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MICROWAVE SOLVENT-FREE SYNTHESIS OF ANTIPYRINE-BASED TRIARYLMETHANES AND EVALUATION OF THEIR PHARMACOLOGICAL PROPERTIES

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A microwave-assisted, solvent-free method for the synthesis of antipyrine-based triarylmethanes was developed. The target compounds were prepared in a dedicated microwave reactor using *p*-toluenesulfonic acid as a catalyst at 100 °C for 1 min. The structures of the synthesized compounds were confirmed by various spectroscopic techniques. The relationship between the chemical structure and potential pharmacological activity was evaluated empirically using appropriate *in silico* software tools. The prediction results indicated that all investigated compounds exhibit favorable oral bioavailability, qualifying them as promising drug candidates. In addition, the antioxidant activity of the synthesized triarylmethanes was assessed. Hydroxy-substituted derivatives demonstrated significant antioxidant potency, with half-maximal inhibitory concentrations lower than that of ascorbic acid, which was used as the reference standard.

Keywords: microwave synthesis; green chemistry; *p*-toluenesulfonic acid; *in silico* prediction; antioxidant activity

МИКРОБРАНОВА СИНТЕЗА БЕЗ РАСТВОРУВАЧИ НА ТРИАРИЛМЕТАНИ БАЗИРАНИ НА АНТИПИРИН И ЕВАЛУАЦИЈА НА НИВНИТЕ ФАРМАКОЛОШКИ СВОЈСТВА

Развиен е метод за синтеза на триарилметани базирани на антипирин, со примена на микробранови и без употреба на растворувач. Целните соединенија беа подготвени во наменски микробранов реактор, со употреба на *p*-толуенсулфонска киселина како катализатор, на температура од 100 °C во времетраење од 1 минута. Структурите на синтетизираните соединенија беа потврдени со примена на различни спектроскопски техники. Врската помеѓу хемиската структура и потенцијалната фармаколошка активност беше емпириски проценета со употреба на соодветни *in silico* софтверски алатки. Резултатите од предвидувањата покажаа дека сите испитувани соединенија поседуваат поволна орална биорасположивост, што ги определува како потенцијално перспективни кандидати за развој на лекови. Дополнително, беше испитана и антиоксидациска активност на синтетизираните триарилметани. Хидрокси-супституираните деривати покажаа значајна антиоксидациска активност, со концентрации потребни за постигнување 50 % инхибиција пониски од оние на аскорбинската киселина, која беше употребена како референтен стандард.

Клучни зборови: микробранова синтеза; зелена хемија; *p*-толуенсулфонска киселина; *in silico* предвидување; антиоксидативна активност

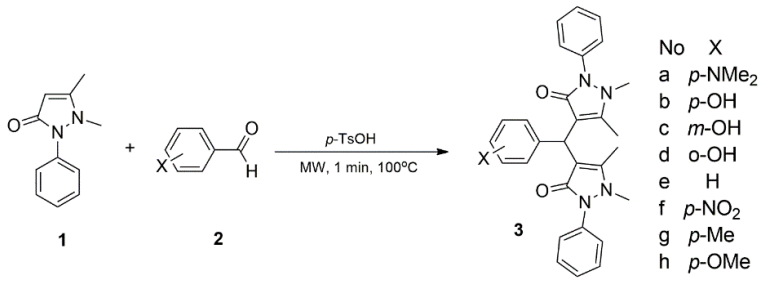
1. INTRODUCTION

Antipyrine (2,3-dimethyl-1-phenyl-3-pyrazoline-5-one, **1**) as well as antipyrine-based compounds possess various biological activities such as antidepressant, antipyretic, anti-inflammatory, antimicrobial, and anticancer activities.[1] The synthesis of triarylmethanes, including antipyrine-based triarylmethanes, has long been a topic in organic chemistry. The simplest synthesis of triarylmethanes is the Baeyer condensation, which is based on the reaction of aromatic aldehyde with an aromatic molecule in the presence of an acidic catalyst. Different catalysts have been used, including zinc chloride ($ZnCl_2$),[2] *p*-toluenesulfonic acid (*p*-TsOH),[3] hydrochloric acid (HCl),[4] polymer-supported sulfonic acid,[5] and zirconyl chloride ($ZrOCl_2$).[6] Triarylmethanes have also been prepared under solvent-free conditions in the presence of cerium(IV) ammonium nitrate,[7] iron(III) phosphate ($FePO_4$),[8] niobium(V) chloride ($NbCl_5$),[9] and *p*-TsOH.[10] In addition, under solvent-free conditions, crystal violet and derivatives, diphenylmethanes, and biphenyls were obtained via microwave irradiation in a clay-mediated reaction of *N,N*-disubstituted anilines.[11] Triarylmethanes can also be obtained under solvent-free conditions via microwave irradiation using *p*-TsOH from different aldehydes and *N*,*N*-dimethylaniline.[12] Synthesis of triarylmethanes using ionic liquids[13] as well as under ultrasonic conditions[14] has also been described in the literature.

From an environmental and economic perspective, the traditional methods used to synthesize active heterocyclic compounds with potential pharmacological activity are unsustainable due to the use of toxic chemicals and long reaction time, so they need to be improved. Hence, multicomponent reactions are attractive, particularly when combined with microwave technology, because they align with the principles of green chemistry.[15] Originally described as a nonclassical heating method and now widely applied in industry, high-speed microwave synthesis has attracted considerable attention in recent years. The use of microwave energy has increased rapidly over the past decades, with numerous innovative applications emerging in organic and drug synthesis, polymer chemistry, material sciences, nanotechnology, and biochemical processes.[16,17] Microwave-assisted organic synthesis is based on efficient heat transfer through dielectric heating, which, in turn, mainly depends on the ability of the solvent or reagents to absorb microwave energy.[18] Numerous green protocols in organic synthesis have demonstrated significant advantages over conventional heating methods. Selective, volumetric dielectric heating has led to substantial time and energy savings, facilitated the use of safer solvents or solvent-free conditions, enabled more selective catalysis in fewer synthetic steps, and generally resulted in improved selectivity and higher yields.[19]

Because of their role in preventing various degenerative diseases, antioxidants have drawn considerable interest from the scientific community. The term "antioxidant" denotes a substance or molecule capable of delaying or preventing the irreversible oxidative damage of other molecules induced by free radicals and unstable metabolites within living systems, thereby conferring potential health benefits.[20] Free radicals are highly reactive, unstable, and short-lived molecular species. An imbalance between reactive oxygen species (ROS) production and antioxidant defense mechanisms leads to oxidative stress, which contributes to cellular damage through the oxidation of lipids, proteins, and nucleic acids, and plays a key role in the development of numerous chronic and degenerative diseases. Therefore, the development of effective antioxidants remains an important strategy for preventing and mitigating oxidative stress-related disorders.[21–26]

In pursuit of new and highly potent antioxidant agents, we examined the radical scavenging properties of eight synthesized antipyrine-based triarylmethanes using the 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assay. In addition, we conducted *in silico* prediction to evaluate the pharmacokinetic profiles of the synthesized compounds. Although a combination of microwave-assisted and solvent-free synthesis of triarylmethanes using *p*-TsOH as a catalyst[12] had been reported, to our knowledge, the combination of solvent-free and microwave-assisted synthesis of antipyrine-based triarylmethanes using *p*-TsOH as a catalyst and medium, in a dedicated microwave reactor, has not yet been described in the literature. Herein, we present, for the first time, the microwave-assisted, solvent-free synthesis of eight triarylmethanes (**3a–h**) starting from aromatic aldehydes and antipyrine in the presence of *p*-TsOH (Scheme 1). The compounds differ in the substituents on the phenyl ring derived from the arylaldehyde, with hydroxy-substituted derivatives varying in the position of the hydroxyl group at the *ortho*-, *meta*-, or *para*-positions.



Scheme 1. The microwave-assisted, solvent-free method for the synthesis of antipyrine-based triarylmethanes

2. EXPERIMENTAL

2.1. *Materials and methods*

All chemicals were obtained from Sigma-Aldrich (Burlington, Massachusetts, United States), Acros Organics (Geel, Belgium), or Fluka (Buchs, Switzerland) and were used as received. The purity of the used chemicals was ≥ 98.5 %.

The obtained compounds were characterized by melting point, Fourier-transform infrared (FT-IR) spectroscopy, ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy, and mass spectrometry. A Stuart SMP30 melting point system (Bibby Scientific Ltd., Stone, Staffordshire, United Kingdom) was used to determine the melting points. An Ascend 400 system (Bruker-Bruker Corporation, Billerica, MA, United States) was used to obtain the ^{1}H and ^{13}C NMR data (400 Hz and 100 Hz, respectively). Deuterated dimethylsulfoxide (DMSO-d_6) was used a solvent, while tetramethylsilane (TMS) was used as an internal standard. FT-IR spectra of the dyes were obtained on a Nicolet™ iS™ 10 FT-IR spectrometer (Thermo Fisher Scientific) with Smart iTR™ attenuated total reflectance (ATR) sampling accessories in the range of 500–4000 cm^{-1}, with 32 scans per spectrum. A Shimadzu 1800 spectrophotometer (Shimadzu Corporation, Kyoto, Japan) was used for the ultraviolet–visible (UV–Vis) analysis. The spectroscopic analysis was performed using quartz cuvettes at room temperature (25 °C) at a dye concentration of 5 × 10^{-5} M in methanol in the range of 210–500 nm. Mass spectra were obtained by a linear ion trap mass spectrometer (LTQ XL, Thermo Scientific) (Thermo Fisher Scientific Inc., Waltham, MA, USA). Ionization was achieved by electrospray ionization (ESI), and analyte was examined in the positive and negative ion mode. The optimized ESI source parameters for positive ion monitoring were as follows: a spray voltage of 5 kV, sheath gas flow of 8 arbitrary units, capillary temperature set to 275 °C, and capillary voltage of 35 V. The optimized ESI source parameters for negative ion monitoring were as follows: a spray voltage of 5 kV, sheath gas flow of 8 arbitrary units, capillary temperature set to 275 °C, and capillary voltage of –10 V. Samples were prepared in methanol at a concentration of 10 mg L^{-1} and directly introduced into the mass spectrometer (5 μL min^{-1}). Data acquisition and processing were carried out using Xcalibur software (Thermo Scientific).

A typical procedure for the synthesis of compounds ***3a-h***: A mixture of *p*-TsOH monohydrate (5 mmol, 0.951 g), antipyrine (**1**, 2 mmol, 0.376 g), and substituted benzaldehyde (**2**, 1 mmol) was placed in the glass microwave reaction vial (30 mL capacity) and irradiated in a Monowave 300 microwave reactor (Anton Paar, GmbH, Graz, Austria) at 100 °C for 1 min. The colored sticky mass was dissolved by the addition of hot water (3 × 10 mL). Ten milliliters of sodium hydroxide (NaOH) solution (20 %) was added, and the white solid was isolated by vacuum filtration. The products were purified by crystallization from aqueous 5 % HCl (10 mL) at 40 °C for 20 minutes and dried at 45 °C. After recrystallization from 5 % HCl, the products were washed with a 5 % NaOH solution. Due to the significant solubility of hydroxy substituted compounds **3b–d** in alkaline media, the work-up procedure was modified. Instead of adding an aqueous NaOH solution, water was removed by evaporation and the solid was purified by crystallization. Even with this modification, isolated yield was not improved significantly. The Supplementary Material included the corresponding FT-IR and NMR spectra (Figures S1–S24), mass spectra (Figures S25–S32), and the UV–Vis spectra (Figure S33).

4,4'-((4-(dimethylamino)phenyl)methylene)bis(1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one) **3a**: White crystalline solid; yield: 40 %; m.p. 166–168 °C; FTIR (KBr, ν/cm^{-1}): 2983 (C–H str. aromatic), 2888, 2798 (C-H str., aliphatic), 1664 (C=O str., carbonyl), 1613, 1592 (C=C skeletal str., phenyl), 1519, 1495 (C-C str., in ring), 1455 (C=C str., antipyrine), 1402 (C-H bend), 1309, 1290 (C-N str., aryl 3° amine), 1154, 1132 (C-N str., aromatic amine), 1058, 947, 747, 707 (=C-H bend); ^{1}H NMR (400 MHz, DMSO-d_6,

δ/ppm): 7.74 (d, 2H, *J* = 6.8 Hz, Ar-H), 7.60–7.52 (m, 6H, Ar-H), 7.48–7.43 (m, 6H, Ar-H), 5.37 (s, 1H, -CH), 3.40 (s, 6H, N–CH_3), 3.07 (s, 6H, N-CH_3 substituent), 2.51 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 160.92 (C=O), 152.19 (Ar), 149.88 (Pyr), 132.41 (Ar), 130.12 (Ar), 130.06 (Ar), 129.12 (Ar), 127.62 (Ar), 105.59 (Pyr), 45.23 (N–Me substituent), 34.71 (CH), 32.69 (N–CH_3), 11.01 (CH_3); ESI-MS m/z calc. 507.26, found (positive mode): 508.50 $[M+H]^+$, 530.50 $[M+Na]^+$, 546.50 $[M+K]^+$, 1037.42 $[2M+Na]^+$; UV–Vis (MeOH) (λ_{max}/nm(log ε)): 255.5 (4.04).

4,4'-((4-hydroxyphenyl)methylene)bis(1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one) **3b**: White crystalline solid; yield: 44 %; m.p. 190–192 °C; FTIR (KBr, ν/cm^{-1}): 2988 (C–H str. aromatic), 2901, 2810 (C-H str., aliphatic), 1633 (C=O str., carbonyl), 1613, 1588 (C=C skeletal str., phenyl), 1511 (C-C str., in ring), 1495 (C=C str., antipyrine), 1455 (C-H bend), 1405, 1364 (C-N str., aryl 3° amine), 1267, 1235, 1135 (C-N str., aromatic amines), 908, 865, 835, 785, 732, 707, 694 (=C-H bend); ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 7.60–7.51 (m, 6H, Ar-H), 7.45 (d, 4H, *J* = 7.2 Hz, Ar-H), 7.04 (d, 2H, *J* = 8.8 Hz, Ar-H), 6.71 (d, 2H, *J* = 8.4 Hz, Ar-H), 5.21 (s, 1H, -CH), 3.37 (s, 6H, N–CH_3), 2.48 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 161.28 (C=O), 156.49 (Ar), 150.10 (Pyr), 132.66 (Ar), 130.67 (Ar), 130.06 (Ar), 129.76 (Ar), 128.60 (Ar), 127.30 (Ar), 115.58 (Ar), 106.62 (Pyr), 34.80 (CH), 32.40 (N–CH_3), 11.03 (CH_3); ESI-MS m/z calc. 480.22, found (positive mode): 481.42 $[M+H]^+$, 503.42 $[M+Na]^+$, 519.42 $[M+K]^+$, 983.25 $[2M+Na]^+$, found (negative mode): 479.50 $[M–H]^–$; UV–Vis (MeOH) (λ_{max}/nm(log ε)): 229.5 (3.96), 279.0 (3.87).

4,4'-((3-hydroxyphenyl)methylene)bis(1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one) **3c**: White crystalline solid; yield: 38 %; m.p. 140–142 °C; FTIR (KBr, ν/cm^{-1}): 3354 (O–H str.), 3065, 2990 (C-H str., aromatic), 2939 (C-H str., aliphatic), 1633 (C=O str., carbonyl), 1606, 1589 (C=C skeletal str., phenyl), 1497 (C=C str., antipyrine), 1482 (C-H bend), 1454, 1311 (C-N str., aryl 3° amine), 1276 (C-N str., aromatic amines), 934, 918, 879, 777, 764, 697 (=C-H bend); ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 9.38 (s, 1H, OH), 7.56 (t, 4H, *J* = 7.2 Hz, Ar-H), 7.49 (d, 2H, *J* = 6.8 Hz, Ar-H), 7.44 (d, 4H, *J* = 7.6 Hz, Ar-H), 7.09 (t, 1H, *J* = 8.0 Hz, Ar-H), 6.67–6.61 (m, 3H, Ar-H), 5.19 (s, 1H, -CH), 3.32 (s, 6H, N–CH_3), 2.42 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 162.00 (C=O), 157.91 (Ar), 150.82 (Pyr), 142.27 (Ar), 134.28 (Ar), 130.06 (Ar), 130.02 (Ar), 129.70 (Ar), 126.98 (Ar), 126.88 (Ar), 118.35 (Ar), 114.76 (Ar), 108.47 (Pyr), 35.00 (CH), 33.19 (N–CH_3), 11.15 (CH_3); ESI-MS m/z calc. 480.22, found (positive mode): 481.42 $[M+H]^+$, 503.42 $[M+Na]^+$, 519.42 $[M+K]^+$, 983.33 $[2M+Na]^+$, found (negative mode): 479.67 $[M–H]^–$; UV–Vis (MeOH) (λ_{max}/nm(log ε)): 224.5 (3.92), 279.0 (3.87).

4,4'-((2-hydroxyphenyl)methylene)bis(1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one) **3d**: White crystalline solid; yield: 42 %; m.p. 140–142 °C; FTIR (KBr, ν/cm^{-1}): 3362 (O–H str.), 2943 (C-H str., aromatic), 1630 (C=O str., carbonyl), 1606, 1589 (C=C skeletal str., phenyl), 1497, 1486 (C=C str., antipyrine), 1454 (C-H bend), 1328 (C-N str., aryl 3° amine), 1283, 1184 (C-N str., aromatic amines), 878, 764, 662 (=C-H bend); ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 9.83 (s, 1H, OH), 7.58–7.40 (m, 11H, Ar-H), 7.04 (t, 1H, *J* = 7.4 Hz, Ar-H), 6.87 (d, 1H, *J* = 8 Hz, Ar-H), 6.73 (t, 1H, *J* = 7.4 Hz, Ar-H), 5.38 (s, 1H, -CH), 3.30 (s, 6H, N–CH_3), 2.40 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 161.55 (C=O), 154.56 (Ar), 149.92 (Pyr), 132.76 (Ar), 130.05 (Ar), 129.66 (Ar), 128.88 (Ar), 128.14 (Ar), 127.82 (Ar), 127.32 (Ar), 121.70 (Ar), 115.65 (Ar), 106.04 (Pyr) 34.86 (CH), 27.90 (N–CH_3), 11.17 (CH_3); ESI-MS m/z calc. 480.22, found (positive mode): 481.50 $[M+H]^+$, 503.50 $[M+Na]^+$, 983.42 $[2M+Na]^+$, found (negative mode): 479.50 $[M–H]^–$; UV–Vis (MeOH) (λ_{max}/nm(log ε)): 222.0 (4.07), 279.5 (4.05).

4,4'-(phenylmethylene)bis(1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one) **3e**: White crystalline solid; yield: 73 %; m.p. 158–160 °C; FTIR (KBr, ν/cm^{-1}): 3058 (C-H str., aromatic), 3024, 2914 (C-H str. aliphatic), 1660 (C=O str., carbonyl), 1591 (C=C str., carbonyl), 1493 (C=C str., antipyrine), 1455 (C-H bend), 1307, 1290 (C-N str., aryl 3° amine), 1133 (C-N str., aromatic amines), 1074, 788, 719, 693 (=C-H bend); ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 7.58–7.44 (m, 10H, Ar-H), 7.34–7.21 (m, 5H, Ar-H), 5.31 (s, 1H, -CH), 3.34 (s, 6H, N–CH_3), 2.44 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 161.02 (C=O), 150.52 (Pyr), 140.74 (Ar), 132.48 (Ar), 130.11 (Ar), 130.05 (Ar), 128.85 (Ar), 128.83 (Ar), 127.68 (Ar), 127.65 (Ar), 127.15 (Ar), 129.96 (Ar), 106.06 (Pyr), 34.74 (CH), 33.07 (N–CH_3), 11.09 (CH_3); ESI-MS m/z calc. 464.22, found (positive mode): 465.50 $[M+H]^+$, 487.42 $[M+Na]^+$, 503.42 $[M+K]^+$, 951.42 $[2M+Na]^+$; UV–Vis (MeOH) (λ_{max}/nm(log ε)): 279.0 (3.82).

4,4'-((4-nitrophenyl)methylene)bis(1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one) **3f**: White crystalline solid; yield: 90 %; m.p. 234–235 °C; FTIR (KBr, ν/cm^{-1}): 3062 (C-H str., aromatic), 2988, 2900 (C-H str. aliphatic), 1655 (C=O str.,

carbonyl), 1590 (C=C skeletal str., phenyl), 1513 (C-C str., in ring), 1493 (C=C str., antipyrine), 1455 (C-H bend), 1342 (C-N str., aryl 3° amine), 1174 (C-N str., aromatic amines), 865, 786, 724, 694 (=C-H bend); ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 8.17 (d, 2H, J = 8.4 Hz, Ar-H), 7.58–7.54 (m, 6H, Ar-H), 7.49–7.43 (m, 6H, Ar-H), 5.44 (s, 1H, -CH), 3.31 (s, 6H, N–CH_3), 2.42 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 161.59 (C=O), 150.88 (Pyr), 148.96 (Ar), 146.68 (Ar), 132.94 (Ar), 130.01 (Ar), 129.46 (Ar), 129.27 (Ar), 126.96 (Ar), 123.82 (Ar), 105.71 (Pyr), 34.98 (CH), 33.35 (N–CH_3), 11.24 (CH_3); ESI-MS m/z calc. 509.21, found (positive mode): 510.42 $[M+H]^+$, 532.33 $[M+Na]^+$, UV–Vis (MeOH) (λ_{max}/nm(log ε)): 279.0 (3.88).

4,4'-(p-tolylmethylene)bis(1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one) **3g**: White crystalline solid; yield: 60 %; m.p. 135–136 °C; FTIR (KBr, ν/cm^{-1}): 3015, 2917 (C-H str.), 1663 (C=O str., carbonyl), 1591 (C=C skeletal str., phenyl), 1510 (C-C str., in ring), 1495 (C=C str., antipyrine), 1455 (C-H bend), 1401, 1307 (C-N str., aryl 3° amine), 1134, 877, 822, 782, 750, 727, 629 (=C-H bend); ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 7.59–7.49 (m, 8H, Ar-H), 7.44 (d, 4H, J = 7.2 Hz, Ar-H), 7.15–7.10 (m, 2H, Ar-H), 5.26 (s, 1H, -CH), 3.35 (s, 6H, N–CH_3), 2.46 (s, 6H, CH_3), 2.26 (s, 3H, CH_3 substituent); ^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 161.23 (C=O), 150.10 (Pyr), 137.69 (Ar), 136.01 (Ar), 132.59 (Ar), 130.09 (Ar), 129.91 (Ar), 129.39 (Ar), 127.54 (Ar), 127.35 (Ar), 106.27 (Pyr), 34.77 (CH), 32.77 (N–CH_3), 20.99 (CH_3 substituent) 11.03 (CH_3); ESI-MS m/z calc. 478.24, found (positive mode): 479.42 $[M+H]^+$, 501.42 $[M+Na]^+$, 979.33 $[2M+Na]^+$; UV–Vis (MeOH) (λ_{max}/nm(log ε)): 221.5 (4.13), 277.0 (4.02).

4,4'-((4-methoxyphenyl)methylene)bis(1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one) **3h**: White crystalline solid; yield: 88 %; m.p. 130–132 ºC; FTIR (KBr, ν/cm^{-1}): 3422, 2988 (C-H str., aromatic), 2901, 2834 (C-H str. aliphatic), 1659 (C=O str., carbonyl), 1609, 1591 (C=C skeletal str., phenyl), 1509 (C-C str., in ring), 1455 (C-H bend), 1289 (C-N str., aryl 3° amine), 1243, 1175 (C-N str., aromatic amines), 918, 750, 706 (=C-H bend); ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 7.60–7.51 (m, 6H, Ar-H), 7.45 (d, 4H, J = 7.2 Hz, Ar-H), 7.18 (d, 2H, J = 8.4 Hz, Ar-H), 6.87 (d, 2H, J = 8.4 Hz, Ar-H), 5.27 (s, 1H, -CH), 3.71 (s, 3H, -OCH_3), 3.38 (s, 6H, N–CH_3), 2.49 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 160.87 (C=O), 158.41 (Ar), 149.58 (Pyr), 132.55 (Ar), 132.32 (Ar), 130.14 (Ar), 129.89 (Ar), 128.70 (Ar), 127.69 (Ar), 114.21 (Ar), 106.15 (Pyr), 55.55 (OMe substituent), 34.64 (CH), 32.33 (N–CH_3), 10.94 (CH_3); ESI-MS m/z calc. 494.23, found (positive mode): 495.42 $[M+H]^+$, 517.42 $[M+Na]^+$, 1011.33 $[M+Na]^+$; UV–Vis (MeOH) (λ_{max}/nm(log ε)): 229.0 (4.00), 279.0 (3.89).

2.2. *In silico prediction of absorption, distribution, metabolism, elimination, and toxicity (ADMET)*

The SwissADME,[27] PreADMET,[28] and Molinspiration[29] software packages were used to determine the relevant molecular descriptors for all synthesized compounds.

2.3. *Antioxidant activity of the compounds **3a–h***

The antioxidant activity of the synthesized compounds **3a**–**h** was evaluated by the 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) radical scavenging assay.[30] To prepare the $ABTS^{\bullet+}$ radical cation stock solution, ABTS (2.456 mL, 7 mM in phosphate-buffered saline [PBS]) was allowed to react with potassium persulfate (0.044 mL, 140 mM in distilled water) in the dark for 16 hours. The resulting solution was subsequently diluted with methanol until the absorbance reached 0.700 ± 0.02 at 734 nm. For the assay, 20 μL of each methanolic compound solution (3 mM) was mixed with 2 mL of the diluted $ABTS^{\bullet+}$ solution, shaken, and incubated in the dark for 10 minutes. Then, the absorbance of the solution was recorded at 734 nm. All experiments were conducted in triplicate. The percentage inhibition of $ABTS^{\bullet+}$ was calculated using the following formula:

$$\text{Inhibition (\%)} = \frac{A_c - A_s}{A_c} \times 100\%$$

where Ac is the absorbance of the control solution and As is the absorbance of the sample solution. Ascorbic acid was used as a reference antioxidant. The antioxidant capacity of the most promising hydroxy substituted compounds (**3b**, **3c** and **3d**) was further assessed by determining their half-maximal inhibitory concentration (IC_{50}). Methanolic solutions of the selected compounds and ascorbic acid were prepared at concentrations ranging from 3 mM to 0.1 mM.

3. RESULTS AND DISCUSSION

3.1. *Microwave synthesis*

Khosropour et al.[12] reported the synthesis of triarylmethanes from *N*,*N*-dimethylaniline and substituted aldehydes using irradiation of 900 W for 15 min using 10 mol% of *p*-TsOH as the catalyst. Here, we used *p*-TsOH not only as the catalyst but also the medium in which the reaction takes place. In the first part of this study, the microwave-assisted synthesis was optimized using *p*-*N*,*N*-dimethylaminobenzaldehyde (**1a**) as a model compound. The effects of reactant ratios, reaction time, and temperature were systematically investigated. The optimal conditions were determined to be 1 minute at 100 °C. Prolonged heating did not improve the reaction yield, while increasing the temperature above 100 °C led to a decrease in yield. The optimal reactant ratio was 5:2:1 (acid:antipyrine:substituted). The reactants were not mixed prior to microwave irradiation. It is important to note that the reagents should be added to the reaction vessel in the following order: *p*-TsOH, the substituted benzaldehyde, and antipyrine. This sequence is critical because *p*-TsOH must melt to enable the reaction. If it is not placed at the bottom of the reaction vessel, microwave irradiation may lead to degradation and carbonization of the starting materials.

After optimization, the same reaction conditions were applied to other substituted benzaldehydes (**1b–h**). During microwave irradiation, due to the oxidation of the target compounds, traces of side products (triarylmethines) are formed. These intensely colored compounds usually give the sticky side-product a red appearance. Because the desired triarylmethanes are colorless, purification by crystallization from 5 % aqueous HCl produced white solids. Upon exposure to air, the triarylmethanes slowly oxidize to the corresponding triarylmethines, resulting in coloration. To prevent this, the crystals were dried at 45 °C and stored in a sealed container in the dark.

3.2. *Evaluation of pharmacological potential*

For most purposes, human oral bioavailability can be defined as the balance between different molecular descriptors that significantly affect the values of pharmacokinetic/pharmacodynamic parameters of potentially pharmacologically active compounds associated with their ADMET properties. Biomolecular characteristics, such as cell membrane permeability and bioavailability, are closely related to basic molecular descriptors such as molecular weight, the partition coefficient, the topological polar surface area (TPSA) of molecules, and the number of hydrogen bond donors/acceptors.[31] In the early stages of drug discovery, computational tools for predicting oral absorption and bioavailability play a crucial role both in selecting the most promising leads for further optimization and in identifying candidates for clinical development.[32] Conventional methods for evaluating oral bioavailability are based on the application of classical empirical rules, among which the most famous is Lipinski's rule of five.[33] According to this rule, most "drug-like" compounds have log $P \leq 5$, a molecular weight ≤ 500 g/mol, ≤ 10 hydrogen bond acceptors, and ≤ 5 hydrogen bond donors. Compounds that violate more than one of these rules are likely to exhibit poor bioavailability.[34] Veber extended Lipinski's rule of five to include fifth and sixth rules, according to which potentially pharmacologically active compound possesses < 10 rotating bonds and a TPSA < 140 Å^2, which significantly limits their flexibility. Based on the modified forms of these criteria, compounds with WlogP ≤ 5.88 and TPSA ≤ 131.6 Å^2 (Egan's criterion) are predicted to have a high probability of therapeutic efficacy.

Based on the calculated molecular descriptors summarized in Table 1, it can be concluded that the synthesized antipyrine-based triarylmethanes generally comply with all classical empirical rules. This indicates that they meet the theoretical requirements for adequate bioavailability in the organism and, consequently, possess potential biological activity. The only exceptions are compounds **3a** and **3f**, which have molecular weights greater than 500 g mol^{-1} and therefore deviate from Lipinski's rule of five. However, because these compounds violate only one of Lipinski's criteria, they are still potentially pharmacologically active.

Based on the calculated TPSA values of the compounds (Table 1), in *in vivo* conditions, the antipyrine-based triarylmethanes are expected to show good intestinal absorption and passage through the blood-brain barrier.[35] The calculated TPSA values of the synthesized triarylmethanes ranged from 53.86 to 99.68 Å^2. Hydroxy-substituted derivatives (**3b**–**3d**) and the *p*-nitro-substituted compound (**3f**) exhibited higher TPSA values, reflecting increased polarity and hydrogen-bonding potential, which can enhance aqueous solubility but may slightly reduce passive membrane permeability.

Table 1. Physicochemical properties of the investigated compounds

Compound	MW, g/mol[a]	NA[a]	Nrotb[a]	HBD[a]	HBA[a]	MR[a]	TPSA, Å^{2a}	log$P_{o/w}$ (Wlog$P$)[a]	log$P$[b]
3a	507.63	38	6	0	2	154.22	57.10	4.53	3.98
3b	480.56	36	5	1	3	142.03	74.09	4.17	3.39
3c	480.56	36	5	1	3	142.03	74.09	4.17	3.37
3d	480.56	36	5	1	3	142.03	74.09	4.17	3.81
3e	464.56	35	5	0	2	140.01	53.86	4.46	3.87
3f	509.56	38	6	0	4	148.83	99.68	4.89	3.83
3g	478.58	36	5	0	2	144.98	53.86	4.77	4.32
3h	494.58	37	6	0	3	146.50	63.09	4.47	3.93

*MW – molecular weight, NA – number of atoms, Nrotb – number of rotatable bonds, HBD – number of hydrogen bond donors, HBA – number of hydrogen bond acceptors, MR – molar refractivity, TPSA – topological polar surface area; [a] reference [27]; [b] reference [28]

A moderate number of rotatable bonds also contribute to the optimal passage of the studied compounds through the blood-brain barrier. According to the literature, compounds acting on the central nervous system generally possess fewer than eight rotatable bonds.[36] The investigated triarylmethanes comply with this empirical rule, with each having fewer than six rotatable bonds.

The calculated partition coefficients of the synthesized triarylmethanes ranged from 4.17 to 4.89 (WlogP) and from 3.37 to 4.32 (logP), indicating that all compounds possess suitable lipophilicity for high gastrointestinal absorption and efficient blood-brain barrier penetration. Compounds bearing hydroxy substituents (**3b**–**3d**) exhibited lower logP values, reflecting increased polarity, whereas the methyl-substituted derivative (**3g**) showed a higher logP, indicating greater lipophilicity. Consequently, the more polar hydroxy-substituted derivatives are expected to have slightly lower permeability compared to the more lipophilic methyl-substituted compounds, but a better aqueous solubility. These findings highlight the delicate balance between lipophilicity and solubility, showing that small modifications on the phenyl ring, both in the type and position of substituents, can fine-tune absorption and distribution properties, providing valuable guidance for the rational design of derivatives with optimized pharmacokinetic profiles.

In addition to the optimal values of the physicochemical parameters, compound with potential pharmacological activity must also have optimal pharmacokinetic parameters. Using relevant software packages, the pharmacokinetic characteristics of the investigated antipyrine-based triarylmethanes were evaluated based on gastrointestinal absorption (Table 2). The investigated compounds exhibit a high degree of gastrointestinal absorption (approximately 97 %) and are able to cross the blood-brain barrier, owing to their favorable partition coefficients. Furthermore, computational analyses revealed that all investigated compounds are predicted not to inhibit P-glycoprotein (P-gp), suggesting a lower risk of efflux-related drug interactions.

Table 2. Quantitative structure–activity relationship (QSAR) pharmacokinetic profiles of the investigated compounds related to absorption properties[27,28]

	SwissADME	PreADMET	SwissADME	PreADMET	SwissADME	PreADMET
Comp.	GI[a] absorption	GI[a] absorption, %	penetrates BBB[b]	c_{brain}/c_{blood}[c]	P-gp I[d]	P-gp I[d]
3a	High	97.89	Yes	0.24	No	No
3b	High	96.98	Yes	0.05	No	No
3c	High	96.98	Yes	0.05	No	No
3d	High	96.98	Yes	0.05	No	No
3e	High	97.81	Yes	0.11	No	No
3f	High	98.82	Yes	0.02	No	No
3g	High	97.86	Yes	0.09	No	No
3h	High	97.76	Yes	1.13	No	No

[a] GI – Gastrointestinal; [b] BBB – blood-brain barrier; [c] (cbrain/cblood) – concentration of the compound in the brain and blood; [d] P-gp I – P-glycoprotein inhibitor

3.3. *Evaluation of antioxidant activity*

The antioxidant capacity of compounds **3a**–**3h** was initially evaluated at a concentration of 3 mM, with the results presented in Figure 1a. Antioxidant activity varied considerably, ranging from 0 % to 91.8 %, depending on the substitution pattern of the phenyl ring derived from the aldehyde moiety. Notably, the presence of a hydroxyl group markedly enhanced activity, as observed for compounds **3b**, **3c**, and **3d**. In contrast, the *para*-substituted *N*,*N*-dimethylamino derivative (**3a**) displayed moderate activity (36.4 %), while the remaining compounds showed no detectable antioxidant activity.

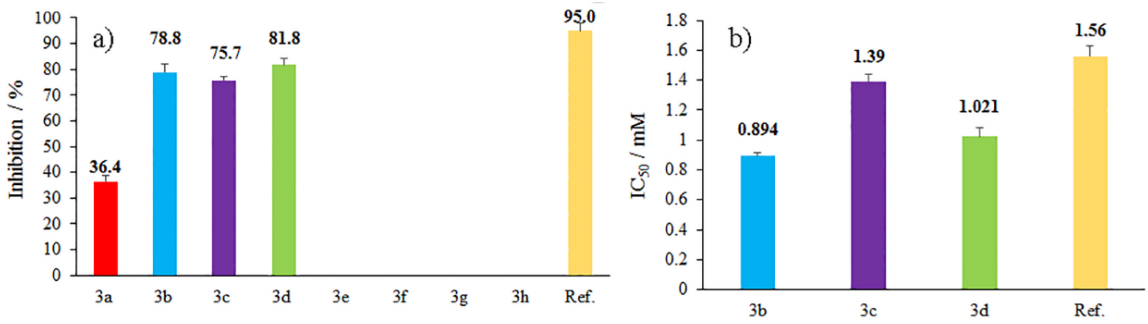
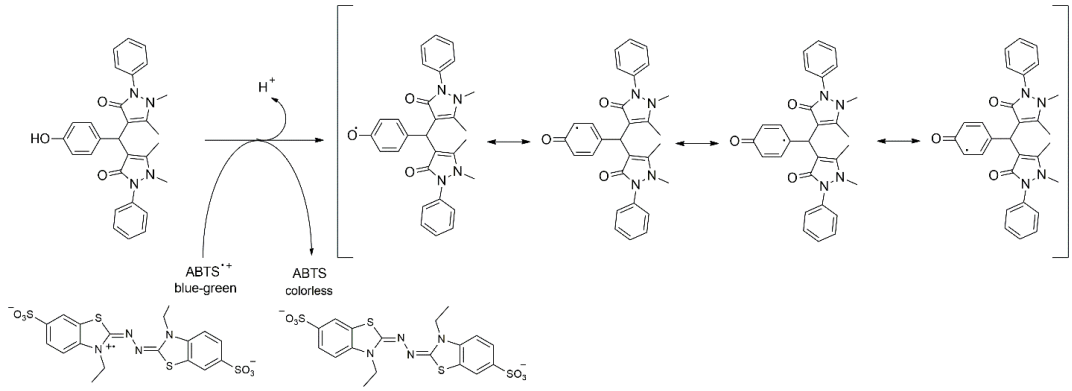


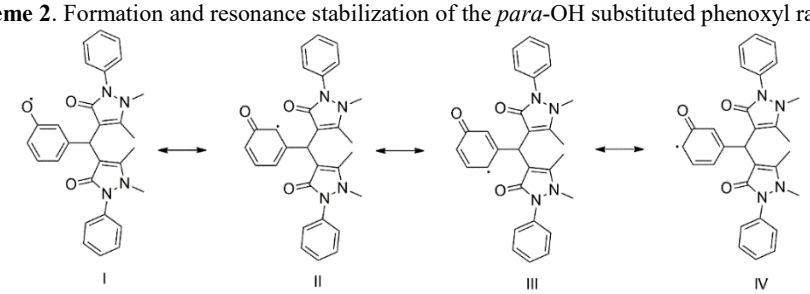
Fig. 1. The antioxidant activity of the investigated compounds compared with the reference (ascorbic acid). (a) The scavenging activity at a sample concentration of 3 mM. (b) IC_{50} of hydroxy-substituted compounds compared with the reference

Compounds with notable antioxidant effects (**3b**, **3c**, and **3d**) were further analyzed to determine their IC_{50} values (Figure 1b). A lower IC_{50} corresponds to greater antioxidant potency. Compared with ascorbic acid, which has an IC_{50} of 1.56 mM, the samples demonstrate superior antioxidant activity, with an IC_{50} ranging from 0.894 to 1.39 mM. The activity decreases in the following order **3b** (*para*-substituted) > **3d** (*ortho*-substituted) > **3c** (*meta*-substituted), suggesting that the position of the –OH group on the phenyl ring significantly influences radical scavenging efficiency.[37] This is consistent with published data suggesting that the strong radical scavenging potential is mainly associated with the presence of –OH group in the phenyl ring.[38]

The scavenging of $ABTS^{\bullet+}$ by phenolic compounds can proceed through various mechanisms, including mixed hydrogen atom transfer (HAT), single electron transfer (SET), or sequential proton loss electron transfer (SPLET) mechanisms.[39] These pathways may occur simultaneously, and their predominance depends on factors like solvent polarity and the pH of the solution.[40] Although the rapid reaction kinetics make it difficult to distinguish between possible mechanisms, they generally lead to the formation of a phenoxyl radical intermediate following deprotonation and one-electron removal of the antioxidant molecule.[41] In the case of the investigated compounds (**3b**, **3c**, and **3d**), the phenoxyl radical formed upon reaction with $ABTS^{\bullet+}$ may be further stabilized through resonance delocalization of the unpaired electron across the phenyl ring (Scheme 2) thereby enhancing their antioxidant activity. The *para*-substitution allows more effective resonance stabilization of the phenoxyl radical compared with *meta*- and *ortho*-substitution. In this case, resonance structure III is additionally stabilized via a negative inductive effect of two antipyrine moieties (the CH atom is sp^3 hybridized, preventing effective delocalization), thereby increasing the stability of the radical intermediate and improving overall antioxidant efficiency. In contrast, *meta*-substitution does not allow for additional stabilization in such way (Scheme 3), while *ortho*-substitution may exhibit steric hindrance that slightly reduces activity when compared to the para-substituted compound.



Scheme 2. Formation and resonance stabilization of the *para*-OH substituted phenoxyl radical.



Scheme 3. Resonance stabilization of the *meta*-OH substituted phenoxyl radical

4. CONCLUSION

In this study, nine antipyrine-based triarylmethanes were successfully synthesized using an optimized microwave-assisted, solvent-free protocol that enabled a significantly shorter reaction time compared with conventional approaches. The results confirm that microwave irradiation is an efficient and convenient strategy for the rapid preparation of this class of compounds. The *in silico* study revealed that most compounds comply with empirical rules indicating their favorable oral bioavailability and potential for central nervous system penetration. The calculated molecular descriptors indicate that the hydroxy-substituted derivatives exhibit slightly lower membrane permeability but enhanced aqueous solubility compared to the more lipophilic methyl-substituted compound. Antioxidant evaluation revealed that substitution of the phenyl ring with hydroxyl groups is responsible for the observed radical scavenging activity, with the *para*-hydroxy derivative showing the highest potency, followed by *ortho*- and *meta*-substituted compounds. The observed activity correlates with the ability of these compounds to stabilize phenoxyl radicals through resonance and the inductive effects of the antipyrine moieties, highlighting the critical role of the substituent type and position in modulating biological activity. Overall, this study demonstrates that careful tuning of substituents on the phenyl ring enables the modulation of physicochemical properties, pharmacokinetic potential, and antioxidant activity. These findings provide a strong foundation for the rational design of triarylmethane derivatives with optimized pharmacological and pharmacokinetic profiles for future drug development.

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