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# Variation of the bromination site on the reaction of (*E*)-1-[5-methyl-1-(aryl)-1*H*-1,2,3-triazol-4-yl]-3-arylprop-2-en-1-ones with *N*-bromosuccinimide

**Bakr F. Abdel-Wahab,[a] Hanan A. Mohamed,[a] Ehab M. Zayed,[b] Benson M. Kariuki,[c] and Gamal A. El-Hiti[d,*]**

*[a] Applied Organic Chemistry Department, Chemical Industries Research Institute, National Research Centre, Dokki, Giza 12622, Egypt; [b] Green Chemistry Department, Chemical Industries Research Institute, National Research Centre, Dokki, Giza 12622, Egypt. [c] School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff CF10 3AT, UK; [d] Department of Optometry, College of Applied Medical Sciences, King Saud University, Riyadh 11433, Saudi Arabia*

*Email: gelhiti@ksu.edu.sa*

**Dedicated to the memory of Professor Alan R. Katritzky and Professor Charles W. Rees**

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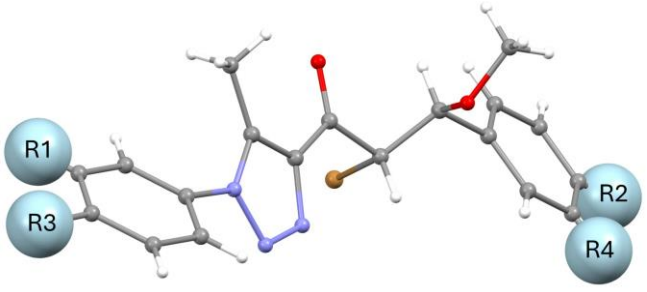
## Abstract

The variation of the bromination site of three chalcones, **1a–c**, using *N*-bromosuccinimide under acidic conditions was investigated. Bromination of **1a** at the aliphatic carbon-carbon double bond gave the α-methoxy bromide derivative **2** in 95% yield. Bromination of **1b** and **1c** under similar conditions produced the corresponding methoxy bromide derivatives **3** and **4** in 89 and 88% yields, respectively. The bromination of **1b** took place at the aliphatic carbon-carbon double bond, and the aryl ring attached to the 1,2,3-triazole moiety at the *ortho*-position next to the methoxy group. In the presence of two methoxy groups on the aryl rings on the two sides of chalcone **1c**, bromination took place on the aryl ring at the *ortho*-position next to the methoxy group and the aliphatic carbon-carbon double bond.




**Keywords:** Chalcone; alkoxybromides; *N*-bromosuccinimide; *p*-toluenesulfonic acid; bromination, X-ray

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## Introduction

Halogen-containing compounds have a vital role in synthetic chemistry.[1] The compounds are widely encountered in marine natural products, agrochemicals, and material molecules.[2–4] For instance, iodocallophycol E is a marine natural product that shows cytotoxicity against different cancer cell lines.[5–7] Halogen compounds are also valuable building blocks in synthetic chemistry. They are involved in various chemical transformations, including substitution, elimination, and coupling reactions, which are frequently used in the synthesis of complex molecules.[8,9] In view of the importance of the compounds, it is beneficial to develop practical and environmentally friendly halogenation reactions for modern organic synthesis.[10–12]

Chalcones (1,3-diaryl-2-propen-1-ones) are a type of open-chain flavonoid naturally produced in plants and have a broad range of applications in organic synthesis.[13–15] Due to their unique structure, chalcones have been used as a basis for developing various lead compounds with different pharmacological properties. As a result, chalcones have received significant attention in the field of medicinal chemistry, and numerous studies have been conducted to explore their potential application in drug development.[16,17] Several chalcones containing the 1,2,3-triazole moiety and with potential medicinal applications are shown in Figure 1.

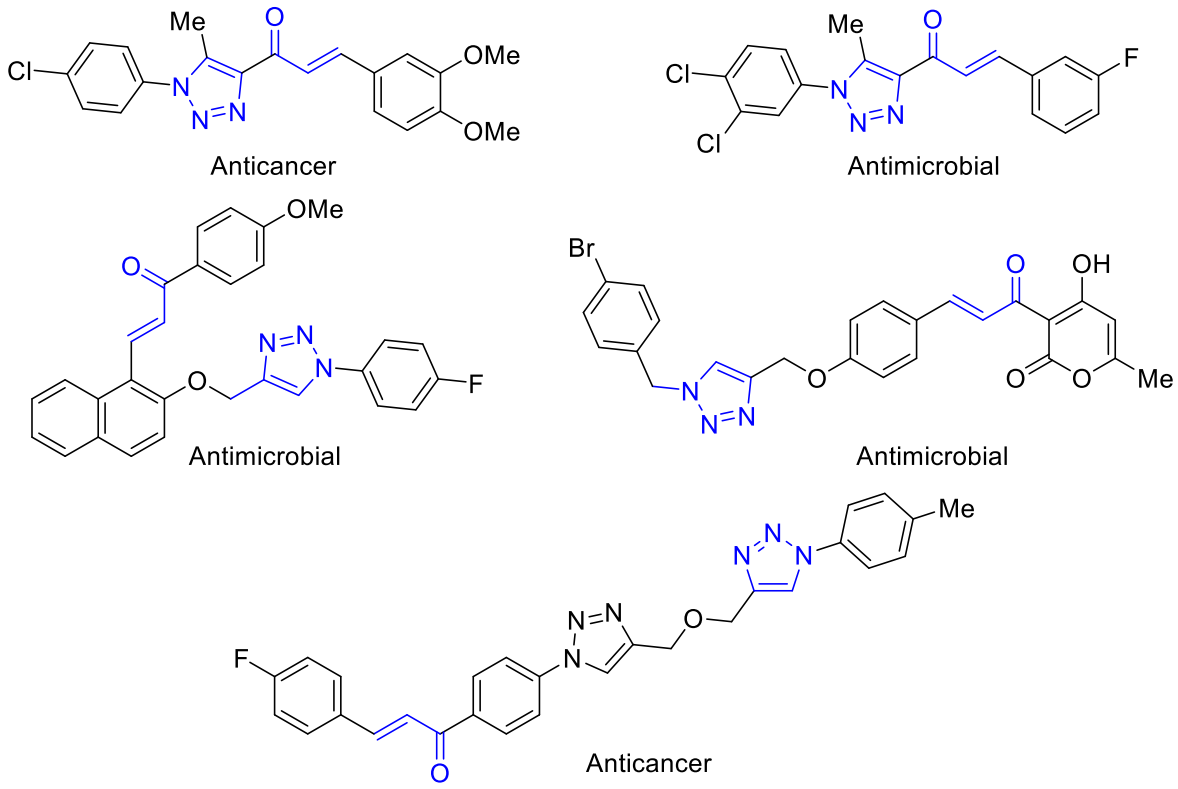



**Figure 1.** Representative chalcones containing 1,2,3-triazole moiety.

Extensive research has been conducted on the bromoalkoxylation of enone-type alkenes in recent decades.[2] An initial study conducted in 1983 revealed that *N*-bromosuccinimide (NBS), activated with sulfuric acid, enabled the reaction.[18] The use of liquid bromine has fallen out of favor due to the associated environmental risk.[19] Therefore, various oxidation methods have been developed to generate the bromonium cation by oxidizing the bromine anion from a green bromide salt, including the use of oxone,[20] potassium bromate,[21] (diacetoxyiodo)benzene,[22,23] and vanadium(V) oxide.[24] Greener and more stable bromine carriers,

such as tetrabutylammonium tribromide[25] or bromodimethylsulfonium bromide,[26] have also emerged. The asymmetric intramolecular variant of this reaction using the powerful *N,N'*-dioxide ligand, and iron catalyst with NBS as the brominating reagent has been reported.[27]

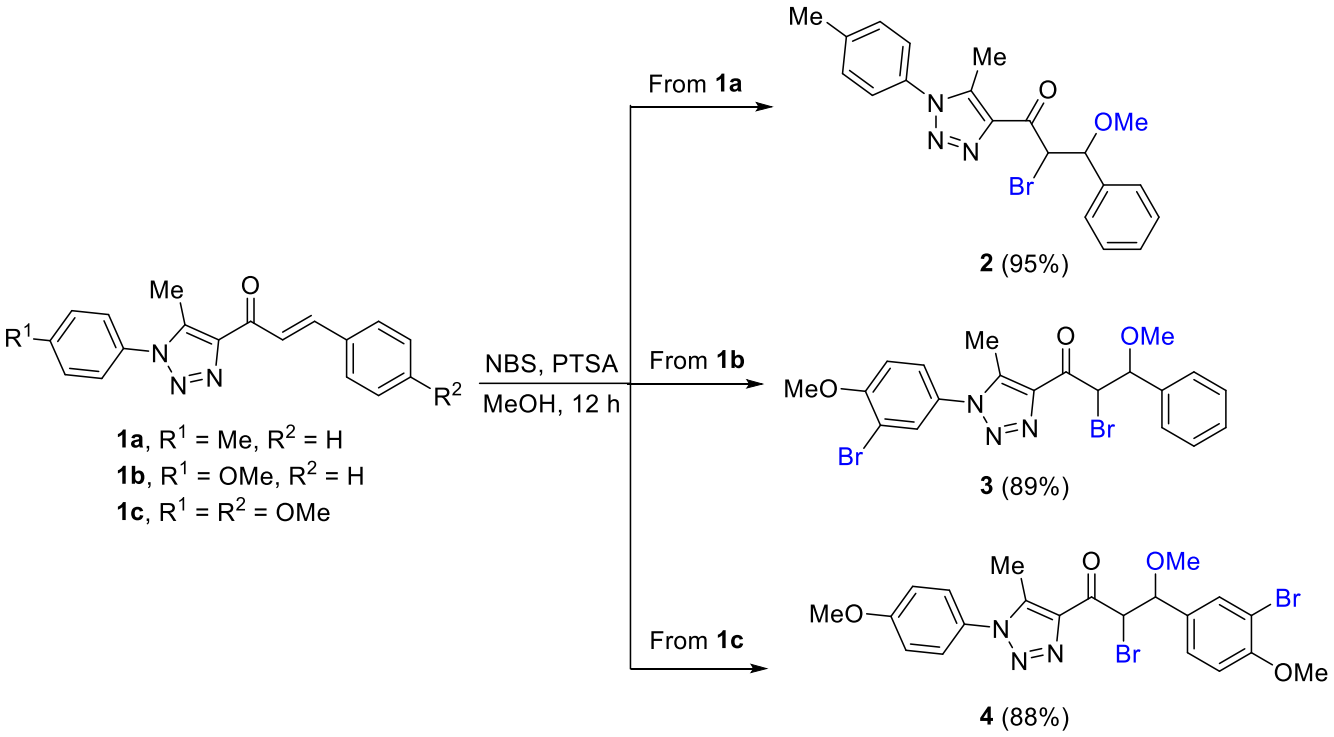
A reliable brominating reagent like NBS is generally utilized in bromoalkoxylation reactions. However, the process requires the assistance of a potent Brønsted acid such as sulfuric acid, the usage of which may be restricted in some situations. Thiourea organocatalysts, on the other hand, have a lower acidity level and can effectively facilitate the reaction.[28]

The current research was conducted following the observation of an unexpected bromination product. Under similar reaction conditions, the location of the bromination site of three chalcones containing the 1,2,3-triazole moiety using NBS in the presence of p-toluenesulfonic acid (PTSA) was investigated. Products **2–4** were produced in excellent yields, and their structures were established. The bromination took place at the aliphatic carbon-carbon double bond and on the aryl ring attached to the 1,2,3-triazole moiety *ortho* to the methoxy group.

## Results and Discussion

The bromination of chalcones using NBS was revealed in 1995. The structure of the product depends on the nature of the substituents.[29] In the current work, treatment of chalcone **1a** ($R^1$ = Me, $R^2$ = H) with NBS in methanol (MeOH) in the presence of PTSA for 12 h gave 2-bromo-3-methoxy-1-[5-methyl-1-(*p*-tolyl)-1*H*-1,2,3-triazol-4-yl]-3-phenylpropan-1-one (**2**) in 95% yield based on the TLC. Bromination of **1b** ($R^1$ = OMe, $R^2$ = H) containing one methoxy (OMe) group under the same conditions afforded 2-bromo-1-[1-(3-bromo-4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]-3-methoxy-3-phenylpropan-1-one (**3**) in 89% yield. The bromination took place at the aliphatic carbon-carbon double bond, and the aromatic ring attached to the 1,2,3-triazole moiety at the *ortho*-position next to the methoxy group. In the crystal, the *ortho* substituent is disordered with 42.6(2)% Br occupancy, indicating that bromination on the location is incomplete. For **1c** ($R^1$ = OMe, $R^2$ = OMe) which contains two OMe groups on the two sides of the chalcone, 2-bromo-3-(3-bromo-4-methoxyphenyl)-3-methoxy-1-[1-(4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]propan-1-one (**4**) was obtained in 88% yield (Scheme 1). In this case, the bromination took place on the aromatic ring at the *ortho*-position next to the methoxy group in addition to the aliphatic carbon-carbon double bond.




**Scheme 1.** Synthesis of **2–4** through bromination of 1,2,3-triazole-based chalcones using NBS under acidic conditions.

The mechanism involves the ionic fragmentation of NBS into a bromide cation and a succinimide anion. The bromide cation attacks the polarized double bond of chalcones to form a bromonium ion intermediate. In the presence of methanol, this intermediate produces the corresponding α-methoxy bromide compounds. The OMe group on the aryl ring activates the *ortho* position towards an electrophilic bromination substitution reaction.

The FTIR spectra of **2–4** showed several characteristic vibration bands that appeared in the regions of 2923–3065, 1679–1689, 1590–1594, and 1548–1552 $cm^{-1}$ due to the C–H, C=O, C=N, and C=C groups, respectively.

The methoxy protons of α-methoxyl bromide in **2–4** appeared as a singlet in the 3.09–3.10 ppm region of the $^{1}H$ NMR spectra. The methyl protons attached to the 1,2,3-triazole ring appeared as singlets in the region of 2.39–2.57 ppm. The two CH protons appeared as two doublets ($J$ = 9 Hz) in the 4.87–4.88 and 5.69–5.70 ppm regions.

The $^{13}C$ NMR spectra **2–4** showed the carbon of the α-methoxyl bromide at a high field in the 56.2–57.0 ppm region. The spectra showed the carbonyl carbon at a low field in the 187.5–187.7 ppm region. The two CH carbons appeared in the 48.1–57.0 and 81.2–82.4 ppm regions.

The crystal structure of **2** is monoclinic, space group $P2_1/n$ (Table 1), with one molecule in the symmetric unit (Figure 2a). The molecule of **2** comprises methylphenyl (*mphen*, C1–C6, C20), methyltriazole (*mtria*, C7–C9, N1–N3), 2-bromo-3-methoxypropanoyl (C10–C12, C19, O1, O2, Br1) and phenyl (*phen*, C13–C18) groups. In the molecule, interplanar twist angles *mphen*/*mtria* and *mtria*/*phen* are 46.28(10)° and 30.73(14)°, respectively. The selected torsion angles shown in Table 2 for the 2-bromo-3-methoxypropanoyl group are in the 141–177° range. In the crystal structure, a C–H…Br intermolecular contact with a C6–H6…Br1 angle of

148.4° and a C6…Br6 distance of 3.909(3) Å is observed and forms chains of molecules along the *b*-axis (Figure 2b).

**Table 1.** Crystal and structure refinement data

| Compound | **2** | **3** | **4** |
|---|---|---|---|
| Formula | $C_{20}H_{20}BrN_3O_2$ | $C_{20}H_{19.58}Br_{1.42}N_3O_3$ | $C_{21}H_{21}Br_2N_3O_4$ |
| Formula weight | 414.30 | 463.44 | 539.23 |
| Temperature (K) | 296(2) | 293(2) | 293(2) |
| Wavelength (Å) | 0.71073 | 0.71073 | 0.71073 |
| Crystal system | Monoclinic | Triclinic | Triclinic |
| Space group | $P2_1/n$ | $P\bar{1}$ | $P\bar{1}$ |
| a (Å) | 15.1917(10) | 8.6657(6) | 7.9084(7) |
| b (Å) | 7.3491(4) | 11.3808(7) | 9.6713(6) |
| c (Å) | 17.3707(9) | 11.7740(8) | 14.9540(12) |
| $\alpha$ (°) | 90 | 66.237(6) | 74.369(6) |
| $\beta$ (°) | 100.068(6) | 77.532(6) | 77.424(7) |
| $\gamma$ (°) | 90 | 74.221(6) | 86.856(6) |
| Volume ($Å^3$) | 1909.49(19) | 1015.21(13) | 1075.02(15) |
| Z | 4 | 2 | 2 |
| Density (calc.) ($Mg/m^3$) | 1.441 | 1.516 | 1.666 |
| Absorp. Coeff. ($mm^{-1}$) | 2.172 | 2.876 | 3.803 |
| Crystal size ($mm^3$) | $0.47 \times 0.16 \times 0.10$ | $0.46 \times 0.26 \times 0.20$ | $0.62 \times 0.40 \times 0.33$ |
| Reflections collected | 17386 | 9540 | 10144 |
| Independent reflections | 4730 | 4833 | 5107 |
| R(int) | 0.0397 | 0.0363 | 0.0299 |
| Parameters | 238 | 257 | 275 |
| Goodness-of-fit on $F^2$ | 1.057 | 1.017 | 1.047 |
| R1 ($I>2\sigma(I)$) | 0.0496 | 0.0475 | 0.0481 |
| wR2 ($I>2\sigma(I)$) | 0.1008 | 0.1021 | 0.1190 |
| Largest diff. peak/hole ($e.Å^{-3}$) | 0.654/–0.586 | 0.684/–0.532 | 0.617/–0.730 |

**Table 2.** Interplanar twist angles and selected torsion angles

| Compound | **2** | **3** | **4** |
|---|---|---|---|
| Twist angles (°) | | | |
| *mphen* or *mophen*/*mtria* | 46.28(10) | 54.26(10) | 38.62(12) |
| *mtria*/*phen* or *brmophen* | 30.73(14) | 30.54(10) | 10.25(14) |
| Torsion angles (°) | | | |
| C9–C10–C11–C12 | 141.35(32) | 131.07(30) | 123.00(37) |
| C10–C11–C12–C13 | 171.23(28) | 178.86(26) | 175.10(31) |
| Br1–C11–C12–O2 | 177.09(19) | 175.01(20) | 172.42(24) |
| C11–C12–O2–C19 | 160.97(26) | 169.02(27) | 149.53(35) |

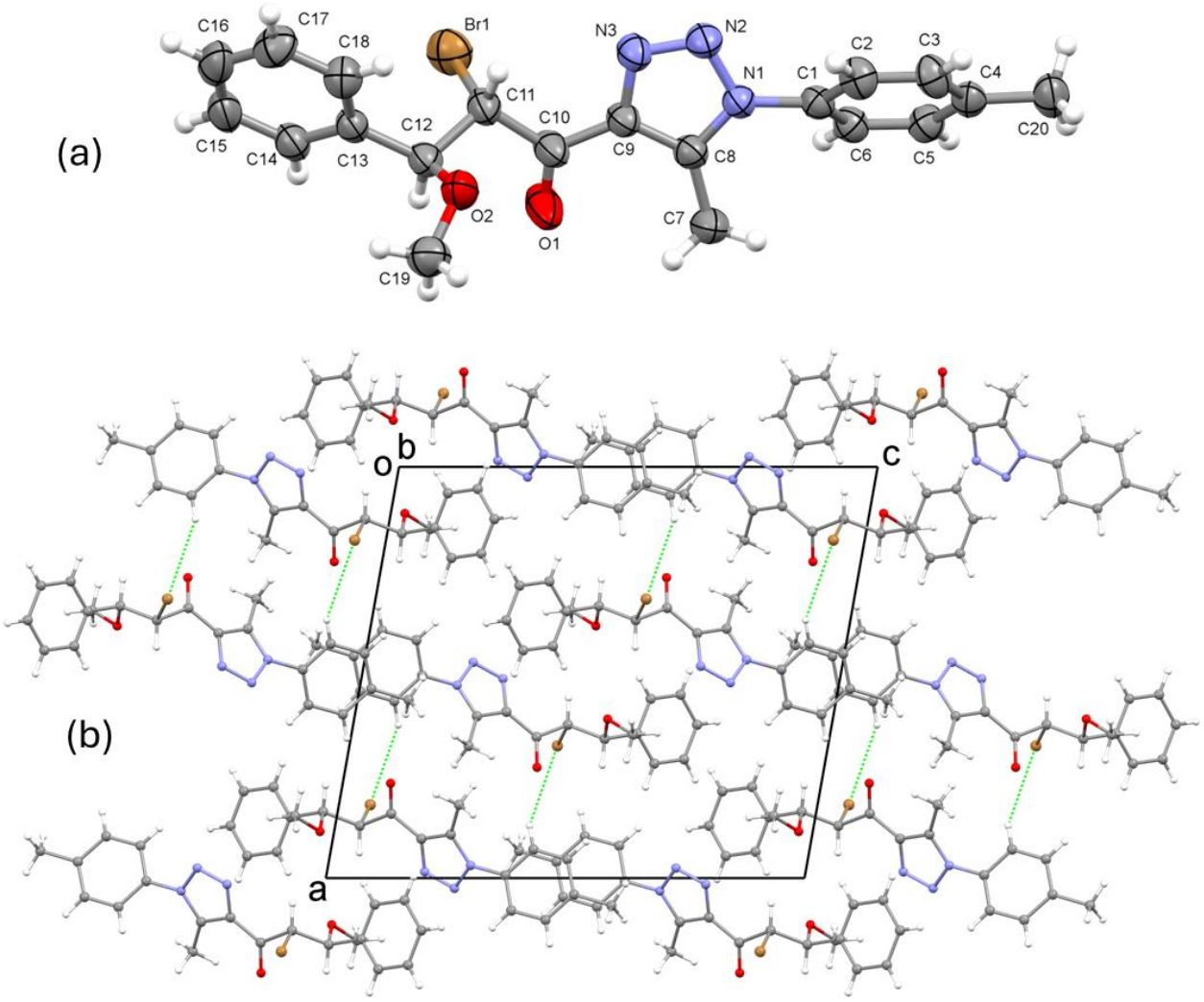



**Figure 2.** (a) The asymmetric unit of **2** depicted in the ortep representation with atomic displacement parameters at 50% probability level. (b) Crystal packing viewed down the *b* axis with C–H…Br contacts shown as green dotted lines.

The crystal structure of **3** is triclinic, space group P$\bar{1}$ (Table 1), with one molecule in the symmetric unit (Figure 3a). The molecule of **3** comprises methoxyphenyl (*mophen*, C1–C6, C20, O3), methyltriazole (*mtria*, C7–C9, N1–N3), 2-bromo-3-methoxypropanoyl (C10–C12, C19, O1, O2, Br1) and phenyl (*phen*, C13–C18) groups. The methoxyphenyl group (*mophen)* is partially substituted on the location *ortho* to the methoxy group (C3) by a Br atom with 43% occupancy. The interplanar twist angles *mophen*/*mtria* and *mtria/phen* are 54.26(10)° and 30.54(10)°, respectively. Selected torsion angles are shown in Table 2 and are in the range 131–179°. In the crystal structure, a C–H…O intermolecular contact with a C6–H6…O1 angle of 176.2 and C6…O1 distance of 3.397(4) Å links pairs of molecules in the structure (Figure 3b).

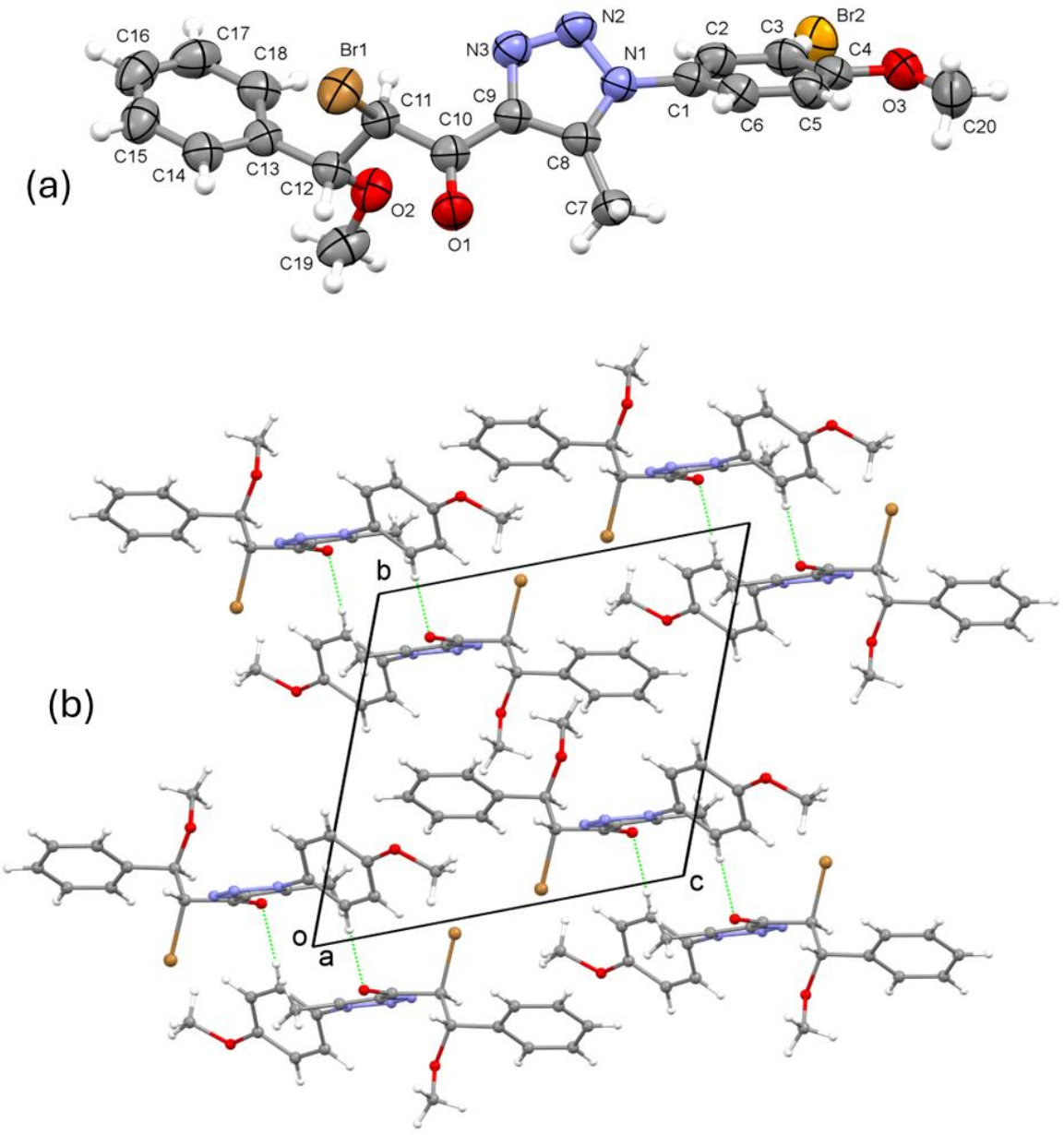



**Figure 3.** (a) The asymmetric unit of **3** depicted in the ortep representation displaying the atomic displacement parameters at 50% probability level. (b) Crystal packing viewed down the *a* axis with C–H…O contacts shown as green dotted lines. The disordered bromine atom (Br2) has been omitted for clarity.

The crystal structure of **4** is triclinic, space group $P\bar{1}$ (Table 1), with one molecule in the symmetric unit (Figure 4a). The molecule of **4** comprises methoxyphenyl (*mophen*, C1–C6, C20, O3), methyltriazole (*mtria*, C7–C9, N1–N3), 2-bromo-3-methoxypropanoyl (C10–C12, C19, O1, O2, Br1) and bromomethoxyphenyl (*brmophen*, C13–C18, C21) groups. The interplanar twist angles *mophen*/*mtria* and *mtria/brmophen* are 38.62(12) and 10.25(14)°, respectively. Selected torsion angles are shown in Table 2 and are in the range of 123–175° (Table 2). C–H…Br intermolecular contacts with a C6–H6…Br2 and C7–H7C...Br2 angles of 151.7 and 148.1°, respectively, and with C6…Br2 and C7…Br2 distances of 3.934(4) and 3.918(4) Å, respectively, link pairs of molecules (Figure 4b).

The molecular conformation is similar to that of related compounds. In **2**, **3**, and **4**, the twist angles between the planes of adjacent phenyl and triazolyl groups are between 38.62(12) and 54.26(10)°, as shown in Table 2. For comparison, the corresponding twist angle in 2-bromo-1-[1-(4-bromophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]ethenone is 52°.[30]

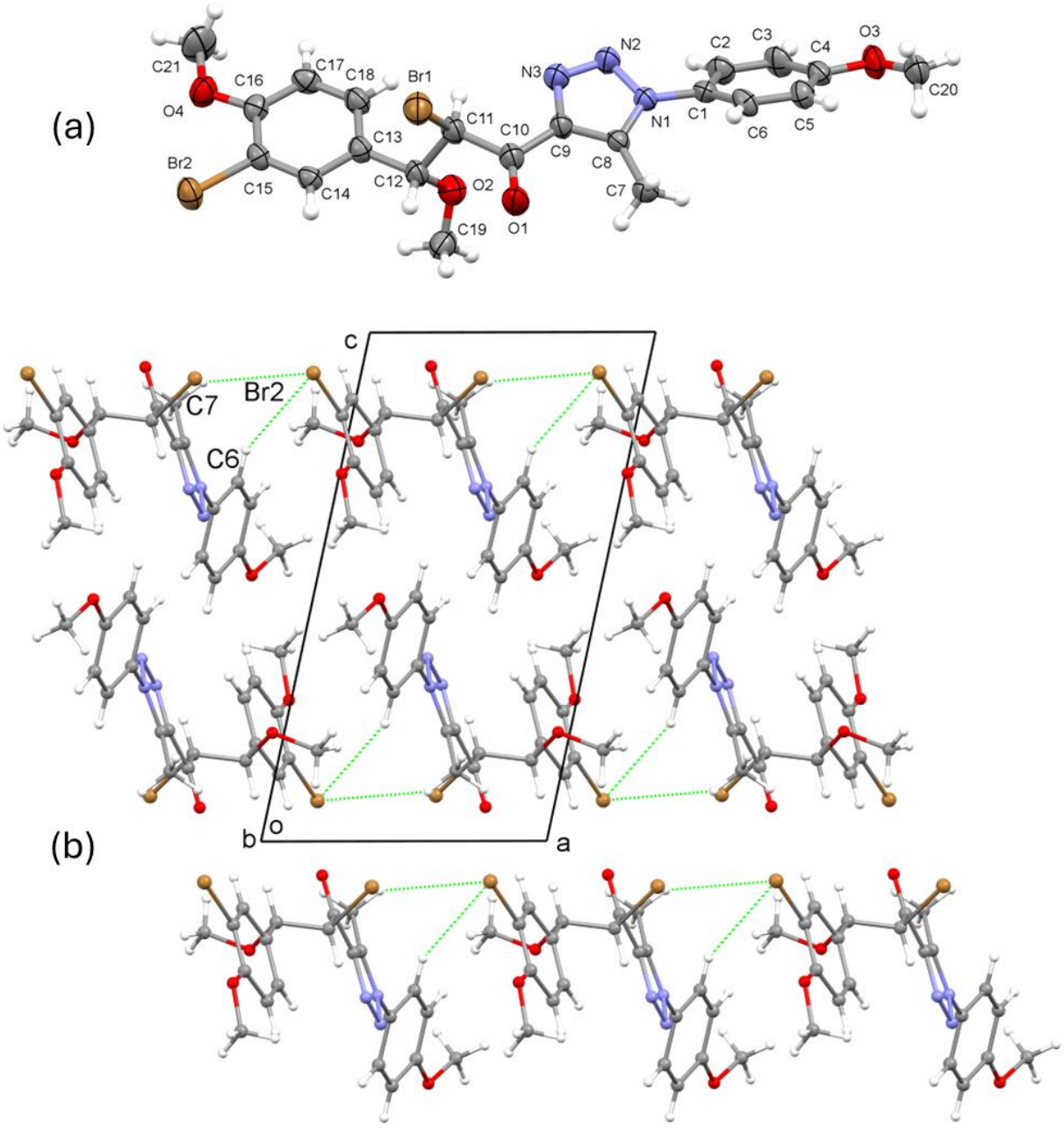



**Figure 4.** (a) The asymmetric unit of **4** depicted in ortep representation with atomic displacement parameters at 50% probability level. (b) Crystal packing viewed down the *b* axis with C–H…Br contacts shown as green dotted lines.

Torsion angles C9–C10–C11–C12 are in the range 123–142° for **2**, **3** and **4** (Table 2). The corresponding values for 2-bromo-3-methoxy-1,3-diphenylpropan-1-one (EBEMIK),[27] 2-bromo-1-(2,4-dichlorophenyl)-3-

methoxy-3-(4-methoxyphenyl)propan-1-one (PILQEH),[31] and 2-bromo-3-(3-bromo-5-*t*-butyl-4-hydroxyphenyl)-3-methoxy-1-phenylpropan-1-one (WIVDIR)[32] are 152, 132, and 148°, respectively. For **2**, **3**, and **4**, torsion angles C10–C11–C12–C13 are in the range 171-178°, whereas the angles for EBEMIK, PILQEH, and WIVDIR are 176, 180, and 174,° respectively. Torsion angles Br1–C11–C12–O2 are between 172–178° for **2**, **3**, and **4**, and they are about 178° for EBEMIK, PILQEH, and WIVDIR. Torsion angles C11–C12–O2–C19 range from 149 to 170° in samples **2**, **3**, and **4**, and they are 163, 166 and 157° for EBEMIK, PILQEH, and WIVDIR, respectively.

## Conclusions

Methoxybromination of three chalcones containing 1-aryl-1,2,3-triazoles using *N*-bromosuccinimide in the presence of 4-toluenesulfonic acid as the catalyst is reported. The process led to the formation of α-methoxyl bromides in high yields. The bromination took place on the aliphatic carbon-carbon double bond, and the aryl ring attached to the triazole moiety next to the methoxy group. The structures of the new heterocycles were determined by X-ray crystallography and NMR spectroscopy. The results reveal a possible route to fine-tuning the bromination of molecules to generate new derivatives. A further study is, however, required to elucidate the detailed reaction mechanism and the reasons for the variation of the bromination sites of the different chalcones. Many chalcones containing the 1,2,3-triazole moiety display biological activity, and the newly synthesized heterocycles will need to be assessed for potential applications.

## Experimental Section

**General.** Chemicals, reagents, and analytical solvents were obtained from Merck. The IR spectra were recorded on a Bruker Vertex 80 ATR-FTIR spectrometer (400–4000 $cm^{-1}$). The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer at 300 MHz for the protons and 75.4 MHz for the carbons in deuterated dimethyl sulfoxide (DMSO-$d_6$). The chemical shift (δ) was reported in ppm, and the coupling constant (*J*) was measured in Hz. Compounds **1a–c** were produced using reported procedures.[33,34]

**Synthesis of 2–4.** A mixture of appropriate chalcone **1a–c** (5 mmol), NBS (7.5 mmol, 1.3 g), and PTSA (0.5 g) in MeOH (20 mL) was stirred at room temperature for 12 h. The mixture was poured into ice water and left to stand for 6 h. The colorless solid was collected, dried, and recrystallized from dimethyl formamide.

**2-Bromo-3-methoxy-1-[5-methyl-1-(*p*-tolyl)-1*H*-1,2,3-triazol-4-yl]-3-phenylpropan-1-one (2).** Yield 95%, MP 118–120 °C. IR: 3063, 2923, 1679, 1590, 1548 $cm^{-1}$. $^1$H NMR: 2.43 (s, 3H, Me), 2.59 (s, 3H, Me), 3.09 (s, 3H, OMe), 4.88 (d, 9 Hz, 1H, CH), 5.70 (d, 9 Hz, 1H, CH), 7.39–7.58 (m, 9H, Ar and Ph).$^{13}$C NMR: 9.9 (Me), 20.8 (Me), 48.1 (CH), 57.0 (OMe), 82.4 (CH), 125.3 (C2/C6 of Ar), 128.2 (C2/C6 of Ph), 128.4 (C4 of Ph), 128.8 (C3/C5 of Ph), 130.1 (C3/C5 of Ar), 132.3 (C1 of Ar), 137.4 C4 of triazolyl), 140.0 (C1 of Ph), 140.2 (C4 of Ar), 140.6 (C5 of triazolyl), 187.7 (C=O). Anal. Calcd. for $C_{20}H_{20}BrN_3O_2$ (414.30): C, 57.98; H, 4.87; N, 10.14. Found: C, 58.12; H, 4.98; N, 10.33%.

**2-Bromo-1-[1-(3-bromo-4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]-3-methoxy-3-phenylpropan-1-one (3).** Yield 89%, MP 144–145 °C. IR: 3063, 2984, 1684, 1594, 1552 $cm^{-1}$. $^1$H NMR: 2.57 (s, 3H, Me), 3.09 (s, 3H, OMe), 3.87 (s, 3H, OMe), 4.87 (d, 9 Hz, 1H, CH), 5.70 (d, 9 Hz, 1H, CH), 7.19 (d, 9 Hz, 2H, Ar), 7.35–27.53 (m, 4H, Ar and Ph), 7.62 (d, 9 Hz, 2H, Ar), 8.00 (d, 3 Hz, 1H, Ar). $^{13}$C NMR: 9.9 (Me), 48.0 (CH), 55.6 (OMe), 57.0 (OMe), 82.4 (CH), 112.9 (C3 of Ar), 114.8 (C5 of Ar), 127.0 (C6 of Ar), 128.2 (C2/C6 of Ph), 128.4 (C4 of Ph),

128.8 (C3/C5 of Ph), 130.1 (C1 of Ar), 137.4 (C2 of Ar), 140.2 (C4 of triazolyl), 140.4 (C1 of Ph), 156.7 (C5 of triazolyl), 160.4 (C4 of Ar), 187.6 (C=O). Anal. Calcd. for $C_{20}H_{19}Br_2N_3O_3$ (509.19): C, 47.18; H, 3.76; N, 8.25. Found: C, 47.26; H, 3.89; N, 8.37%.

**2-Bromo-3-(3-bromo-4-methoxyphenyl)-3-methoxy-1-[1-(4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]propan-1-one (4).** Yield 88%, MP 158–160 °C. IR: 3065, 2932, 1689, 1592, 1548 $cm^{-1}$. $^1H$ NMR: 2.39 (s, 3H, Me), 3.10 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.90 (s, 3H, OMe), 4.87 (d, 9 Hz, 1H, CH), 5.69 (d, 9 Hz, 1H, CH), 7.17–7.73 (m, 7H, Ar). $^{13}C$ NMR: 9.8 (Me), 48.1 (CH), 55.6 (OMe), 56.2 (OMe), 56.9 (OMe), 81.2 (CH), 110.5 (C5 of Ar), 112.4 (C6 of Ar), 114.8 (C3 of Ar), 127.0 (C3/C5 of Ar), 127.5 (C2/C6 of Ar), 129.0 (C2 of Ar), 131.2 (C1 of Ar), 131.6 (C1 of Ar), 140.1 (C4 of triazolyl), 140.5 (C5 of triazolyl), 155.6 (C4 of Ar), 160.4 (C4 of Ar), 187.5 (C=O). Anal. Calcd. for $C_{21}H_{21}Br_2N_3O_4$ (539.22): C, 46.78; H, 3.93; N, 7.79. Found: C, 46.89; H, 4.08; N, 7.90%.

**Crystal structure determination.** Single-crystal diffraction data were recorded on an Agilent SuperNova Dual Atlas diffractometer using Mo radiation. The structures were solved using SHELXT[35] and refined by SHELXL.[36] Atoms were refined with anisotropic displacement parameters apart from hydrogens. A riding model was applied for hydrogen atoms with idealized geometry with *Uiso*(H) set to either 1.2 or 1.5 times *Ueq* for the atoms to which the hydrogens were bonded. For **3**, the bromine substituent (Br2) on the methoxyphenyl ring is disordered on a site shared with hydrogen. The refined occupancy for the bromine atom was 0.426(2). Crystal and structure refinement data are shown in Table 1. The crystal structures have been deposited in the CSD with reference numbers 2351127–2351129.

## Acknowledgements

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## Supplementary Material

The Supporting Information is available free of charge and contains the synthesized heterocycles' FTIR and NMR spectra and CheckCIF.

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