized from the indicated solvents to give 2, 6-diphenyl-5-(*p*-tolyldiazenyl)nicotinonitrile (**4b**) (84%, [14]) and 6-(4-chlorophenyl)-2-phenyl-5-(phenyl diazenyl)nicotinonitrile (**4c**) (90%, [14]) as pure products (Scheme 6).

2.2.4. Synthesis of pyrazolo[3,4-c]pyridines (5b,c)

Independent mixtures of compounds **4b** or **4c** (2.5 mmol) in dry toluene (10 mL), containing *N*,*N*-dimethylformamide-dimethylacetal (DMF-DMA) (0.5 mL, 5 mmol) sequentially added in a 35 mL Q-tube pressure tube. A Teflon septum was placed on the top of the tube, and an appropriate cap and pressure adapter were used. The mixture was heated in an oil bath at 140 °C. After about 1 h, the reaction mixture was monitored by TLC and GC/MS and stopped. The hot reaction mixture was filtrated and washed with ethanol while the %yield was calculated and compared with the reported method. The separated solid products (**5b** (93%, [14]) and **5c** (%94, [14])) obtained on standing at room temperature were collected by filtration, washed with ethanol (Scheme 6).

3-(Dimethylamino)-5, 7-diphenyl-2-p-tolyl-2H-pyrazolo[3, 4-c]pyridine-4-carbonitrile (**5b**): Color: Orange. Yield: 93%. M.p.: 220-221 °C. FT-IR (KBr, ν, cm^{-1}): 2215 (CN). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.46 (s, 3H, Ar-CH_3), 2.88 (s, 6H, $2CH_3$), 7.47 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.57-7.63 (m, 8H, Ar-H), 8.02 (d, 2H, *J* = 8.0 Hz, Ar-H), 8.73-8.76 (m, 2H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 20.81, 43.40, 94.04, 118.56, 120.23, 125.57, 128.18, 128.43, 128.57, 129.29, 129.75, 131.11, 135.89, 136.70, 138.11, 138.29, 139.51, 140.14, 143.88, 151.98, 152.25. MS (EI, *m/z* (%)): 430 (M^+, 25.88), 429 (M, 100). HRMS (EI, *m/z*) calcd. for $C_{28}H_{23}N_5$, 429.1948; Found: 429.1948.

7-(4-Chlorophenyl)-3-(dimethylamino)-2, 5-diphenyl-2H-pyrazolo[3,4-c]pyridine-4-carbonitrile (**5c**): Color: Orange. Yield: 95%. M.p.: 230-231 °C. FT-IR (KBr, ν, cm^{-1}): 2212 (CN). ^{1}H NMR (600 MHz, DMSO-d_6, δ, ppm): 2.88 (s, 6H, $2CH_3$), 7.56-7.70 (m, 8H, Ar-H), 7.75 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.01 (d, *J* = 7.2 Hz, 2H, Ar-H), 8.79 (d, *J* = 8.4 Hz, 2H, Ar-H). ^{13}C NMR (150 MHz, DMSO-d_6, δ, ppm): 43.35, 94.46, 118.39, 120.29, 124.59, 125.83, 128.44, 128.83, 129.37, 129.41, 129.68, 129.80, 131.38, 134.57, 136.09, 137.93, 139.04, 140.10, 144.14, 150.53, 152.17. MS (EI, *m/z* (%)): 450 (M^+, 47), 449 (M, 100), 77 (13). HRMS (EI, *m/z*) calcd. for $C_{27}H_{20}ClN_5$, 449.1402; Found: 449.1402.

3. Results and discussion

In continuation to our interest in exhibiting the merits of performing reactions under increased pressure utilizing a Q-tube safe reactor, we investigated the reaction of compounds **1a**-**c** with active methylene in a multi-component reaction. We

were unable to obtain compound **3** via condensation reaction of compound **1a** with malononitrile via the conventional heating method in multi-component reaction (MCR) (Table 1). In this study, we found that the condensation of compound **1a** with malononitrile **2** in Q-tube produces compound **3** in excellent yield, where the only isolable product was compound **3** (Scheme 5). We were compared with the nature of the reaction product and its rate and yield with the reported products, yield, and rates. It could be concluded that the readily scalable reactions under these conditions can proceed at rates comparable to those conducted in the microwave and in some multi-component reaction reactions under increased pressure produce different products perhaps by changing the sequences of these reactions. In addition, the compounds **1b** and **1c** were reacted with benzoyl acetonitrile to yield compounds **4b** and **4c**. The obtained compounds **4b** and **4c** were reacted with dimethylformamide-dimethyl acetal (DMF-DMA) to yielding compounds **5b** and **5c** (Scheme 6). We found that compounds **4b**, **4c**, **5b**, and **5c** are produced under increased pressure at much faster rates and higher yields in this study via Q-tube (Table 1, Scheme 6).

4. Conclusion

A new route of green chemistry using a new technique in which the reactions occur under increased pressure in Q-tube revealed that the important of the reaction yields with a record time was achieved. In conclusion, the method of Q-tube represents a promising benign route to replace many conventional basic methods. The utility of the Q-tube method showed the acceleration of several reactions in a better way. It is a logical outcome after several researches and comparisons with several old methods, that an improvement of the reaction yields with a record time was achieved.

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Disclosure statement

Conflict of interests: The author declares that he has no conflict of interest.
Ethical approval: All ethical guidelines have been adhered.
Sample availability: Samples of the compounds are available from the author.

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