Article

Synthesis and Structural Characterization of Isostructural 4-(4-Aryl)-2-(5-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazoles

Benson M. Kariuki 1, Bakr F. Abdel-Wahab 2 and Gamal A. El-Hiti 3,*

1 School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff CF10 3AT, UK; kariukib@cardiff.ac.uk
2 Applied Organic Chemistry Department, National Research Centre, Dokki, Giza 12622, Egypt; bakrfacebook@gmail.com
3 Department of Optometry, College of Applied Medical Sciences, King Saud University, P.O. Box 10219, Riyadh 11433, Saudi Arabia
* Correspondence: gelhiti@ksu.edu.sa; Tel.: +966-11469-3778; Fax: +966-11469-3536

Abstract: 4-(4-Chlorophenyl)-2-(5-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazole (4) and 4-(4-fluorophenyl)-2-(5-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazole (5) have been synthesized in high yields. Crystallization of 4 and 5 from dimethylformamide solvent produced samples suitable for structure determination by single crystal diffraction. The materials are isostructural with triclinic, P¯1 and symmetry and comprise two independent molecules in the asymmetric unit. The two independent molecules in the asymmetric unit assume similar conformation. The molecule is essentially planar apart from one of the two fluorophenyl groups, which is oriented roughly perpendicular to the plane of the rest of the molecule.

Keywords: crystal structure; heterocycle; 1,2,3-triazole; 1,3-thiazole; biological activity; 4,5-dihydro-1H-pyrazole; synthesis

1. Introduction

The progressive development of microbial resistance to current drugs is of global concern and, consequently, the design and synthesis of new medications are an ongoing challenge [1]. The majority (85%) of biologically active compounds contain different heterocycles and hence the synthesis of new molecules is important for the quest to generate potential additions to the established heterocyclic systems for therapeutic use [2].

1,2,3-Triazoles are highly stable heterocycles that have a wide range of medicinal applications [3]. They have anti-HIV, anticancer, antibacterial, anti-inflammatory, antitubercular and antiviral activities [4–16]. The common synthetic routes for 1,2,3-triazoles include 1,3-dipolar cycloaddition between azides and terminal alkynes [17]. However, the procedure results in a mixture of 1,4-disubstituted and 1,5-disubstituted 1,2,3-triazoles due to poor regioselectivity. The use of a copper(I)-catalyzed version of azide–alkyne cycloaddition and click chemistry approaches resulted in the production of various substituted 1,2,3-triazoles in high yields [18–22].

Pyrazoline-containing heterocycles are involved in different therapeutic applications. They are used as antimicrobial, anti-inflammatory, analgesic, antidepressant and anticancer agents [23–25]. Many pyrazolines exist in vitamins, pigments, alkaloids and cells of many plants and animals [26]. Substituted pyrazolines can be synthesized in one-pot procedures. For example, condensation of carbonyl compounds and hydrazine hydrochloride in methanol for 1 h at 65 °C produced substituted pyrazolines [27]. They can also be produced from 3-butynol and arylhydrazines through hydroxydrazination in the presence of a catalyst containing zinc [28].
1,3-Thiazoles exist in nature and have diverse pharmacological applications as bioactive compounds. For example, tiazofurin, ritonavir, ravuconazole, nitazoxanide, meloxicam, fentiazac, nizatidine and thiamethoxam act as antimicrobial agents [29,30]. The synthesis of compounds containing the thiazole system is therefore a useful venture due to their potential for medicinal applications. Recent synthetic procedures for 1,3-thiazoles include a copper-catalyzed oxidative reaction of aldehydes and amines in the presence of sulfur [31]. Furthermore, the Hantzsch condensation of thiourea and 2-bromoacetophenones provided 2-aminothiazoles [32]. Recently, we have synthesized a number of heterocycles containing pyrazole, thiazole and 1,2,3-triazole moieties [33,34] and some crystal structures have been established [35,36].

This work involved the synthesis of 4-(4-chlorophenyl)-2-(5-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazole (4) and 4-(4-fluorophenyl)-2-(5-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazole (5). The crystal structures obtained enabled a comparison of the structural properties of the materials; the structures are identical in this case. The study of isostructurality in crystalline solids contributes to the general understanding of the factors that may be important in the design of solid materials for particular applications [37]. Investigation of the properties of isostructural materials containing different substituents continues to attract interest [38–41], including compounds in which different halogens have been exchanged [42–44]. Although it is not surprising that two similar molecules can display similar structural properties, it is not a certainty that this will be the case. Thus, for example, 3-chlorocinnamic acid and 3-bromocinnamic acid can display different crystal structures [45] and, indeed, one molecule can crystallize in more than one crystal structure type, as observed for 3-chlorobenzoic acid [46,47].

Compounds 4 and 5 allow a comparison of isostructural chloro and bromo derivatives of 4-(4-aryl)-2-(5-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazole. Rationalization of intermolecular contacts may, for example, reveal information about possible interactions with binding sites in therapeutic application. A potential application of 4 and 5 and related compounds is as therapeutics. An example is 4-(4-chlorophenyl)-2-(5-(4-fluorophenyl)-3-(5-methyl-1-p-tolyl-1H-1,2,3-triazol-4-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazole, which displays antimicrobial activity [48]. However, the focus of this work was the synthesis and characterization of new materials.

2. Materials and Methods

2.1. General

IR spectra of compounds 4 and 5 were recorded on a AIM-9000 Shimadzu spectrometer. 1H (500 MHz) and 13C NMR (125 MHz) spectra of compounds 4 and 5 were recorded on JEOL spectrometers in DMSO-d6 as solvent. Compound 1 was synthesized following a reported procedure [49]. The IR, 1H and 13C NMR spectra, CIFs and checkcif reports for compounds 4 and 5 are available in the supplementary material.

2.2. Synthesis of 2

A mixture of 1 (1.20 g, 5.0 mmol) and 4-fluorobenzaldehyde (0.62 g, 5.0 mmol) in EtOH (15 mL) containing NaOH (0.8 g) was stirred for 4 h at room temperature. The solid obtained was added to an ice/water (100 mL) mixture, filtered, dried and recrystallized from dimethylformamide to produce colorless crystals of 2 (M.p. 168–170 °C) in 90% yield.

2.3. Synthesis of 3

A mixture of 2 (0.97 g, 3.0 mmol) and thiosemicarbazide (0.30 g, 3.0 mmol) in EtOH (15 mL) containing NaOH (0.30 g, 2.5 mol) was refluxed for 2 h. The solid formed upon cooling was filtered, dried and recrystallized from dimethylformamide to produce colorless crystals of 3 (M.p. 229–231 °C) in 87% yield.
2.4. Synthesis of 4 and 5

A mixture of 3 (0.40 g, 1.0 mmol) and 4-chloro- or 4-bromophenacyl bromide (1.0 mmol) in dry EtOH (15 mL) was refluxed for 2 h. The solid product was filtered, dried and recrystallized from dimethylformamide to produce 4 (M.p. 267–268 °C) in 82% yield or 5 (M.p. 275–276 °C) in 85% yield, respectively, as pale-yellow crystals. Compound 4: IR (KBr) ν\text{max}: 1544 (C=N) and 1604 (C=C) cm\(^{-1}\). \(^1\)H NMR: δ 2.47 (s, 3H, Me), 3.42 (dd, \(J = 3.5\) and 17.2 Hz, 1H), 4.16 (dd, \(J = 11.3\) and 17.2 Hz, 1H), 5.66 (m, 1H), 7.18 (t, \(J = 7.7\) Hz, 2H, Ar), 7.36–7.39 (m, 3H, Ar), 7.46–7.49 (m, 4H, Ar) and 7.70–7.71 (m, 4H, Ar). \(^{13}\)C NMR: δ 10.47, 44.85, 63.16, 105.78, 115.91 (d, \(J_{C-F} = 21.5\) Hz), 117.25 (d, \(J_{C-F} = 22.7\) Hz), 127.71, 128.31 (d, \(J_{C-F} = 8.4\) Hz), 129.08, 129.34 (d, \(J_{C-F} = 8.3\) Hz), 132.34, 132.53, 134.69 (d, \(J_{C-F} = 88.2\) Hz), 137.86 (d, \(J_{C-F} = 78.7\) Hz), 148.28, 149.86, 161.58 (d, \(J_{C-F} = 121.6\) Hz), 162.55 (d, \(J_{C-F} = 122.5\) Hz) and 165.18. Compound 5: IR (KBr) ν\text{max}: 1572 (C=N) and 1602 (C=C) cm\(^{-1}\). \(^1\)H NMR: δ 2.47 (s, 3H, Me), 3.43 (dd, \(J = 3.6\) and 18.1, 1H), 4.15 (dd, \(J = 11.4\) and 18.1 Hz, 1H), 7.18 (t, \(J = 7.8\) Hz, 2H, Ar), 7.38 (s, 1H, Ar), 7.49–7.52 (m, 6H, Ar), 7.62 (d, \(J = 7.8\) Hz, 2H, Ar) and 7.64–7.65 (m, 2H, Ar). \(^{13}\)C NMR: δ 10.48, 44.84, 63.14, 105.87, 115.91 (d, \(J_{C-F} = 21.5\) Hz), 117.25 (d, \(J_{C-F} = 22.7\) Hz), 121.12, 128.01, 128.30 (d, \(J_{C-F} = 8.3\) Hz), 129.36 (d, \(J_{C-F} = 8.3\) Hz), 131.99, 132.33, 134.36 (d, \(J_{C-F} = 45.3\) Hz), 137.86 (d, \(J_{C-F} = 78.7\) Hz), 148.29, 148.29, 149.90, 161.57 (d, \(J_{C-F} = 120.4\) Hz), 163.33 (d, \(J_{C-F} = 121.3\) Hz) and 165.17.

2.5. X-ray Crystal Structure

Single-crystal XRD data were recorded at ambient temperature on an Agilent SuperNova Dual Atlas diffractometer (mirror monochromator, MoK\(\alpha\) (\(\lambda = 0.71073\) Å) radiation). Crystal structures were solved by direct methods using SHELXS [50] and refined using SHELXL2018 [51]. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were inserted in idealized positions and refined using a riding model with \(U_{	ext{eq}}(\text{H})\) set to 1.2 or 1.5 times the value of \(U_{	ext{eq}}(\text{C})\) for the atoms to which they are bonded. CCDC 2077559 and 2077560 contain the supplementary crystallographic data for this paper. Hirshfeld surfaces were calculated using CrystalExplorer [52,53].

3. Results and Discussion

3.1. Synthesis of Compounds 4 and 5

Compounds 4 and 5 were synthesized using a multi-step reaction from 1-(1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)ethanone (1) via 3-(4-fluorophenyl)-1-(1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)prop-2-en-1-one (2) and 5-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (3) as intermediates. Reaction of 3 and 2,4'-dibromoacetophenone or 2-bromo-4'-chloroacetophenone under reflux in ethanol (EtOH) produced 4-(4-chlorophenyl)-2-(5-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazole (4) or 4-(4-chlorophenyl)-2-(5-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazole (5) in 82% or 85% yield, respectively (Scheme 1). The structures of compounds 4 and 5 were confirmed using IR, \(^1\)H and \(^{13}\)C NMR spectroscopy. The IR spectra showed characteristic absorption bands in the 1544–1572 cm\(^{-1}\) and 1602–1604 cm\(^{-1}\) regions due to the stretching vibrations of the C=N and C=C groups, respectively. The \(^1\)H NMR spectra showed separate peaks for the methane protons in the pyrazoline moiety, indicating that they are diastereotopic. In addition, the \(^{13}\)C NMR spectra confirmed the coupling between carbon and fluorine atoms and showed overlap between the signals of some carbons.
3.2. Crystal Structures of 4 and 5

Compounds 4 and 5 are isostructural as evidenced by their similar unit cell parameters and triclinic, P\textbar I, symmetry (Table 1). The molecules of 4 and 5 comprise linked systems of rings (Figure 1). The rings are chloro/bromo-phenyl [A (C1-C6, Cl1/Br1), (C28-C33, Cl2/Br2)], thiazolyl [B (C7-C9, N1, S1), (C34-C36, N7, S2)], pyrazolyl [C (C10-C12, N2, N3), (C37-C39, N8, N9)], fluorophenyl [D (C13-C18, F1), (C40-C45, F3)], methyltriazolyl [E (C19-C21, N4-N6), C46-C48, N10-N12] and a second fluorophenyl [F (C22-C27, F2), (C49-C54, F4)].

The asymmetric unit in both structures contains two independent molecules (Figure 2a,b). Products 4 and 5 were obtained as racemic mixtures and the two molecules in the asymmetric unit are enantiomers with C10 and C37 as chiral centers. In all the molecules, rings A, B, C and E are almost coplanar with twist angles between adjacent rings in the range 3.58(1)° to 13.38(13)° (Table 2). Ring F is twisted by ca 30° and D is almost perpendicular to the plane of A, B, C and E. The two independent molecules in each structure have similar conformations although they are not identical. Additionally, molecular conformations are similar in both crystal structures.
Table 1. Crystal and structure refinement data for 4 and 5.

|                     | 4                     | 5                     |
|---------------------|-----------------------|-----------------------|
| **Formula**         | C₂₇H₁₉ClF₂N₆S        | C₂₇H₁₉BrF₂N₆S        |
| **Formula weight**  | 532.99                | 577.45                |
| **Temperature/K**   | 293(2)                | 293(2)                |
| **Wavelength/Å**    | 0.71073               | 0.71073               |
| **Crystal system**  | Triclinic             | Triclinic             |
| **Space group**     | P̅I                   | P̅I                   |
| **a/Å**             | 7.7344(6)             | 7.7607(3)             |
| **b/Å**             | 18.2776(12)           | 18.2950(11)           |
| **c/Å**             | 19.4909(12)           | 19.5252(14)           |
| **α/°**             | 116.181(6)            | 115.910(6)            |
| **β/°**             | 96.410(6)             | 96.971(4)             |
| **γ/°**             | 92.091(6)             | 92.567(4)             |
| **Volume/Å³**       | 2445.9(3)             | 2460.2(3)             |
| **Z**               | 4                     | 4                     |
| **Density (calculated)/Mg m⁻³** | 1.447                | 1.559                |
| **µ/mm⁻¹**          | 0.287                 | 1.801                 |
| **F(000)**          | 1096                  | 1168                  |
| **Crystal size/mm³**| 0.270 × 0.065 × 0.026 | 0.623 × 0.148 × 0.118 |
| **Reflections collected** | 23,275              | 23,703                |
| **Independent reflections** | 11,546               | 11,617                |
| **R(int)**          | 0.0496                | 0.0448                |
| **Data/parameters** | 11,546/670           | 11,617/669            |
| **Goodness-of-fit on F²** | 1.014             | 1.032                 |
| **R1 [I > 2σ(I)]**  | 0.0652                | 0.0669                |
| **wR2 [I > 2σ(I)]** | 0.1239                | 0.1722                |
| **R1 (all data)**   | 0.1802                | 0.1364                |
| **wR2 (all data)**  | 0.1666                | 0.2137                |
| **Extinction coefficient** | 0.0012(3)             | n/a                   |
| **Largest diff. peak and hole/e.Å⁻³** | 0.238 and −0.243 | 0.689 and −0.680  |

Table 2. Inter-ring twist angles (°) and centroid-to-centroid distances (Å). (The centroid-to-centroid distances shown are longer than is conventionally shown for π–π contacts but are used in this case for ease of comparison of the structures. (i) and (ii) refer to the first and second independent molecules).

| Inter-Ring Twist Angle | 4(i) | 4(ii) | 5(i) | 5(ii) |
|-----------------------|------|------|------|------|
| A–B                   | 9.44 (11) | 13.38 (10) | 9.68 (13) | 13.36 (14) |
| B–C                   | 5.38 (14)  | 5.30 (15)  | 5.17 (17)  | 5.03 (20)   |
| C–D                   | 88.15 (1)  | 84.53 (13) | 88.15 (16) | 84.17 (16)  |
| C–E                   | 10.39 (15) | 10.78 (16) | 10.86 (18) | 10.53 (21)  |
| E–F                   | 33.09 (9)  | 32.59 (10) | 35.39 (11) | 31.86 (13)  |

| Centroid-centroid distance | 4 | 5 |
|----------------------------|---|---|
| d₁                          | 3.75(1) | 3.73(1) |
| d₂                          | 4.05(1) | 4.09(1) |
| d₃                          | 3.81(1) | 3.79(1) |
| d₄                          | 4.14(1) | 4.20(1) |

The following discussion applies to the structures of both 4 and 5, although only the former is used for illustration. In the crystals, the molecules are stacked parallel to the a-axis (Figure 3). In the stack, the mean plane of the fragment containing rings A, B, C and E is parallel to (10-1) in one stack and to (201) in the adjacent stack in the direction of the b-axis (Figure 4). Within a given stack, there is very limited π–π interaction between aromatic rings of neighboring molecules. The closest rings in the stack are fluoroaryl/chlorophenyl in 4 (Figure 5) and fluoroaryl/bromophenyl in 5 and the distances between the ring centroids are in the range from 3.73 Å to 4.20 Å (d₁–d₄ in Table 2). The planes of the rings...
involved are not parallel and the angles between the rings of neighboring molecules are 12.18° and 14.42° for 4 and the corresponding angles are 12.95° and 13.70° for 5.

Figure 2. Ortep representation of the asymmetric unit showing 50% probability ellipsoids for (a): 4 and (b): 5.

Figure 3. The crystal structure packing in 4 viewed down the a-axis.

Figure 5. The crystal structure packing in 4 viewed down the a-axis.
Figure 4. The crystal structure of 4 viewed down the b-axis with hydrogen atoms omitted for clarity.

Generally, an asymmetric unit comprising one molecule would be expected in such a structure as the second enantiomer can be generated by inversion symmetry. However, the structures of 4 and 5 comprise two independent molecules with slightly different conformations in order to attain the most efficient molecular packing in the crystal. An alternative method to maximize packing efficiency would be by the incorporation of solvent molecules, for example.

The crystals of 4 and 5 are isostructural despite the different halogen substituents, which are Cl and Br, respectively. The difference in the calculated densities of 1.447 Mg m$^{-3}$ and 1.559 Mg m$^{-3}$ is consistent with the presence of chlorine and bromine atoms in the structures. Despite the different halogen substituents, the molecules have assumed essentially the same crystal structure but with slight adjustment of conformation and intermolecular contacts by virtue of the larger size of the Br atom rendering the molecular volume of 5 about 1% greater than that of 4.
Figure 5. A segment of the crystal structure of 4 viewed approximately along the c-axis showing the stacking of molecules with ring centroid separation shown as red dashed lines.

For the title compounds, the substituents on rings A, D and F are (4: Cl, F and F) and (5: Br, F and F). Crystal structures have also been reported for molecules with other substituents on the same rings, namely (6: Cl, F and Me) [48], (7: H, Cl and Me) [54], (8: Br, F and Me) [55] and (9: H, F and Me) [56]. Molecular conformation in structures 6–9 is similar to that in 4 and 5 since rings A, B, C and E are roughly coplanar, ring F is twisted and ring D is oriented out of the plane. However, unlike 4 and 5, the other crystal structures have just one molecule in the asymmetric unit. Exchanging F for methyl (5 vs. 8) and (4 vs. 6) results in different crystal structures, as does the replacement of Cl by F (7 vs. 9). In contrast, the crystal structures in which Cl and Br are exchanged (6 vs. 8) are identical, which is an observation consistent with the results obtained in this work for 4 and 5.
The Hirshfeld surfaces show different intermolecular contacts for the two independent molecules of each structure. The surfaces are shown in Figure 6b,d for 4 and Figure 7b,d for 5. The red regions clearly indicate that the intermolecular contacts are not identical for the two independent molecules of the same structure. Conversely, the contacts are essentially the same for the corresponding molecules in 4 and 5. Highlighted in the fingerprint plots in Figure 6a,c for 4 and Figure 7a,c for 5 are the contributions by chlorine and bromine. The plots follow the same pattern as the Hirshfeld surfaces; the two independent molecules of the same structure show differences whereas comparable molecules from different structures have similar characteristics. The contributions in 4 by Cl are 3.7% and 4.1% for the two independent molecules and 3.9% and 4.2% by Br for 5.

**Figure 6.** (a): Two-dimensional fingerprint plot for one independent molecule of 4 with Cl interactions highlighted; (b): the associated Hirshfeld surface. (c): Two-dimensional fingerprint plot for the second independent molecule with Cl interactions highlighted; (d): the associated Hirshfeld surface.
Figure 7. (a): Two-dimensional fingerprint plot for one independent molecule of 5 with Br interactions highlighted; (b): the associated Hirshfeld surface. (c): Two-dimensional fingerprint plot for the second independent molecule with Br interactions highlighted; (d): the associated Hirshfeld surface.

4. Conclusions

Two materials, 4-(4-chlorophenyl)-2-(5-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazole (4) and 4-(4-fluorophenyl)-2-(5-(4-fluorophenyl)-3-(1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazole (5), have been synthesized in high yields and characterized spectroscopically. The materials have been recrystallized using dimethylformamide as the solvent and their structures have been established by single crystal diffraction. The two materials are isostructural and contain two independent molecules in the asymmetric unit. The two independent molecules in each structure have similar conformations although they are not identical. The crystal structures of 4 and 5 are identical but with slight adjustments necessary to accommodate the different halogen (Cl and Br) substituents. Comparison with related materials shows similarity in molecular conformation but with different crystal packing.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/cryst11070795/s1, IR, $^1$H and $^{13}$C NMR spectra, CIFs and checkcif reports for compounds 4 and 5.
Author Contributions: Conceptualization: B.M.K. and G.A.E.-H.; methodology: B.M.K., B.F.A.-W. and G.A.E.-H.; X-ray crystal structures: B.M.K.; investigation: B.M.K., B.F.A.-W. and G.A.E.-H.; writing—original draft preparation: B.M.K., B.F.A.-W. and G.A.E.-H.; writing—review and editing: B.M.K. and G.A.E.-H. All authors have read and agreed to the published version of the manuscript.

Funding: The authors thank the Researchers Supporting Project number (RSP-2021/404), King Saud University, Riyadh, Saudi Arabia.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are contained within the article.

Acknowledgments: We thank Cardiff University for their technical support.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Abu-Hashem, A.A. Synthesis of new furothiazolo pyrimido quinazolinolines from visnagenone or khellinone and antimicrobial activity. 
*Crystals* 2018, 23, 2793. [CrossRef] [PubMed]

2. Jampilek, J. Heterocycles in medicinal chemistry. 
*Molecules* 2019, 24, 3839. [CrossRef] [PubMed]

3. Dheer, D.; Singh, V.; Shankar, R. Medicinal attributes of 1,2,3-triazoles: Current developments. 
*Bioorg. Chem.* 2017, 71, 30–54. [CrossRef] [PubMed]

4. Gondru, R.; Kanugala, S.; Raj, S.; Kumar, C.G.; Pasupuleti, M.; Banothu, J.; Bavantula, R. 1,2,3-Triazole-thiazole hybrids: Synthesis, in vitro antimicrobial activity and antibiofilm studies. 
*Bioorg. Med. Chem. Lett.* 2020, 33, 127746. [CrossRef] [PubMed]

5. El Malah, T.; Nour, H.F.; Satti, A.A.E.; Hemdan, B.A.; El-Sayed, W.A. Design, synthesis, and antimicrobial activities of 1,2,3-triazole glycoside clickamers. 
*Molecules* 2020, 25, 790. [CrossRef] [PubMed]

6. Ellouz, M.; Sebbar, N.K.; Fichtali, I.; Ouzidane, Y.; Mennane, Z.; Charof, R.; Mague, J.T.; Urrutigoity, M.; Essassi, E.M. Synthesis and antibacterial activity of new 1,2,3-triazolylmethyl-2H-1,4-benzothiazin-3(4H)-one derivatives. 
*Chem. Cent. J.* 2018, 12, 123. [CrossRef] [PubMed]

7. López-Rojas, P.; Janeczko, M.; Kubínski, K.; Amesty, Á.; Maslyk, M.; Estévez-Braun, A. Synthesis and antimicrobial activity of 4-substituted 1,2,3-triazole-coumarin derivatives. 
*Molecules* 2018, 23, 199. [CrossRef]

8. Da Silva, F.D.C.; De Souza, M.C.B.V.; Frugulhatti, I.I.P.; Castro, H.C.; Souza, S.L.D.O.; De Souza, T.M.L.; Rodrigues, D.Q.; Souza, A.M.T.; Abreu, P.A.; Passamani, F.; et al. Synthesis, HIV-RT inhibitory activity and SAR of 1-benzyl-1H-1,2,3-triazole derivatives of carbohydrates. 
*Eur. J. Med. Chem.* 2009, 44, 373–383. [CrossRef]

9. Doiron, J.; Soultan, A.H.; Richard, R.; Tourné, M.M.; Picot, N.; Richard, R.; Cuperlovic-Cufí, M.; Robichaud, G.A.; Touaibia, M. Synthesis and structure activity relationship of 1- and 2-substituted-1,2,3-triazole letrozole-based analogues as aromatase inhibitors. 
*Eur. J. Med. Chem.* 2011, 46, 4010–4024. [CrossRef]

10. Sert, Y.; El-Hiti, G.A.; Gökce, H.; Ucun, F.; Abdel-Wahab, B.F.; Kariuki, B.M. DFT, molecular docking and experimental FT-IR, laser-Raman, NMR and UV investigations on a potential anticancer agent containing triazole ring system. 
*J. Mol. Struct.* 2020, 1211, 128077. [CrossRef]

11. Abd-Rabou, A.A.; Abdel-Wahab, B.F.; Bekheit, M.S. Synthesis, molecular docking, and evaluation of novel bivalent pyrazolyl-1,2,3-triazoles as potential VEGFR TK inhibitors and anti-cancer agents. 
*Chem. Pap.* 2018, 23, 2017. [CrossRef]

12. Abdel-Wahab, B.F.; Khidre, R.E.; Awad, G.E.A. Design and synthesis of novel 6-(5-methyl-1H-1,2,3-triazol-4-yl)-5-[(2-(thiazol-2-yl)hydrazono)methyl]imidazo[2,1-b]thiazoles as antimicrobial agents. 
*J. Heterocycl. Chem.* 2017, 54, 489–494. [CrossRef]

13. Abdel-Wahab, B.F.; Aqoobi, I.K.; El-Hiti, G.A. Synthesis of new symmetrical N,N'-diacylhydrazines and 2-(1,2,3-triazol-4-yl)-1,3,4-oxadiazoles. 
*lett. Org. Chem.* 2017, 14, 591–596. [CrossRef]

14. Peníhala, N.R.; Madhukuri, L.; Thakkar, S.; Madadi, N.R.; Lamture, G.; Eoff, R.L.; Crooks, P.A. Synthesis and anti-cancer screening of novel heterocyclic-(2H)-1,2,3-triazoles as potential anti-cancer agents. 
*Med. Chem. Commun.* 2015, 6, 1535–1543. [CrossRef]

15. Stefely, J.A.; Palchauhdur, R.; Miller, P.A.; Peterson, R.J.; Moraski, G.C.; Hergenrother, P.J.; Miller, M.J. N-[(1-Benzyl-1H-1,2,3-triazol-4-yl)methyl] arydamide as a new scaffold that provides rapid access to antimicrotubule agents: Synthesis and evaluation of antiproliferative activity against select cancer cell lines. 
*J. Med. Chem.* 2010, 53, 3389–3395. [CrossRef]

16. Jiang, B.; Huang, X.; Yao, H.; Jiang, J.; Wu, X.; Jiang, S.; Wang, Q.; Lu, T.; Xu, J. Discovery of potential anti-inflammatory drugs: Diaryl-2,4-triazoles bearing N-hydroxyurea moiety as dual inhibitors of cyclooxygenase-2 and 5-lipoxygenase. 
*Org. Biomol. Chem.* 2012, 14, 2114–2124. [CrossRef]

17. Huisgen, R.; Szmien, G.; Möbius, L. 1,3-Dipolare cycloadditionen, XXXII. Kinetik der additionen organischer azide an CC-mehrfachbindungen. 
*Chem. Ber.* 1967, 100, 2494–2507. [CrossRef]

18. Kolb, H.C.; Finn, M.G.; Sharpless, K.B. Click chemistry: Diverse chemical function from a few good reactions. 
*Angew. Chem. Int. Ed.* 2001, 40, 2004–2021. [CrossRef]
19. Seus, N.; Gonçalves, L.C.; Deobald, A.M.; Savegnago, L.; Alves, D.; Paixão, M.W. Synthesis of arylselenyl-1H,1,2,3-triazole-4-carboxylates by organocatalytic cycloaddition of azidophenyl arylselenides with β-keto-esters. *Tetrahedron* 2012, 68, 10456–10463.

20. Schmieder, P.; Khne, R.; Rademann, J. Metal-free, regioselective triazole ligations that deliver locked cis peptide mimetics. *Angew. Chem. Int. Ed.* 2009, 48, 5042–5045. [CrossRef]

21. Dey, S.; Pathak, T.A. General route to 1,5-disubstituted 1,2,3-triazoles with alkyl/alkyl, alkyl/aryl, aryl/aryl combinations: A metal-free, regioselective, one-pot three component approach. *RSC Adv.* 2014, 4, 9275–9278. [CrossRef]

22. Cai, Z.-J.; Lu, X.-M.; Zi, Y.; Yang, C.; Shen, L.-J.; Li, J.; Wang, S.-Y.; Ji, S.-J. I$_2$/TBP mediated oxidative reaction of N-tosylhydrazones with anilines: Practical construction of 1,4-disubstituted 1,2,3-triazoles under metal-free and azide free conditions. *Org. Lett.* 2014, 16, 5108–5111. [CrossRef]

23. Shaaban, M.R.; Mayhoub, A.S.; Farag, A.M. Recent advances in the therapeutic applications of pyrazolines. *Expert. Opin. Ther. Pat.* 2012, 22, 253–291. [CrossRef] [PubMed]

24. Varghese, B.; Al-Busafi, S.N.; Suliman, F.O.; Al-Kindy, S.M.Z. Unveiling a versatile heterocycle: Pyrazoline—A review. *RSC Adv.* 2017, 7, 46999–47016. [CrossRef]

25. Tok, E.; Abas, B.I.; Çevik, O. Koçyiğit-Kaymakçuoğlu, B. Design, synthesis and biological evaluation of some new 2-Pyrazoline derivatives as potential anticancer agents. *Bioorg. Chem.* 2020, 102, 104063. [CrossRef] [PubMed]

26. Yusuf, M.; Jain, P. Synthetic and biological studies of pyrazolines and related heterocyclic compounds. *Arab. J. Chem.* 2014, 7, 553–596. [CrossRef]

27. Lellek, V.; Chen, C.-Y.; Yang, W.; Liu, J.; Ji, X.; Faessler, R. An efficient synthesis of substituted pyrazoles from one-pot reaction of ketones, aldehydes, and hydrazine monohydrchloride. *Synlett* 2018, 29, 1071–1075. [CrossRef]

28. Alex, K.; Tillack, A.; Schwarz, N.; Beller, M. Zinc-catalyzed synthesis of pyrazolines and pyrazoles via hydrodehydrazination. *Org. Lett.* 2008, 10, 2577–2579. [CrossRef]

29. Ayati, A.; Emami, S.; Asadipour, A.; Shafiee, A.; Foroumadi, A. Recent applications of 1,3-thiazole core structure in the identification of new lead compounds and drug discovery. *Eur. J. Med. Chem.* 2015, 97, 699–718. [CrossRef]

30. Sharma, P.K.; Amin, A.; Kumar, M. A review: Medicinally important nitrogen sulphur containing heterocycles. *Open Med. Chem. J.* 2021, 14, 49–64. [CrossRef]

31. Wang, X.; Qiu, X.; Wei, J.; Liu, J.; Song, S.; Wang, W.; Jiao, N. Cu-catalyzed aerobic oxidative sulfuration/annulation approach to thiazoles via multiple Csp 3-H bond cleavage. *Org. Lett.* 2018, 20, 2632–2636. [CrossRef] [PubMed]

32. Facchinetti, V.; Avellar, M.M.; Nery, A.C.S.; Gomes, R.B.; Vasconcelos, T.R.A.; de Souza, M.V. An eco-friendly, Hantzsch-based, solvent-free approach to 2-aminothiazoles and 2-aminoselenazoles. *Synthesis* 2016, 48, 437–440. [CrossRef]

33. Mohamed, H.A.; Alshammarie, M.B.; El-Hitti, G.A. Synthesis of new 6-(1H-1,2,3-triazol-4-yl)-5-(1-(thiazol-2-yl)-4,5-dihydro-1H-pyrazol-5-yl)imidazo[2,1-b]thiazoles. *Indian J. Heterocycl. Chem.* 2018, 28, 529–533.

34. Abdel-Wahab, B.F.; Khidre, R.E.; Mohamed, H.A.; El-Hitti, G.A. A simple process for the synthesis of novel pyrazolyltriazole and dihydropyrazolylthiazole derivatives as antimicrobial agents. *Arab. J. Sci. Eng.* 2017, 42, 2441–2448. [CrossRef]

35. Ghabbour, H.A.; Abdel-Wahab, B.F.; Alamri, M.; Al-Omar, M.A.; El-Hitti, G.A. Crystal structure of 2-(5-(4-fluorophenyl)-3-p-tolyl-4,5-dihydro-1H-pyrazol-1-yl)-4(5-methyl-1-p-tolyl-1H-1,2,3-triazol-4-yl)thiazole, C$_{29}$H$_{25}$FN$_{6}$S. Z. Kristallogr. New Cryst. Struct. 2017, 232, 21–23. [CrossRef]

36. El-Hitti, G.A.; Mohamed, H.A.; Abdel-Wahab, B.F.; Alotaibi, M.H.; Hegazy, A.S.; Kariuki, B.M. 4-(4-Bromophenyl)-2-(3-(4-chlorophenyl)-5-[3-[5-methyl-1-(4-methylphenyl)-1H-1,2,3-triazol-4-yl]-1-phenyl-1H-pyrazol-4-yl]-4,5-dihydro-1H-pyrazol-1-yl)thiazole. *IUCrData* 2018, 3, x180036. [CrossRef]

37. Braga, D.; Desiraju, G.R.; Miller, J.S.; Orpend, A.G.; Price, S.L. Innovation in crystal engineering. *CrystEngComm* 2002, 4, 500–509. [CrossRef]

38. Ebenezer, S.; Muthiah, P.T.; Butcher, R.J. Design of a series of isostructural co-crystals with aminopyrimidines: Isostructurality through chloro/methyl exchange and studies on supramolecular architectures. *Cryst. Growth Des.* 2011, 11, 3579–3592. [CrossRef]

39. Chia, T.S.; Quah, C.C. Temperature-induced order-disorder structural phase transitions of two-dimensional isostructural hexamethyleneetetramine co-crystals. *Acta Crystallogr. Sect. B* 2017, 73, 879–890. [CrossRef]

40. Panicker, L. Thermal, spectroscopic and structural characterization of isostructural phase transition in 4-hydroxybenzaldehyde. *Phase Transit.* 2018, 91, 530–536. [CrossRef]

41. Galcera, J.; Frišče, T.; Hejczyk, K.E.; Fabián, L.; Clarke, S.M.; Day, G.M.; Molinsa, E.; Jones, W. Isostructural organic binary-host frameworks with tuneable and diversely decorated inclusion cavities. *CrystEngComm* 2012, 14, 7898–7906. [CrossRef]

42. Reddy, C.M.; Kirchner, M.T.; Gundakaram, R.C.; Padmanabhan, K.A.; Desiraju, G.R. Isostructurality, polymorphism and mechanical properties of some hexahalogenated benzenes: The nature of halogen···halogen interactions. *Chem. Eur. J.* 2006, 12, 2222–2234. [CrossRef]

43. Saraswatula, V.G.; Saha, B.K. The effect of temperature on interhalogen interactions in a series of isostructural organic systems. *New J. Chem.* 2014, 38, 897–901. [CrossRef]

44. Cincic, D.; Frisic, T.; Jones, W. A cocrystallisation-based strategy to construct isostructural solids. *New J. Chem.* 2008, 32, 1776–1781. [CrossRef]

45. Kanao, S.; Kashino, S.; Haisa, M. Topochemical studies. XIII. Structures of 3-bromocinnamic acid and 3-chlorocinnamic acid. *Acta Cryst.* 1990, C46, 2436–2438. [CrossRef]
46. Gougoutas, J.Z.; Lessinger, L. Solid state chemistry of organic polyvalent iodine compounds. IV. Topotactic transformations of 2-iodo-3′-chlorodibenzoyle peroxide and the crystal structure of m-chlorobenzoic acid. *J. Solid State Chem.* 1975, 12, 51–62. [CrossRef]

47. Hursthouse, M.B.; Hibbs, D.E.; Ramachandran, V.N. 3-Chlorobenzoic acid. Private communication to the Cambridge Structural Database. 2003; MCBZAC01.

48. Abdel-Wahab, B.F.; Abdel-Latif, E.; Mohamed, H.A.; Awad, G.E.A. Design and synthesis of new 4-pyrazolin-3-yl-1,2,3-triazoles and 1,2,3-triazol-4-yl-pyrazolin-1-ylthiazoles as potential antimicrobial agents. *Eur. J. Med. Chem.* 2012, 52, 263–268. [CrossRef]

49. Kamalraj, V.R.; Senthil, S.; Kannan, P. One-pot synthesis and the fluorescent behavior of 4-acetyl-5-methyl-1,2,3-triazole regioisomers. *J. Mol. Struct.* 2008, 892, 210–215. [CrossRef]

50. Sheldrick, G.M. A short history of SHELX. *Acta Crystallogr. Sect. A* 2008, 64, 112–122. [CrossRef]

51. Sheldrick, G.M. Crystal structure refinement with SHELXL. *Acta Crystallogr. Sect. C* 2015, 71, 3–8. [CrossRef]

52. Turner, M.J.; McKinnon, J.J.; Wolff, S.K.; Grimwood, D.J.; Spackman, P.R.; Jayatilaka, D.; Spackman, M.A. *CrystalExplorer17*; The University of Western Australia: Perth, Australia, 2017.

53. MacKenzie, C.F.; Spackman, P.R.; Jayatilaka, D.; Spackman, M.A. CrystalExplorer model energies and energy frameworks: Extension to metal coordination compounds, organic salts, solvates and open-shell systems. *IUCrJ* 2017, 4, 575–587. [CrossRef] [PubMed]

54. Dong, W.-J.; Cui, F.-H.; Gao, Z.-L.; Li, R.-S.; Shen, G.-L.; Dong, H.-S. An efficient synthesis of 5-aryl-4,5-dihydro-3-(5-methyl-1-p-tolyl-1H-1,2,3-triazol-4-yl)-1-(4-phenylthiazol-2-yl)pyrazoles. *J. Heterocycl. Chem.* 2011, 48, 1154–1160. [CrossRef]

55. Abdel-Wahab, B.F.; Mohamed, H.A.; Ng, S.W.; Tiekink, E.R.T. 4-[1-[4-(4-Bromophenyl)-1,3-thiazol-2-yl]-5-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-3-yl]-5-methyl-1-(4-methylphenyl)-1H-1,2,3-triazole. *Acta Crystallogr. Sect. E Struct. Rep. Online* 2012, 68, o1956–o1957. [CrossRef] [PubMed]

56. Abdel-Wahab, B.F.; Ng, S.W.; Tiekink, E.R.T. 4-[5-(4-Fluorophenyl)-1-(4-phenyl-1,3-thiazol-2-yl)-4,5-dihydro-1H-pyrazol-3-yl]-5-methyl-1-(4-methylphenyl)-1H-1,2,3-triazole. *Acta Crystallogr. Sect. E Struct. Rep. Online* 2013, 69, o618. [CrossRef] [PubMed]