

Review

Hydrazides as Powerful Tools in Medicinal Chemistry: Synthesis, Reactivity, and Biological Applications

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Abstract

The increase in drug resistance and the high toxicity of current drugs have inspired the scientific community to develop new drugs for various diseases. Hydrazides have become an attractive functional group to easily obtain a plethora of novel compounds with a broad range of biological activities. This review, which contains studies in the literature from the previous five years, focuses on the synthesis methods and biological applications of hydrazides and their derivatives. Here, the details of the experimental reaction conditions used for the synthesis of hydrazides and their derivatives (hydrazide–hydrazones and heterocycle derivatives) are presented, as well as the purification methods and the biological activity of the synthesized compounds.

Keywords: hydrazides; hydrazide derivatives; synthesis; bioactive hydrazide derivatives



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1. Introduction

According to the World Health Organization [1], diabetes, cardiovascular (ischemic heart disease and stroke), respiratory (chronic obstructive pulmonary disease and respiratory infections), cancers, and Alzheimer's and dementia diseases are some of the leading causes of death worldwide. Besides these diseases, malaria, tuberculosis, HIV/AIDS, and cirrhosis of the liver are among the leading causes of death in low-income countries. The main obstacles to treating/eradicating these diseases include the increase in drug resistance to current drugs [2–9] and the high toxicity of the drugs used in the treatments [2,10–12].

Nowadays, many efforts have been made to develop novel and safer therapeutic alternatives. The scientific community has been searching for new compounds with reduced toxicity and improved biological efficacy, or even potential probes for bioimaging in disease diagnosis [13].

Hydrazides are a class of organic compounds with the functional group $R-CON-R^1N-R^2R^3$ [14]. It is an extremely important group in organic chemistry, being an effective substrate in both domains of chemical reactions and medicinal chemistry [15,16].

Since the 20th century, several hydrazides such as isoniazid **1** (isonicotinic acid hydrazide) [9,17,18], *p*-aminosalicylic acid hydrazide **2** [19], fonturacetam hydrazide **3** [20,21], isocarboxazide **4** [22], iproniazid **6** [23], nialamide **7** [11] and benserazide **5** [24] have been introduced for therapeutic purposes, as antituberculosis, antiviral, anticonvulsant, neurostimulator, antidepressive (monoamine oxidase inhibitor), and anti-Parkinson agents (Figure 1).

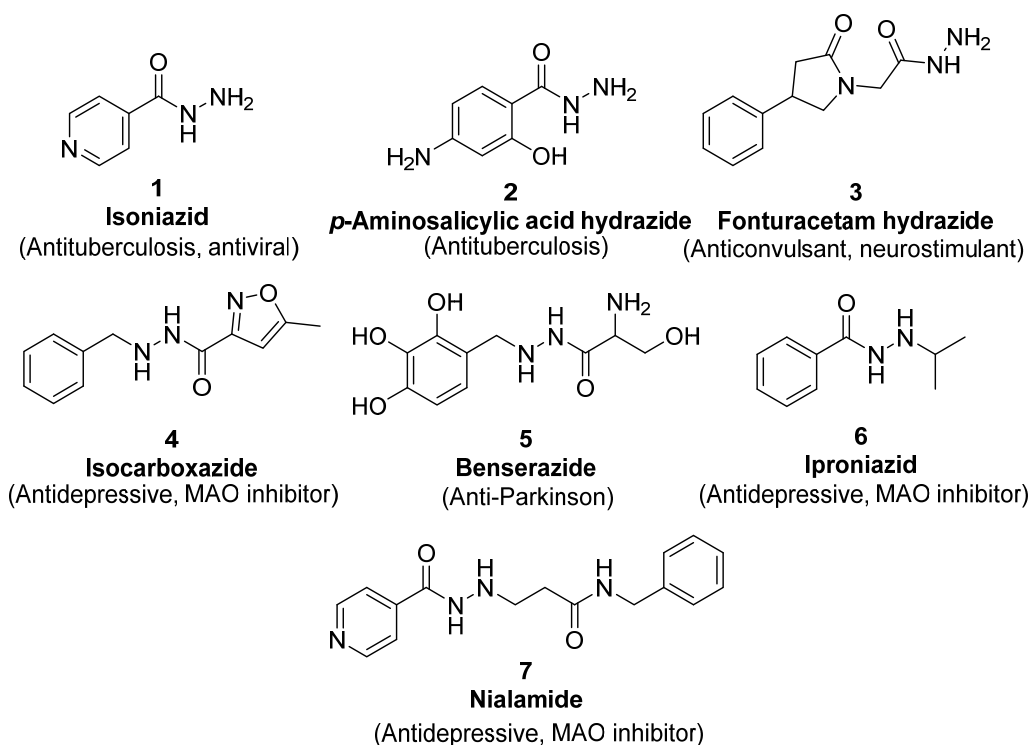


Figure 1. Examples of hydrazides and their therapeutic applications.

Over time, hydrazides **8** were found to be great precursors of other bioactive compounds such as hydrazine–hydrazones **9** [25,26]. Hydrazides **8** were also employed as building block synthons of different classes of heterocycles, like pyrrolones **10** [27,28], pyrazoles **11** [29,30], oxadiazoles **12** [31], thiadiazoles **13** [30,32], triazoles **14** [30], by cyclization or cycloaddition reactions with other reagents [28,33] (Figure 2). These hydrazide derivatives similarly revealed a wide range of biological activities, including antitumor [34–37], antimicrobial [38], antifungal [39], antimalarial [2], antileishmanial [40], anti-inflammatory [41], antidiabetic [42,43] and antioxidant [44] properties. They also showed herbicide activity or were used as dyes [45,46].

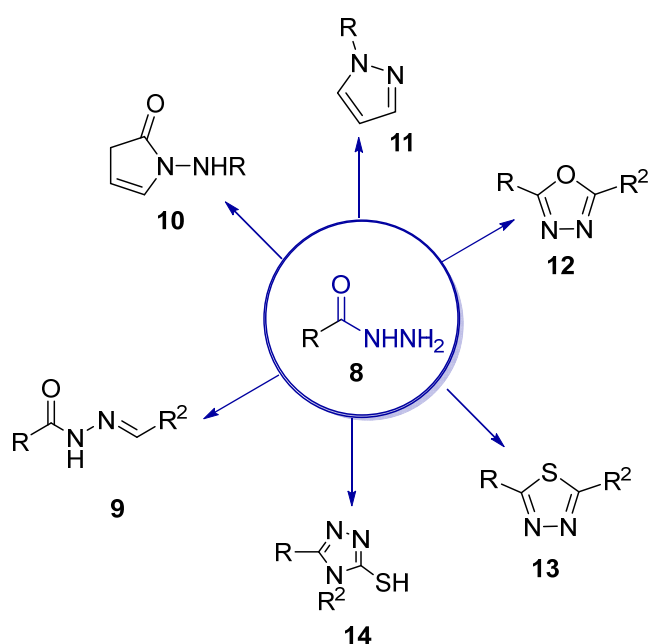


Figure 2. Linear and heterocyclic compounds synthesized from hydrazides.

A review describing the synthesis of hydrazides and heterocyclic rings from hydrazides was published in 2014 by Majumdar et al. [47]. In 2018, Hosseini et al. [32] reported a compilation of the synthesis of heterocycles from cyanoacetohydrazides. Also, in 2021, Mali et al. [48] briefly reported the importance of the hydrazides and their derivatives (specifically hydrazide–hydrazones) as bioactive compounds over the years.

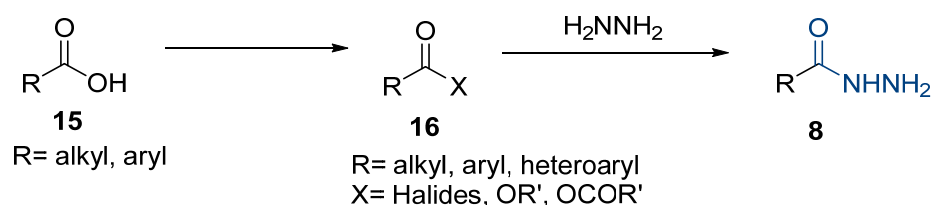
This review presents a comprehensive compilation and description of the methods used to synthesize hydrazides in the last 5 years, their use as precursors or synthons to generate new derivatives, and their main biological applications.

Moreover, throughout the review, tables will be provided summarizing the experimental conditions for the synthesis and purification of hydrazides and their derivatives.

2. Hydrazides

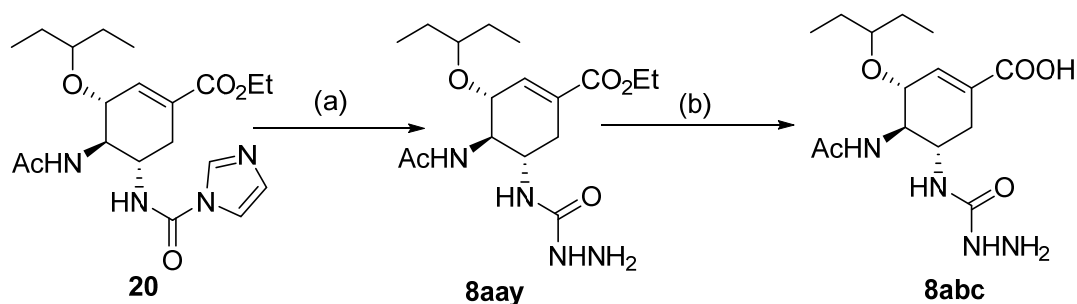
2.1. Synthesis of Hydrazides

The first existing hydrazides, specifically formic and acetic acid hydrazides, were produced by Kurzius in 1895 [49]. Currently, many hydrazides with alkyl, aryl, and heteroaryl substituents are being synthesized to overcome drug resistance and toxicity. Hydrazides **8** (Scheme 1) are conventionally synthesized from compounds **16**, such as esters [2,13,26,34–41,43,44,50–95], anhydrides [96], and acyl chlorides [2,97,98], or others [99–103] that possess a good leaving group, and hydrazine. When it is not possible to have compounds **16** available, the leaving group is produced from the acid derivative **15** [82,85,88,96]. According to the reaction conditions outlined in Table 1, the experimental reaction conditions to generate hydrazide **8** from precursor **16** do not differ much, and usually, the reaction takes place in an alcohol solvent, at room temperature, or under reflux. The reactions did not last more than 24 h, and generally, product **8** was purified by recrystallization or by column chromatography. Hydrazides **8a** to **8abb** were obtained in low to excellent yields (26–98%) from esters (**17a–17aaw**), anhydrides (**18**), acyl chlorides (**19a–c**), or others (**20–23**).



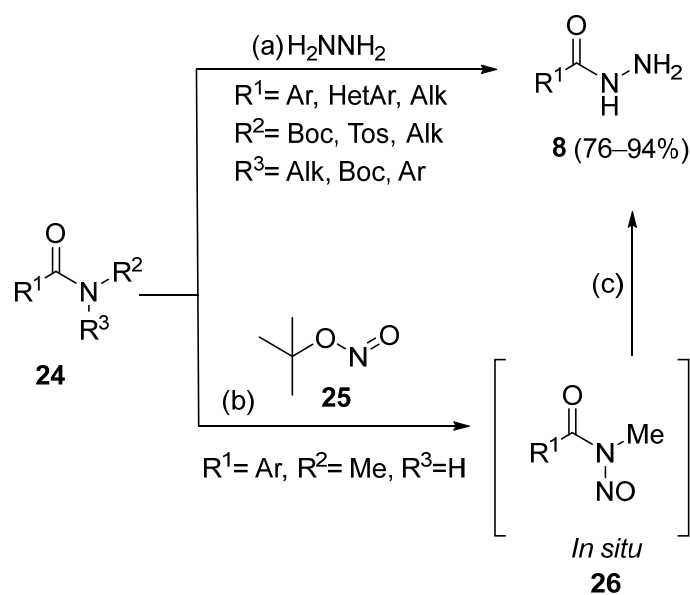
Scheme 1. Representative scheme of hydrazide synthesis.

Besides the regular functional groups, Zhao et al. [99] obtained the hydrazide **8aay** from activated intermediary **20** by reaction with hydrazine hydrate (Scheme 2). The acid derivative **8abc** was obtained from **8aay** by reaction with sodium hydroxide in aqueous methanol.



Scheme 2. Synthesis of hydrazide **8abc**. (a) $\text{H}_2\text{NNH}_2 \cdot \text{H}_2\text{O}$, Et_3N , Na_2SO_4 , CHCl_3 , 35°C ; (b) NaOH , $\text{MeOH}/\text{H}_2\text{O}$, r.t.

Singh et al. [104] obtained hydrazides via the transamidation of *N*-Boc, *N*-nitroso, and *N*-tosyl amides with hydrazine hydrate, at room temperature, in 76–94% yields (Scheme 3).



Scheme 3. Synthesis of hydrazides **8** by transamidation; (a) 2HNNH_2 (2–3 eq), DCM, r.t., 30 min–2 h; when $\text{R}^2 = \text{Boc}$ and $\text{R}^3 = \text{Me}$, or $\text{R}^1 = \text{Alk}$, DBU (1 eq) is also used; (b) **25** (3 eq), DCM, r.t., 1 h; (c) 2HNNH_2 (3 eq), DCM, r.t., 1 h.

Table 1. Reaction conditions for the synthesis and purification of hydrazides from esters, anhydrides, acyl chlorides, and others.

Ref.	Starting Material	Experimental Conditions	Purification Process	Hydrazide Compounds ($\eta\%$)
[50]	17a	Hydrazine hydrate (1.2 eq) EtOH 75–80 °C 2 h	Silica gel column chromatography	8a X = N, O; R = Alk (70–95%)
[51]	17b	Hydrazine hydrate (10 eq) MeOH Reflux 3 h	-	8b
[26]	17c	Hydrazine hydrate (n.s.) EtOH or MeOH 85 °C 6 h	Recrystallization from aqueous ethanol or methanol	8c (88%)
[26]	17d	Hydrazine hydrate (n.s.) EtOH or MeOH 85 °C 6 h	Recrystallization from aqueous ethanol or methanol	8d (54%)

Table 1. Cont.

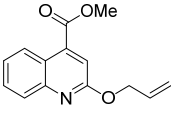
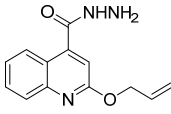
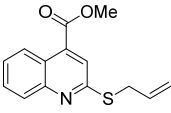
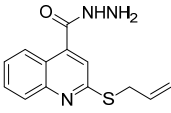
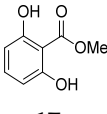
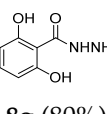
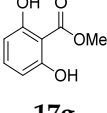
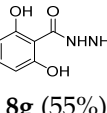
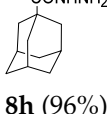
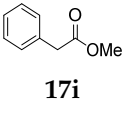
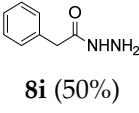
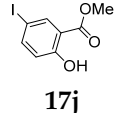
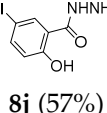
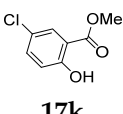
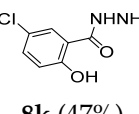
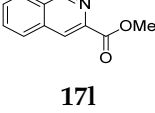
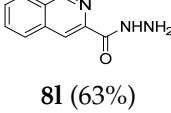
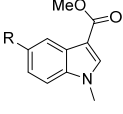
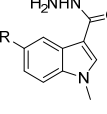
Ref.	Starting Material	Experimental Conditions	Purification Process	Hydrazide Compounds (η %)
[26]	 17e	Hydrazine hydrate (n.s.) EtOH or MeOH 85 °C 6 h	Recrystallization from aqueous ethanol or methanol	 8e (75%)
[26]	 17f	Hydrazine hydrate (n.s.) EtOH or MeOH 85 °C 6 h	Recrystallization from aqueous ethanol or methanol	 8f (83%)
[55]	 17g	Hydrazine hydrate (10 eq added dropwise) MeOH Reflux 2 h	-	 8g (80%)
[56]	 17g	Hydrazine hydrate (9 eq added dropwise) MeOH Reflux 2 h	Silica gel column chromatography	 8g (55%)
[57]	 17h	Hydrazine hydrate (80%) (20.6 eq) Neat Reflux n.s.	-	 8h (96%)
[43]	 17i	Hydrazine 80% (n.s.) EtOH Reflux 6h	n.s.	 8i (50%)
[43]	 17j	Hydrazine 80% (n.s.) EtOH Reflux 6 h	n.s.	 8j (57%)
[43]	 17k	Hydrazine 80% (n.s.) EtOH Reflux 6 h	n.s.	 8k (47%)
[13]	 17l	Hydrazine hydrate (1.7 eq) MeOH Reflux 4.5 h	Recrystallization from methanol	 8l (63%)
[34]	 17m	Hydrazine hydrate (n.s.) EtOH Reflux 8–10 h	n.s.	 8m R = H, Br (n.s.)

Table 1. Cont.

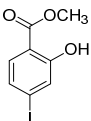
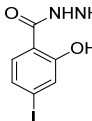
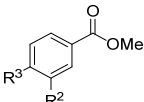
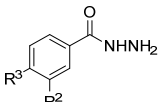
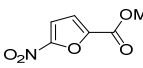
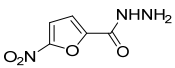
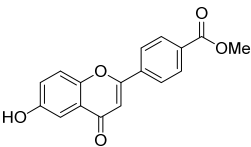
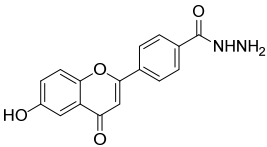
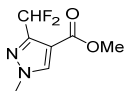
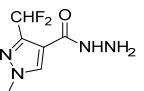
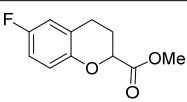
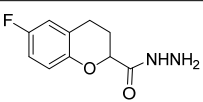
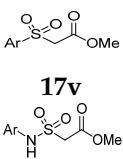
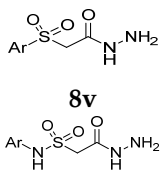
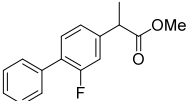
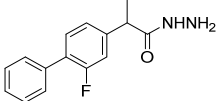
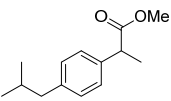
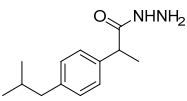
Ref.	Starting Material	Experimental Conditions	Purification Process	Hydrazide Compounds (η %)
[38]	 17n	Hydrazine hydrate (1.1 eq) EtOH Reflux 3 h	Recrystallization from ethanol	 8n (75%)
[40]	 17o $R^2 = H, R^3 = H$ 17p $R^2 = Cl, R^3 = H$ 17q $R^2 = H, R^3 = Cl$	Hydrazine hydrate 80% (n.s.) EtOH Reflux 3 h	n.s.	 8o $R^2 = H, R^3 = H$ 8p $R^2 = Cl, R^3 = H$ 8q $R^2 = H, R^3 = Cl$ (n.s.)
[53]	 17r	Hydrazine hydrate (1 eq) Anhydrous EtOH $\sim 0^\circ C$ 30 min	Recrystallization from ethanol	 8r (73%)
[54]	 17s	Hydrazine hydrate (n.s.) MeOH Reflux 6 h	Recrystallization from ethanol	 8s (n.s.)
[39]	 17t	Hydrazine monohydrate (8 eq) EtOH Ice bath 30 min	-	 8t (n.s.)
[59]	 17u	Hydrazine hydrate (2 eq) EtOH Reflux 8 h	-	 8u (91%)
[105]	 17v 17w	Hydrazine hydrate (1.1 eq) MeOH Pyridine (cat.) Reflux 6–7 h	Recrystallization from methanol	 8v 8w (n.s.)
[61]	 17x	Hydrazine hydrate (2 eq) EtOH Reflux 4 h	-	 8x (n.s.)
[62]	 17y	Hydrazine hydrate 80% (~8 eq, dropwise) EtOH 95–100 $^\circ C$ 12 h	Recrystallization from ethanol	 8y (89%)

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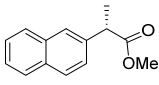
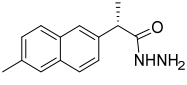
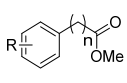
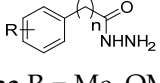
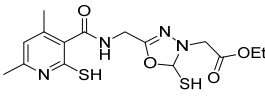
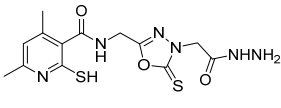
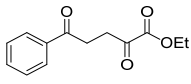
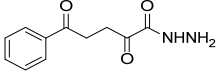
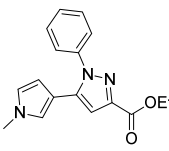
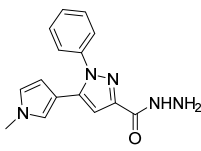
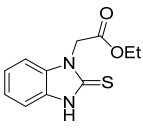
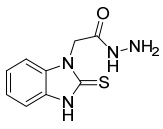
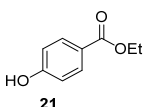
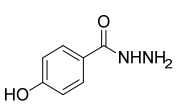
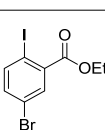
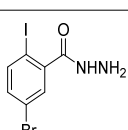
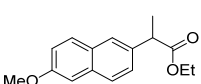
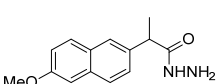
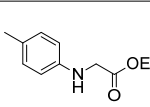
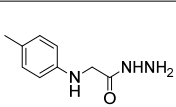
Ref.	Starting Material	Experimental Conditions	Purification Process	Hydrazide Compounds (η %)
[36]	 17z	Hydrazine hydrate (n.s.) EtOH 80–90 °C 8 h	-	 8z (n.s.)
[41]	 17aa	Hydrazine hydrate 85% (~6.5 eq) MeOH Reflux 8 h	-	 8aa R = Me, OMe (82–92%)
[63]	 17ab	Hydrazine hydrate (~10 eq) MeOH Reflux 5 h	Recrystallization from methanol	 8ab (37%)
[64]	 17ac	Hydrazine hydrate (n.s.) EtOH Reflux 6 h	-	 8ac (78%)
[35]	 17ad	Hydrazine (4 eq) EtOH Reflux 5 h	Recrystallization from ethanol	 8ad (73%)
[65]	 17ae	Hydrazine hydrate (6 eq.) EtOH 30 °C 1 h	Recrystallization from ethanol	 8ae (26%)
[66]	 17af	Hydrazine hydrate 80% (31 eq) EtOH Reflux 8 h	Recrystallization from ethanol	 8af (n.s.)
[67]	 17ag	Hydrazide hydrate (4.6 eq) EtOH Reflux 3 h	Recrystallization from ethanol	 8ag (78%)
[68]	 17ah	Hydrazine hydrate 80% (31 eq) EtOH Reflux 4 h	Recrystallization from ethanol	 8ah (70%)
[43]	 17ai	Hydrazine hydrate 80% (15 eq) EtOH Reflux 8 h	Recrystallization from ethanol	 8ai (63%)

Table 1. Cont.

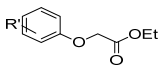
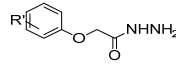
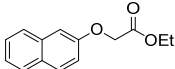
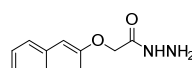
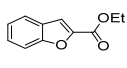
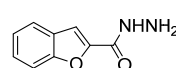
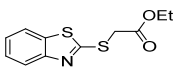
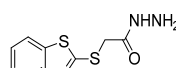
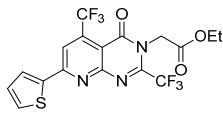
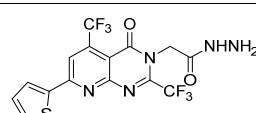
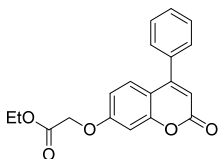
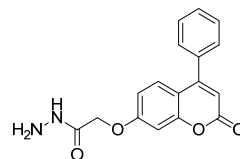
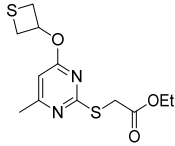
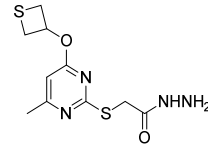
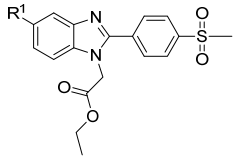
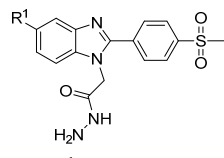
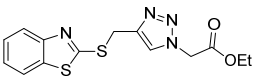
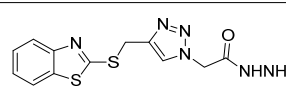
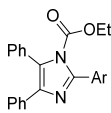
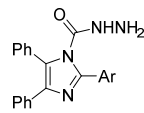
Ref.	Starting Material	Experimental Conditions	Purification Process	Hydrazide Compounds (η %)
[43]	 17aj	Hydrazine 80% (n.s.) EtOH Reflux 6 h	n.s.	 8aj R' = Alk, Halide (39–54%)
[43]	 17ak	Hydrazine 80% (n.s.) EtOH Reflux 6 h	n.s.	 8ak (46%)
[43]	 17al	Hydrazine 80% (n.s.) EtOH Reflux 6 h	n.s.	 8al (57%)
[43]	 17am	Hydrazine 80% (n.s.) EtOH Reflux 6 h	n.s.	 8am (56%)
[72]	 17ao	Hydrazine hydrate (~3 eq) EtOH Reflux 12 h	-	 8ao (n.s.)
[73]	 17ap	Hydrazine hydrate (2 eq) EtOH Reflux 8 h	-	 8ap (80%)
[75]	 17aq	Hydrazine hydrate 85% (3 eq) EtOH r.t. 4 h	Recrystallization from isopropyl alcohol	 8aq (67%)
[76]	 17ar	Hydrazine hydrate 99% (1 eq) EtOH Reflux 6 h	Recrystallization from ethanol	 8ar R ¹ = H, Cl, CH ₃ (67–73%)
[77]	 17as	Hydrazine hydrate (1.5 eq) EtOH Reflux 4 h	Recrystallization from ethanol	 8as (90%)
[78]	 17at	Hydrazine hydrate (1.02 eq) EtOH Reflux 3 h	Recrystallization from ethanol or methanol	 8at (89–97%)

Table 1. Cont.

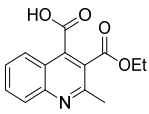
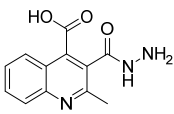
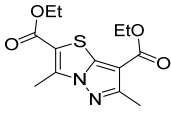
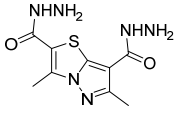
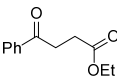
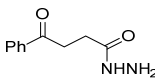
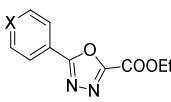
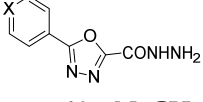
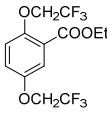
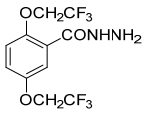
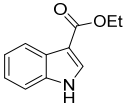
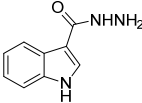
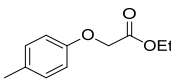
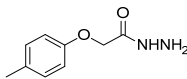
Ref.	Starting Material	Experimental Conditions	Purification Process	Hydrazide Compounds ($\eta\%$)
[79]	 17au	Hydrazine hydrate (20 eq) EtOH Reflux 4 h	Recrystallization from ethanol	 8au (61%)
[37]	 17av	Hydrazine hydrate 80% (3 eq) EtOH Reflux 3 h	Recrystallization from ethanol/DMF	 8v (90%)
[80]	 17ac	Hydrazine monohydrate (1 eq) EtOH Reflux 4 h	Recrystallization from dioxane	 8ac (90%)
[81]	 17w	Hydrazine hydrate (4 eq) EtOH Reflux 6 h	-	 8aw X = N, CH (48–55%)
[82]	 17x	Hydrazine (1 eq) EtOH Reflux 3 h	-	 8ax (94%)
[83]	 17ay R = 4-F-C ₆ H ₄ , 17az R = 4-CH ₃ -C ₆ H ₄ 17aaa R = 2-Cl,4-Cl-C ₆ H ₃	Hydrazine hydrate (n.s.) EtOH Reflux n.s.	n.s.	 8ay R = 4-F-C ₆ H ₄ , 8az R = 4-CH ₃ -C ₆ H ₄ 8aaa R = 2-Cl,4-Cl-C ₆ H ₃ (n.s.)
[84]	 17aab	Hydrazine hydrate (10 eq) EtOH Reflux 7 h	-	 8aab (80%)
[2]	 17aac R = 2-furyl 17aad R = 3,4,5-(MeO) ₃ C ₆ H ₂ 17aai R = 3,4-(MeO) ₂ C ₆ H ₃	Hydrazine hydrate (n.s.) - Reflux n.s.	-	 8aac R = 2-furyl 8aad R = 3,4,5-(MeO) ₃ C ₆ H ₂ 8aai R = 3,4-(MeO) ₂ C ₆ H ₃ (n.s.)
[85]	 17al	Hydrazine hydrate (~11 eq) EtOH r.t. 3–4 h	-	 8al (98%)

Table 1. Cont.

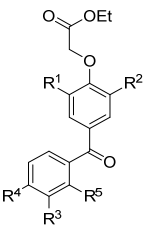
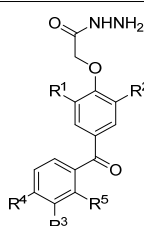
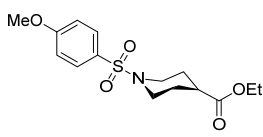
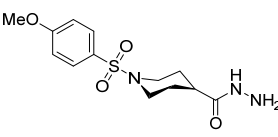
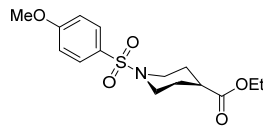
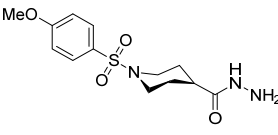
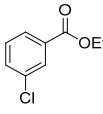
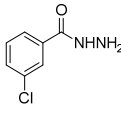
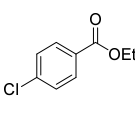
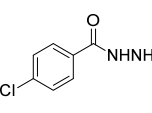
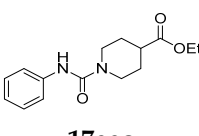
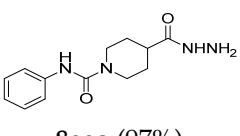
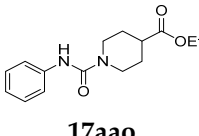
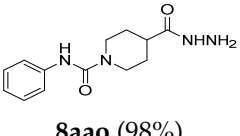
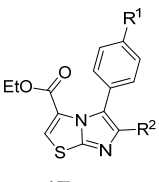
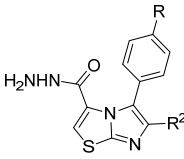
Ref.	Starting Material	Experimental Conditions	Purification Process	Hydrazide Compounds (η %)
[86]	 17aaj	Hydrazine hydrate (1.2 eq) EtOH r.t. 5–6 h	Recrystallization from ethanol	 8aaj $R^1 = \text{H, CH}_3, \text{F}$; $R^2 = \text{H, Cl}$; $R^3 = \text{H, Cl}$; $R^4 = \text{H, Cl, I}$; $R^5 = \text{H, Cl}$ (92% as an example)
[87]	 17aak	Hydrazine (1 eq) MeOH Reflux 2 h	-	 8aak (n.s.)
[42]	 17aal	Hydrazine hydrate (n.s.) MeOH Reflux 4 h	-	 8aal (n.s.)
[88]	 17aam	Hydrazine hydrate 80% (1 eq) Neat r.t. 4–5 h	-	 8p (96%)
[89]	 17aan	Hydrazine hydrate 80% (~11 eq) Neat r.t. 5–6 h	-	 8q (96%)
[90]	 17aao	Hydrazine monohydrate (~34 eq) Neat r.t. 4–5 h	-	 8aao (97%)
[91]	 17aao	Hydrazine monohydrate 80% (~20 eq) Neat r.t. 4–5 h	-	 8aao (98%)
[92]	 17aap	Hydrazine hydrate (10 eq, dropwise) EtOH and chloroform r.t. 24 h	Recrystallization from ethanol/water (60:40)	 8aap $R^1 = \text{Me, OMe, Br}$; $R^2 = \text{Alk}$ (72–80%)

Table 1. Cont.

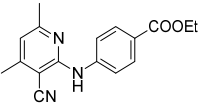
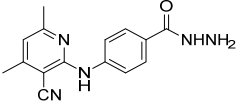
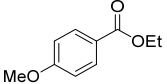
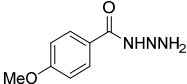
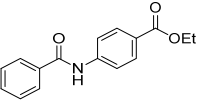
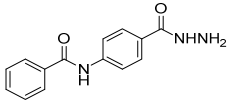
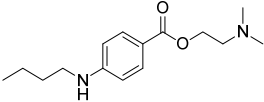
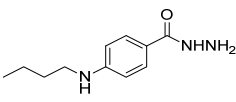
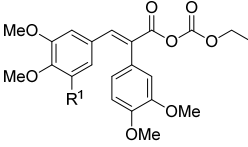
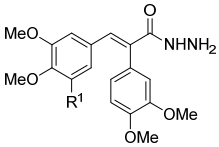
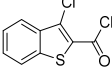
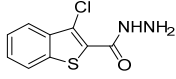
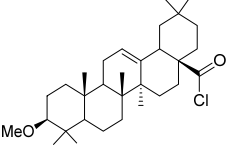
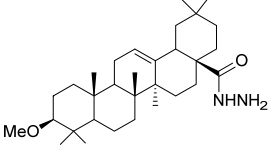
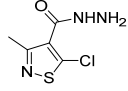
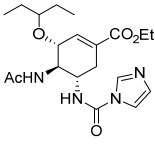
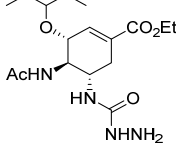
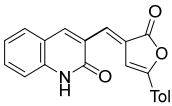
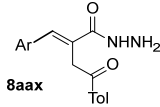
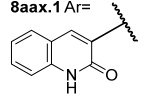
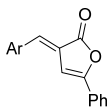
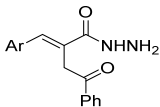
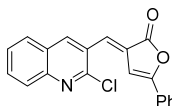
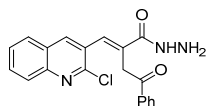
Ref.	Starting Material	Experimental Conditions	Purification Process	Hydrazide Compounds (η %)
[44]	 17aaq	Hydrazine hydrate (2 eq) EtOH Reflux 8 h	Recrystallization from ethanol	 8aaq (52%)
[93]	 17aar	Hydrazine hydrate (~4 eq) MeOH Reflux 6 h	Recrystallization from methanol	 8aar (92%)
[94]	 17aas	Hydrazine hydrate (n.s.) EtOH Reflux n.s.	n.s.	 8aas (n.s.)
[95]	 17aat	Hydrazine hydrate 80% (32.6 eq) EtOH Reflux n.s.	Recrystallization from ethanol	 8aat (n.s.)
[96]	 18	Hydrazine hydrate (n.s.) THF r.t. 4 h	n.s.	 8aaU R ¹ = Alk (80–95%)
[2]	 19a	Hydrazine hydrate (n.s.) - Reflux n.s.	-	 8aav (n.s.)
[97]	 19b	Hydrazine hydrate (2 eq) DCM 25 °C Overnight	Silica gel column chromatography	 8aaw (89%)
[98]	 19c	1. Acetone NaN ₃ (aq.) 8 °C, 30 min 2. Anhydrous hydrazine (4 eq) 2-propanol Reflux 45 min	-	 8aax (57%)
[99]	 20	Hydrazine hydrate (2.2 eq) Et ₃ N (1.5 eq), Na ₂ SO ₄ , CHCl ₃ 1. r.t. 2. 35 °C. 1. 30 min 2. Overnight	-	 8aay (92%)

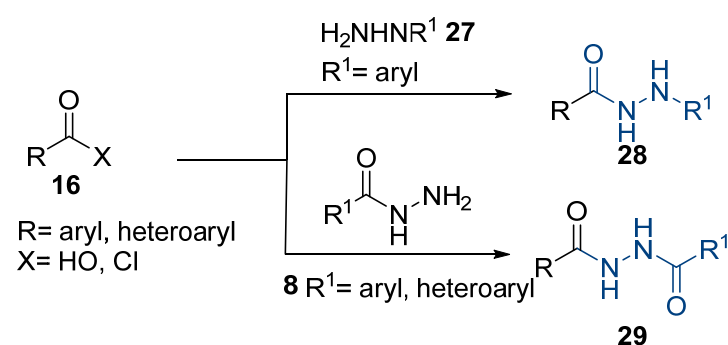
Table 1. Cont.

Ref.	Starting Material	Experimental Conditions	Purification Process	Hydrazone Compounds (η %)
[28]	 21	Hydrazine hydrate (1 eq) [100] EtOH r.t. 1 h	Recrystallization from ethanol	 8aax  8aax.1 (81%)
[101]	 22	Hydrazine hydrate (1.1 eq.) EtOH r.t. n.s.	-	 8aba (n.s.)
[103]	 23	Hydrazine hydrate 85% (1 eq added dropwise) EtOH r.t. n.s.	Recrystallization from ethanol	 8abb.1 (78%)

n.s.—not specified by the authors.

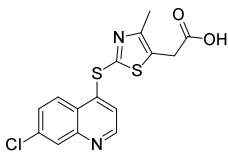
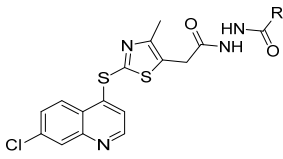
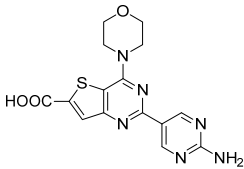
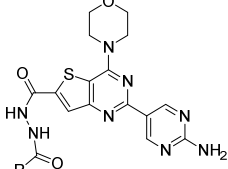
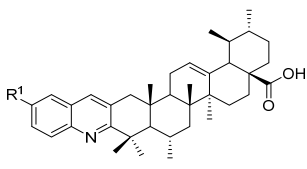
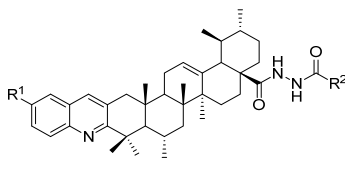
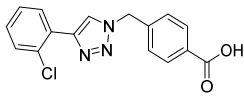
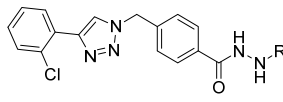
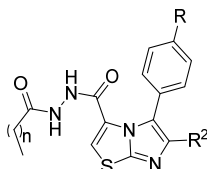
Aside from the synthesis of unsubstituted hydrazides, substituted ones can be synthesized as illustrated in Scheme 4 and outlined in Table 2. In these cases, acids [106–109] or acyl halides [92,110] **16** react with hydrazides **8** or hydrazines **27** to acylate the most nucleophilic amine unit. When an acid is used as the starting material, the reaction is performed in the presence of a coupling agent, such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) [106,107,109]. Generally, products **28** and **29** were obtained in low to good yields (35–97%).

Substituted hydrazides were also obtained via the alkylation of hydrazides **8** by reaction with primary or secondary alcohols as alkylating agents, under ruthenium complex catalysis (Scheme 5). Joly et al. [111] reported the synthesis of dialkylated and monoalkylated hydrazides **34** or **35**, respectively, in reasonable to excellent yields using diaminocyclopentadienone ruthenium tricarbonyl complex **Ru1**. On the other hand, Thiagarajan et al. [112] reported the synthesis of both symmetrical and unsymmetrical *N,N*-disubstituted hydrazides **34** and **37**. The use of diols led to the intramolecular cyclization of acylhydrazides to generate **38**.



Scheme 4. Representative scheme of substituted hydrazide synthesis.

Table 2. Reaction conditions for the synthesis and purification of substituted hydrazides from acid or acyl chlorides.

Ref.	Starting Material	Experimental Conditions	Purification Process	Products ($\eta\%$)
[106]	 30a	1. CH_2Cl_2 EDC, DMAP, 0°C , 1 h 2. RCONHNH_2 , r.t., 24 h	Recrystallization from ethyl acetate/ CH_2Cl_2 (1:1)	 29a (72–88%)
[107]	 30b	RCONHNH_2 , EDC, DMF, r.t., 12 h	Silica column chromatography	 29b (68–78%)
[108]	 30c	1. SOCl_2 , benzene, reflux, 3 h 2. $\text{R}^2\text{CONHNH}_2$, Et_3N , CH_2Cl_2 /ether, r.t., 8–12 h	Silica column chromatography	 29d $\text{R}^1 = \text{Halide}$, $\text{R}^2 = \text{Alk}$ (46–88%)
[109]	 30d	RNHNH_2 , EDC, HOBT, Et_3N , CH_2Cl_2 , r.t., 12–24 h	Silica column chromatography	 28a (35–97%)
[92]	 19c	8aap , CHCl_3 , r.t., 1 h	-	 29c (65–70%)

n.s.—not specified by the authors.

Barbor et al. [113] reported a novel nickel-catalyzed method for the synthesis of hydrazides **28** and **40** through N-N cross-coupling reactions from hydroxamates **39** in the presence of aromatic or aliphatic amines. These reactions occurred by catalysis with the nickel complex presented in Scheme 6. According to the authors, N-N coupling occurs efficiently when hydroxamates with electron-donating or -withdrawing *para*-substituents are used together with aniline derivatives. The aniline derivatives may have *para*-electron-donating or sterically hindered *ortho* substituents, such as halide (with no indication of protodehalogenation) or alkyl groups. Additionally, the reaction is also compatible with aniline derivatives bearing unprotected ketone and hydroxyl moieties. Primary, secondary, and tertiary aliphatic hydroxamates were also well tolerated. Moreover, in the presence of secondary aliphatic amines, in situ silylation allows N-N coupling in low to good yields [113].

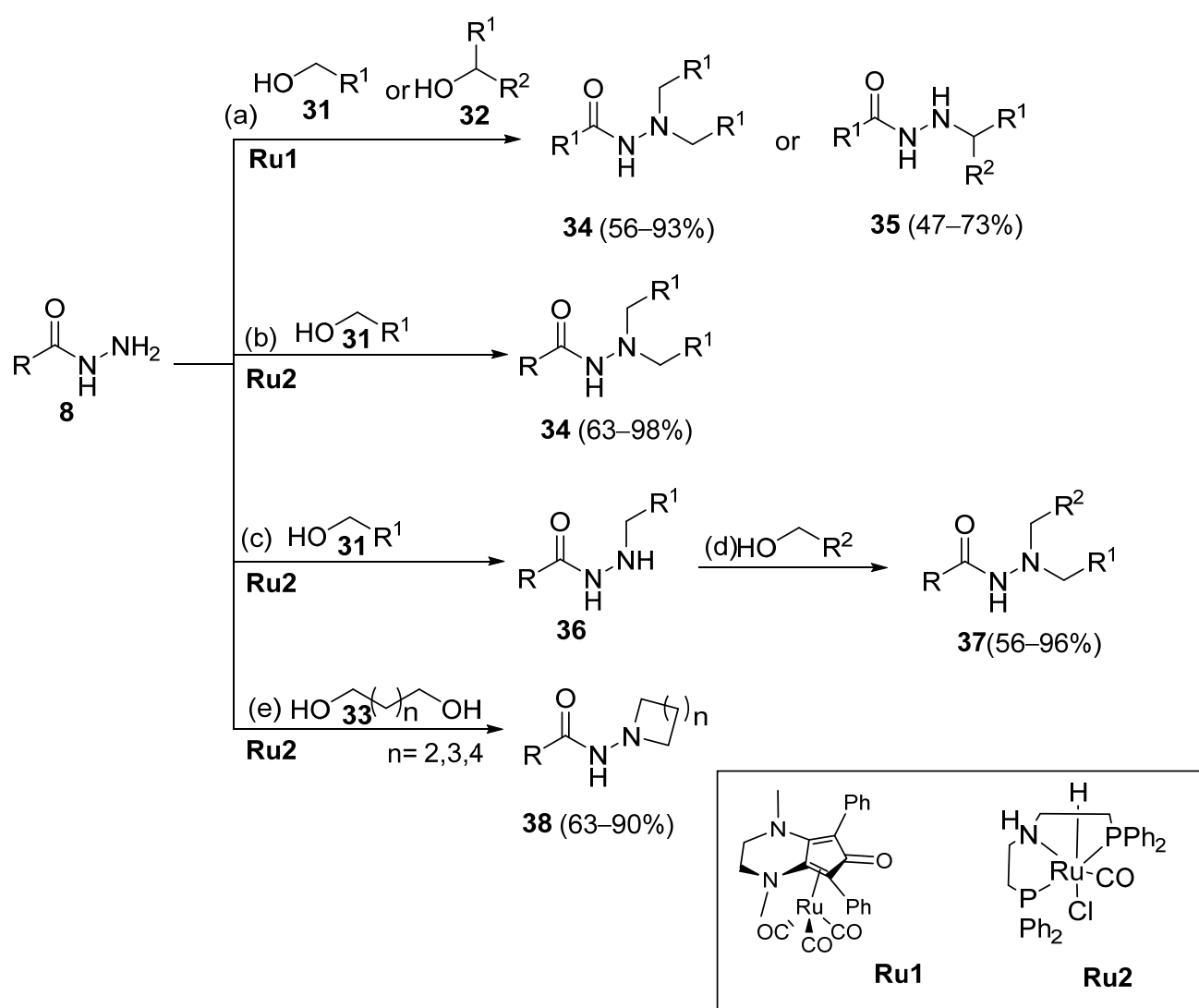
On the other hand, nickel-catalyzed photochemical C-N coupling reactions were performed by Li et al. [114] to react (hetero)aryl halides **41** with hydrazides/N-Boc hydrazine **42** (Scheme 7). This arylation reaction was catalyzed by a Ni(II)-bipyridine complex in the presence of purple LEDs. The reaction of N-Boc hydrazine with aryl chlorides **41** with electron-deficient and electron-neutral substituents at the *para* position yielded aryl

hydrazides **43** with low to good yields (33–89%). Also, the synthesis of rizatriptan was conducted after applying this method for the synthesis of intermediate **43a** [114].

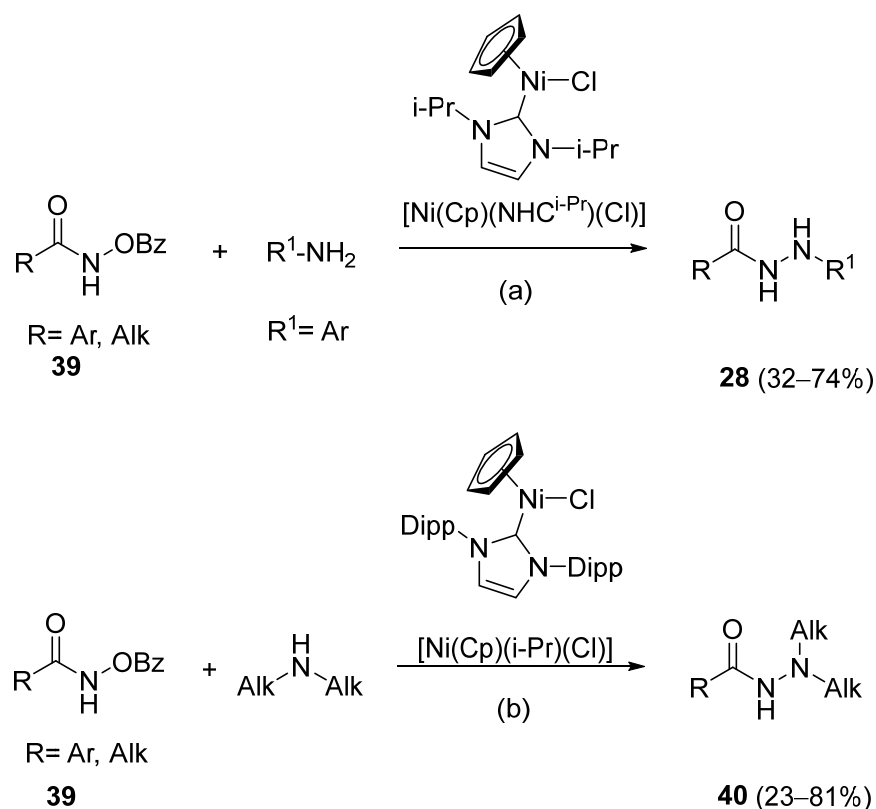
Moreover, many alkyl and aryl hydrazides **8** were coupled with 4-chloroacetophenone **41a**, yielding hydrazides **28b** generally in good yields (Scheme 8). Aryl hydrazides with electron-rich and electron-neutral substituents and heteroaryl hydrazides were well tolerated in this reaction (48–77%) [114].

Hydrazides **47** were obtained from substituted azodicarboxylates **46** and allylic or heteroallylic acylsilanes **45** in the presence of visible light. This reaction afforded hydrazides **47** in good yields (53–93%). The drug moclobemide was obtained from the precursor **47a**, which was synthesized by the previous method (Scheme 9) [115].

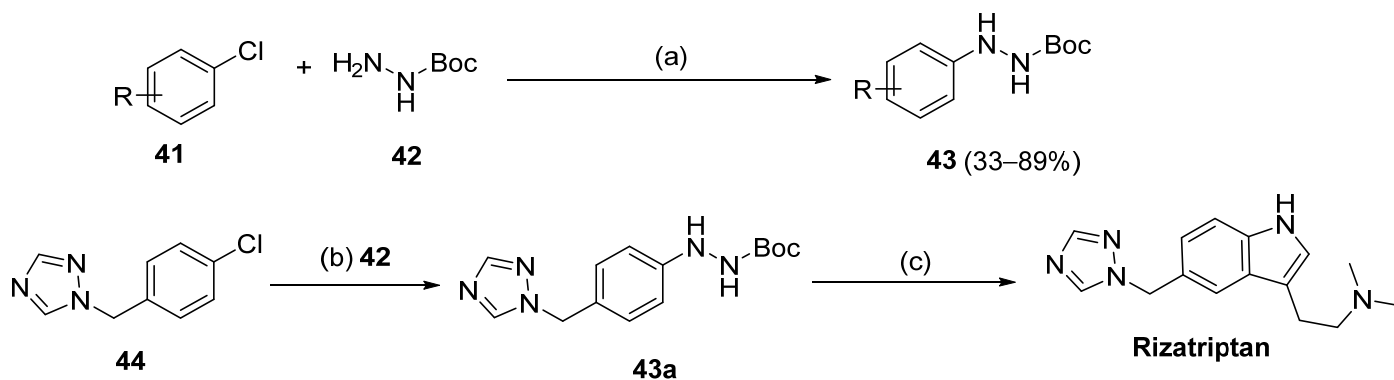
N,N'-disubstituted benzohydrazides **50** were obtained from benzoyl acrylates **49** via a hydrazine insertion into the β -position through an unexpected carbon–carbon bond cleavage (Scheme 10) [116].



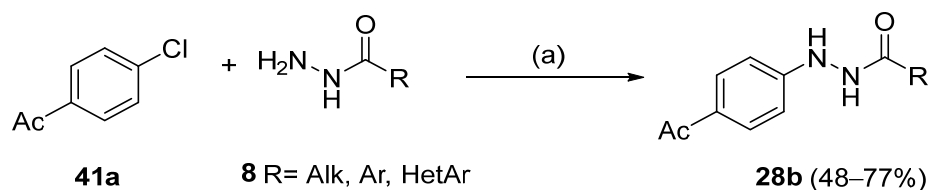
Scheme 5. Synthesis of dialkylated and monoalkylated hydrazides; (a) alcohol (5 eq), **Ru1** catalyst (1 mol%), Me_3NO (2 mol%), NaO^tBu (0.5 eq), $t\text{-BuOH}$ (0.5 M), 130°C , 24 h; (b) alcohol (2.2 eq), **Ru2** catalyst (2 mol%), KO^tBu (5 mol%), toluene, 135°C , 24 h; (c) alcohol (1.1 eq), **Ru2** catalyst (1 mol%), KO^tBu (5 mol%), toluene, 135°C , 12 h; (d) alcohol (1.1 eq), **Ru2** (1 mol%), KO^tBu (5 mol%), toluene, 135°C , 12 h; (e) diol (2 eq), **Ru2** catalyst, KO^tBu (5 mol%), toluene, 135°C , 24 h.



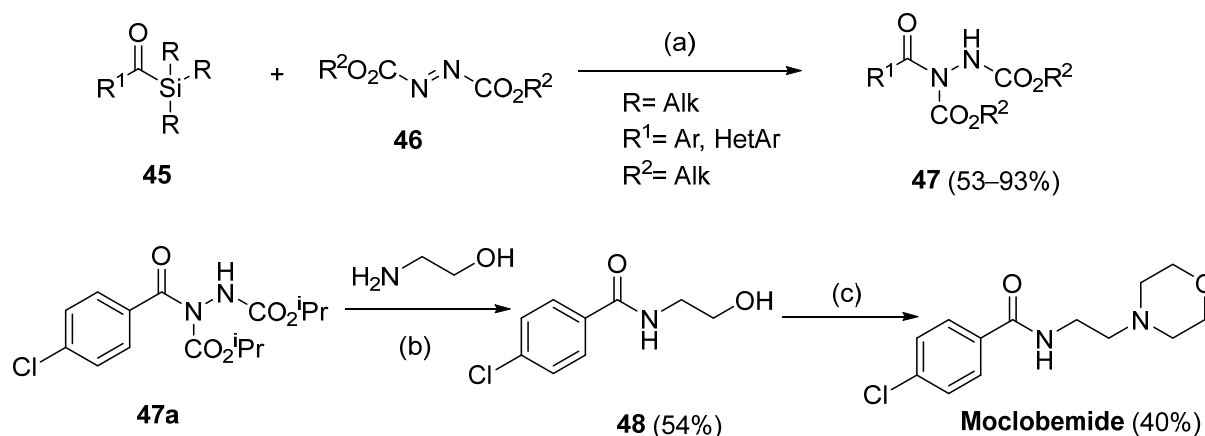
Scheme 6. Synthesis of substituted hydrazides from hydroxamates. (a) Ni catalyst (10 mol%), PhSiH₃ (1 eq), 1:4 CH₂Cl₂/THF (0.2 M), 30 °C, 24 h; (b) Ni catalyst (10 mol%), PhSiH₃ (1 eq), MSTFA (1.5 eq), 1:4 CH₂Cl₂/THF (0.2 M), 30 °C, 24 h.



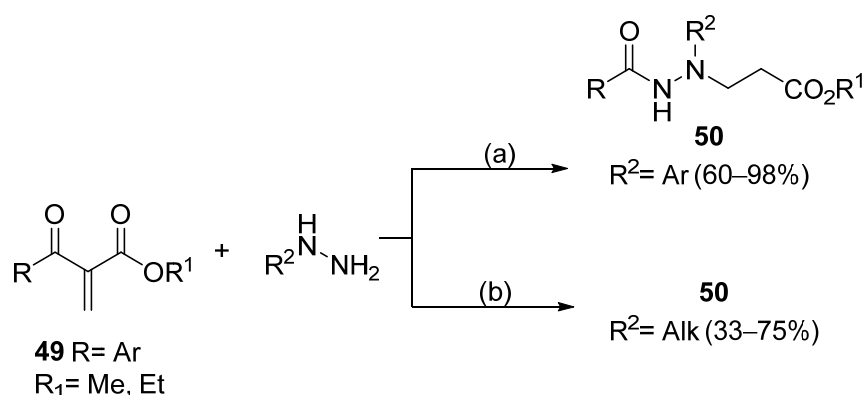
Scheme 7. Synthesis of **43** and rizatriptan: (a) (NiBr₂·glyme, d-Mebpy) (10 mol%) purple LEDs (390–395 nm), Cy₂NMe, TBAI, CH₃CN, 80 °C, Ar, 12 h; (b) **42** (NiBr₂·glyme, d-Mebpy), purple LEDs (390–395 nm) Cy₂NMe, TBAI, CH₃CN, 80 °C, Ar, 24 h; (c) i. 4 M HCl, THF, r.t., 6 h; ii. Me₂N(CH₂)₃CH(OEt)₂, HCl, H₂O, 70 °C, 2 h.



Scheme 8. Synthesis of hydrazides **28b**: (a) (NiBr₂·glyme, d-Mebpy) (10 mol%) purple LEDs (390–395 nm), Cy₂NMe, TBAI, CH₃CN, 80 °C, Ar, 12 h.



Scheme 9. Synthesis of hydrazides **47** and moclobemide: (a) toluene, 456 nm, rt, 16 h; (b) DCM, r.t., 20 h; (c) i. MsCl, DCM, Et₃N, DMAP, r.t., 24 h; ii. morpholine, 100 °C, 6 h.



Scheme 10. Synthesis of compounds **50**; (a) Et₃N (0.5–3.5 eq), CH₃CN, r.t., 30 min–15 h; (b) Et₃N (3.5 eq), H₂O, CH₃CN, r.t., 24 h.

2.2. Biological Activity of Hydrazides

The compounds presented in Figure 3 showed anticancer activity against various cancer cell lines. Hydrazide **8ac** showed good anticancer activity against MCF-7 breast cancer and HepG2 hepatocellular carcinoma cell lines with IC₅₀ = 8.1 μM and IC₅₀ = 28.6 μM, respectively [64]. Hydrazides **8aap.1** and **29c.1** also displayed anticancer activity towards the MCF-7 cancer cell line with IC₅₀ values of 2.37 and 1.83 μM, respectively [92]. Besides that, Sabry et al. [92] reported that these hydrazides showed a strong dual inhibition activity of EGFR/HER2 kinase with IC₅₀ values of 0.153 μM (EGFR) and 0.108 μM (HER2) for **29c.1** and 0.122 μM (EGFR) and 0.108 μM (HER2) for **8aap.1**. In in vivo studies in Swiss albino mice mammary glands, compounds **8aap.1** and **29c.1** showed tumor volume reductions by 65.3 and 76.5%, respectively, at 10 mg/kg.

Derivatives **29a.1** and **29a.2**, reported by Ramírez et al. [106], were also tested against the MCF-7 cancer cell line. Compounds **29a.1** and **29a.2** presented IC₅₀ values of 15.41 and 12.99 μM, respectively. In addition, derivatives **29a.3** and **29a.2** were active against the A549 cell line (lung cancer) with IC₅₀ values of 37.17 and 31.02 μM, respectively [106].

Hydrazides **8ad** and **29b.1**, reported by Abdelrehim et al. [35] and Han et al. [107], presented activity against the HCT-116 colorectal cancer cell line with IC₅₀ values of 8.44 μg/mL and 2.02 μM (Figure 3). Compound **29b.1** also showed activity against PC-3 (prostatic adenocarcinoma), A549 (lung cancer), and MDA-MB-231 (triple-negative breast cancer) cancer cell lines, with IC₅₀ values of 1.95, 1.62, and 1.55 μM. It also showed potent inhibitory activities against phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic sub-

unit alpha isoform (PI3K α) with an IC₅₀ = 0.46 nM and mammalian targeting of rapamycin (mTOR) with an IC₅₀ = 12 nM [107].

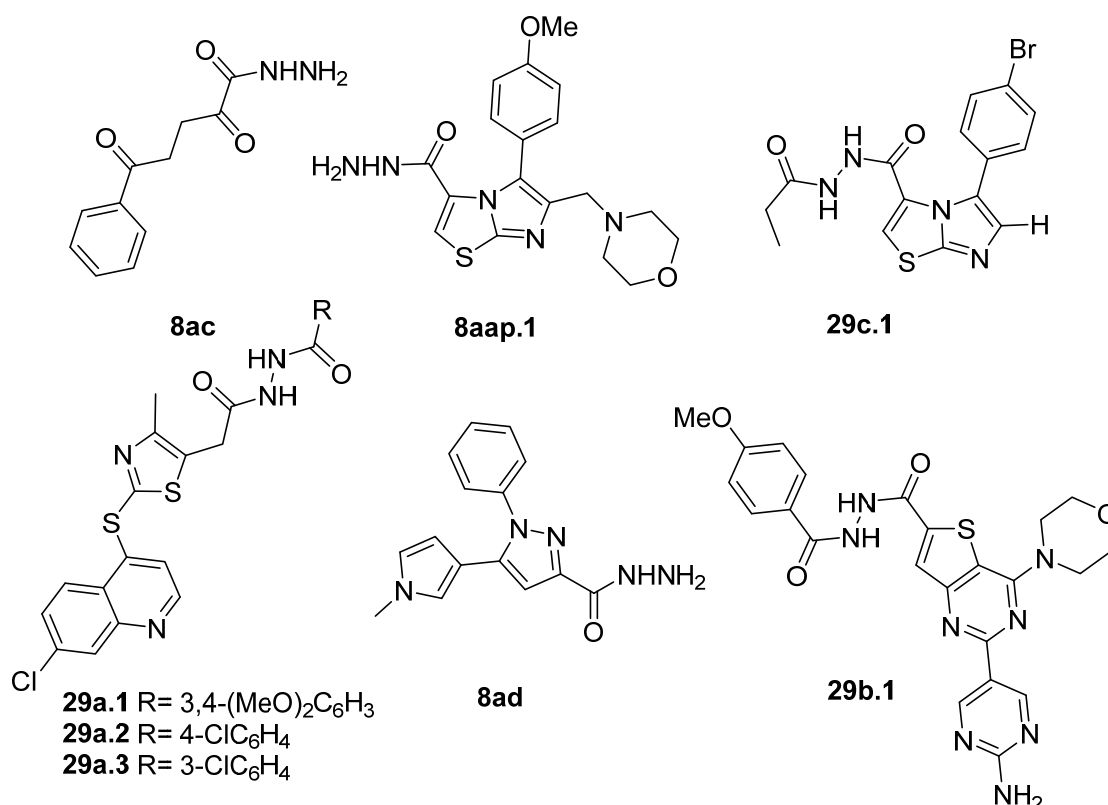


Figure 3. Hydrazides with anticancer activity.

Hydrazide **8b** (Figure 4) was evaluated for its antibacterial and antifungal activities. It showed a strong antibacterial and antifungal activity, with inhibition zones of 29, 30, 28 and 16 mm against *Bacillus subtilis*, *Escherichia coli*, *Candida albicans* and *Aspergillus niger*, respectively [51]. Compounds **8c–8f** also exhibited activity against *E. coli*, *B. subtilis*, and *Asp. niger* strains, presenting inhibition zones varying between 2 and 5 mm [26].

Compounds **28** (Figure 4) were evaluated as fungicides [109]. Compounds **28a.1–28a.5** exhibited growth inhibition activity against *Botryosphaeria dothidea*, *Rhizoctonia solani*, and *Gibberella zeae* with EC₅₀ values within the 10.0–0.306 µg/mL range, which were higher activity than those of the commercial agrochemicals azoxystrobin, boscalid, and fluxapyroxad [109].

Disubstituted hydrazides **29** were tested as antimalarial agents. Compounds **29a.4** and **29a.5** (Figure 5) showed antimalarial activity with IC₅₀ values of 0.65 and 0.64 µM, respectively [106].

Hydrazides present in Figure 6 were evaluated as antivirals. Compound **8abc** showed antiviral activity against influenza A as a Neuraminidase inhibitor against H5N1 and H1N1 subtypes with IC₅₀ values of 26.8 nM and 11.9 nM, respectively [99]. Moreover, hydrazide **8aax.1** was presented as a great immunomodulator, presenting 80% protection against the highly pathogenic avian influenza virus (H5N8) [28].

Myeloperoxidase plays a key role in the human antimicrobial system by oxidizing vital molecules of microorganisms in phagolysosomes through the production of hypochlorous acid. It has been associated with inflammatory diseases such as renal injury, multiple sclerosis, and cardiovascular and neurodegenerative diseases. Saylam et al. [65] reported compound **8ae** (Figure 7) as an excellent myeloperoxidase inhibitor with an IC₅₀ = 0.393 µM, which is comparable to the standard drug 4-aminobenzoic acid hydrazide.

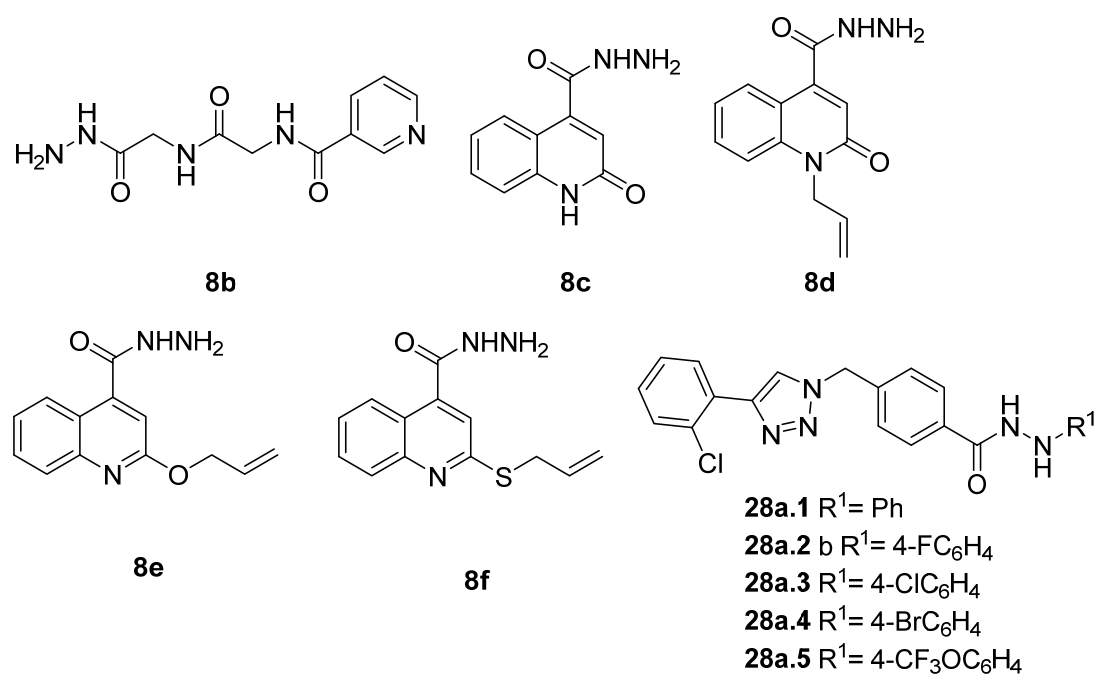


Figure 4. Hydrazides with antibacterial and antifungal activity.

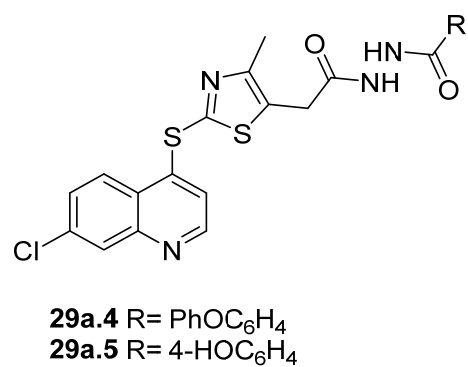


Figure 5. Hydrazides with antiparasitic activity.

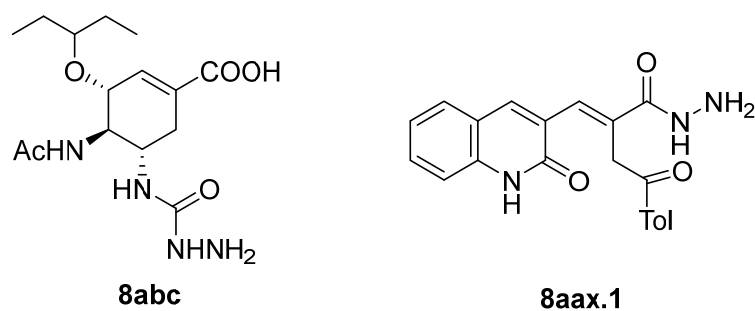


Figure 6. Hydrazides with antiviral activity.

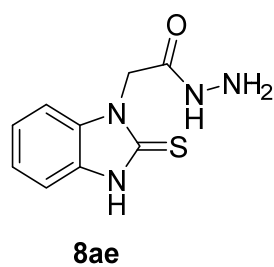


Figure 7. Myeloperoxidase inhibitor.

Table 3. Cont.

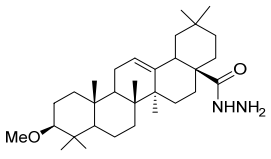
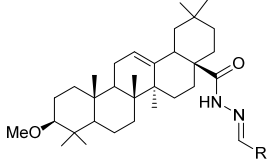
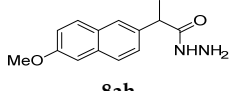
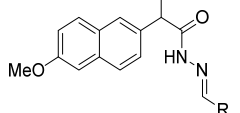
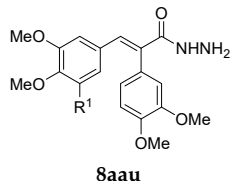
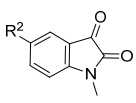
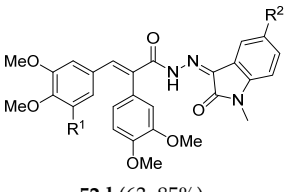
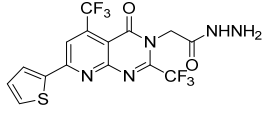
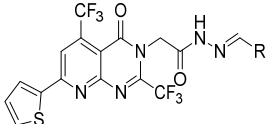
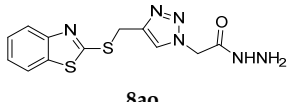
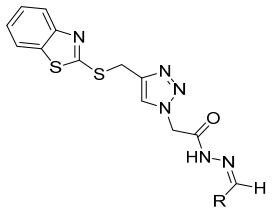
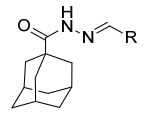
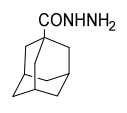
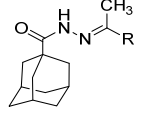
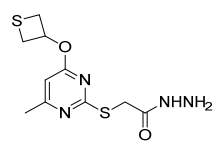
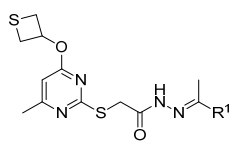
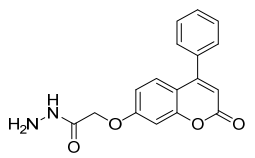
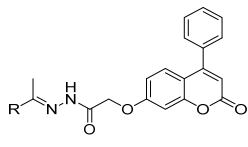
Ref.	Starting Material	Experimental Conditions	Purification Process	Hydrazone Compounds (η %)
[97]	 8aaw	RCHO (1.25 eq) MeCN:CHCl ₃ (1:1), HOAc (0.9 eq), 65 °C, 24 h R = Ar	Silica gel column chromatography	 52b R = Ar (72–94%)
[68]	 8ah	RCHO (1.1 eq) EtOH, glacial CH ₃ COOH (drops), reflux, 8 h R = Ar	Recrystallization from ethanol	 52c R = Ar (56–95%)
[96]	 8aau	 (1 eq) MeOH, CH ₃ COOH (cat.), reflux, 1h	Flash column chromatography	 52d (63–85%)
[72]	 8as	RCHO (1 eq), EtOH, piperidine (0.3 eq), reflux, 2 h R = Ar	-	 52e R = Ar (n.s.)
[77]	 8ao	RCHO (1 eq), EtOH, CH ₃ COOH (drops), reflux, 6–8 h R = Ar	Recrystallization from ethanol	 52f R = Ar (85–92%)
[57]	 8h	RCHO (1 eq) EtOH, reflux R = Ar	-	 52g R = Ar (26–55%)
[57]	 8h	MeCOR (1 eq) EtOH, reflux R = Ar	-	 52h R = Ar (15–61%)
[75]	 8aq	MeCOR ¹ (n.s.) EtOH, reflux, 1 h	Recrystallization from EtOH, n-BuOH, or <i>i</i> -PrOH	 52j (61–89%)
[73]	 8ap	MeCOR (1 eq), CH ₃ COOH (17 eq), EtOH, reflux, 6–8 h R = Ar	Recrystallization from acetic acid	 52k R = Ar (85–95%)

Table 3. Cont.

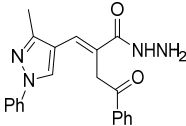
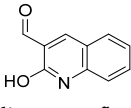
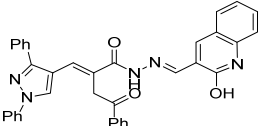
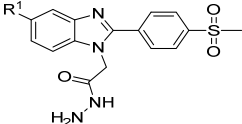
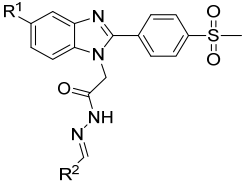
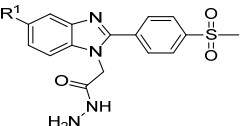
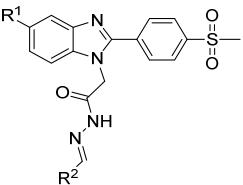
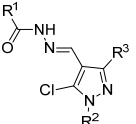
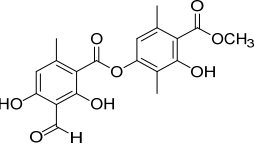
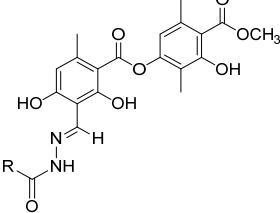
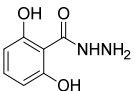
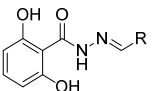
Ref.	Starting Material	Experimental Conditions	Purification Process	Hydrazone Compounds (η %)
[101]	 8aba.1	 (1 eq) dioxane, reflux, 30 min	Recrystallization from ethanol/dioxane mixture (1:1) or dioxane	 52l (77%)
[76]	 8ar	$R^2\text{CHO}$ (1 eq) EtOH, CH_3COOH (cat.), reflux, 6 h $R^2 = \text{Ar}$	Recrystallization from ethanol	 52m $R^2 = \text{Ar}$ (41–60%)
[76]	 8ar	MeCOR (1 eq) EtOH, CH_3COOH (cat.), reflux, 6 h $R = \text{Ar}$	Recrystallization from ethanol	 52n $R = \text{Ar}$ (46–62%)
[117]	$\text{H}_2\text{N}-\text{N}(\text{R}^1)-\text{C}(=\text{O})-\text{R}^2$ 8abe $\text{R}^1 = \text{H}$ 8abf $\text{R}^1 = \text{CH}_3$	 (1 eq) EtOH, CH_3COOH (0.9 eq), r.t.	Recrystallization from dichloromethane/ethanol (1:2)	 52o (40–84%)
[43]	$\text{R}-\text{C}(=\text{O})-\text{NHNH}_2$ 8ai–8am	 (antranorin) EtOH, CH_3COOH , 50 °C, 2h	Silica gel column chromatography	 52p (73–89%) 52p.1 $\text{R} = \text{C}_6\text{H}_5$ 52p.2 $\text{R} = \text{C}_6\text{H}_4$ 52p.3–7 $\text{R} = \text{C}_6\text{H}_3$ 52p.3 $\text{R} = 2\text{-CH}_3$ 52p.4 $\text{R} = 3\text{-CH}_3$ 52p.5 $\text{R} = 4\text{-CH}_3$ 52p.6 $\text{R} = 4\text{-Br}$ 52p.7 $\text{R} = 2\text{-i-Pr-5-CH}_3$ 52p.8 $\text{R} = \text{C}_6\text{H}_4$ 52p.9 $\text{R} = \text{C}_6\text{H}_4$
[55]	 8g	RCHO (1 eq) MeOH, $p\text{-TsOH}$ (cat.), r.t., 2 h $R = \text{Ar}$	Silica gel column chromatography	 52q $R = \text{Ar}$ (90–95%)

Table 3. Cont.

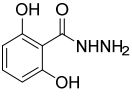
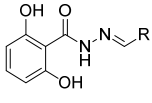
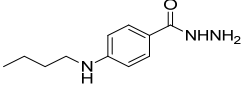
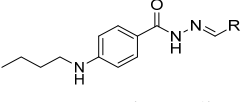
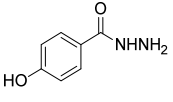
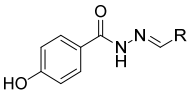
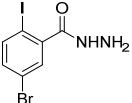
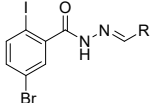
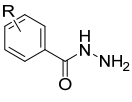
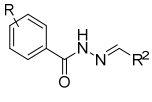
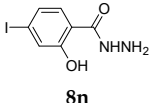
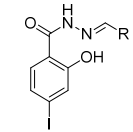
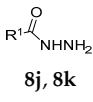
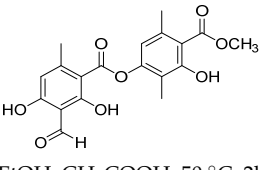
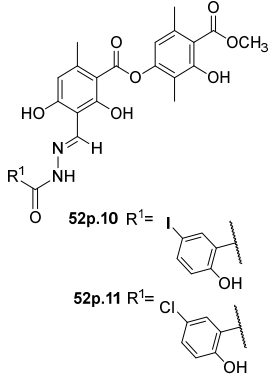
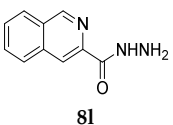
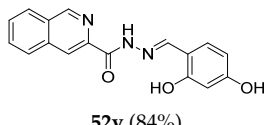
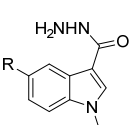
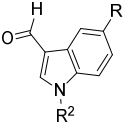
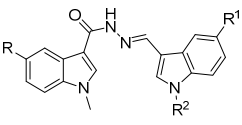
Ref.	Starting Material	Experimental Conditions	Purification Process	Hydrazone Compounds (η %)
[56]	 8g	RCHO (n.s.) MeOH, p-TsOH (cat.), r.t., overnight R = Ar	Silica gel column chromatography	 52q R = Ar (60–79%)
[95]	 8aat	RCHO (1.1 eq) EtOH, CH ₃ COOH (few drops), reflux, 12 h R = Ar	Recrystallization from ethanol	 52s R = Ar (68–90%)
[66]	 8af	RCHO (1.1 eq) EtOH, CH ₃ COOH (few drops), reflux, 8 h R = Ar	Recrystallization from ethanol	 52t R = Ar (55–80%)
[67]	 8ag	RCHO (1.1 eq) EtOH, reflux, 3 h R = Ar	Recrystallization from ethanol	 52u R = Ar (24–90%)
[118]	 8abj R = 2-HO 8af R = 4-HO	R ² CHO (0.99 eq) EtOH or <i>i</i> -PrOH, 60 °C, 0.5–6 h R ² = Ar	Recrystallization from <i>i</i> -PrOH	 52v R = 2-HO, 4-HO; R ² = Ar (66–92%)
[38]	 8n	RCHO (1.1 eq) EtOH, reflux, 3–35 min R = HetAr	Recrystallization from ethanol	 52w R = HetAr (18–97%)
[43]	 8j, 8k	 (n.s.) EtOH, CH ₃ COOH, 50 °C, 2h	Silica gel column chromatography	 52p (73–89%)
[13]	 8l	2,4-(HO) ₂ C ₆ H ₃ CHO (1 eq) MeOH, reflux, 6 h	-	 52y (84%)
[34]	 8m	1.  (1 eq) CH ₃ COOH (28 eq), 90 °C, 6 h 2. NaHCO ₃	Recrystallization from ethanol	 52z R, R ¹ , R ² = alkyl or halide (86–90%)

Table 3. Cont.

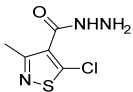
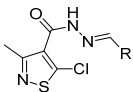
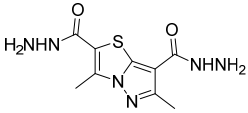
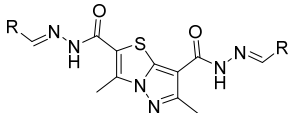
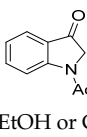
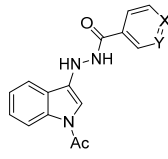
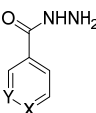
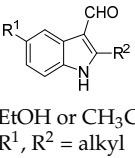
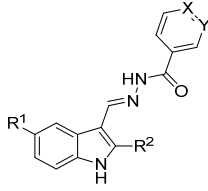
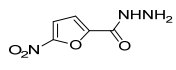
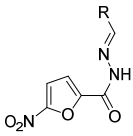
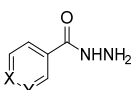
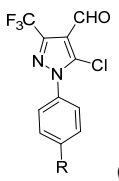
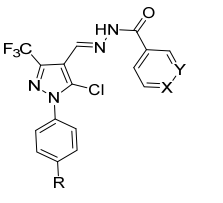
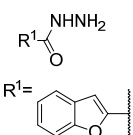
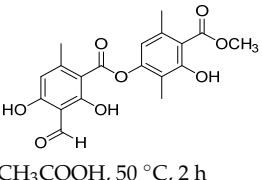
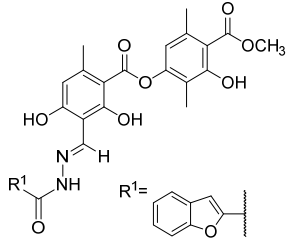
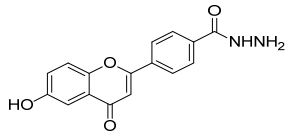
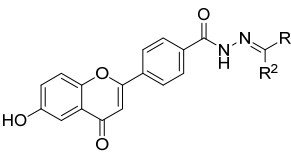
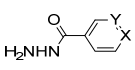
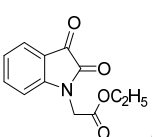
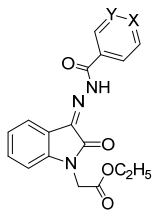
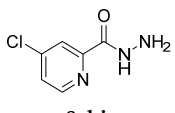
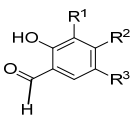
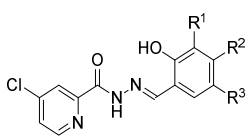
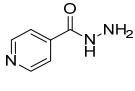
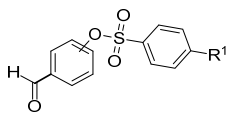
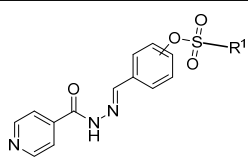
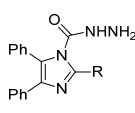
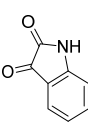
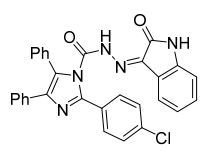
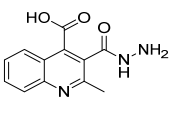
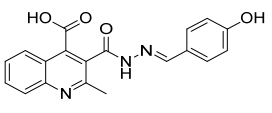
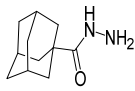
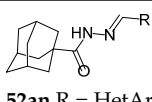
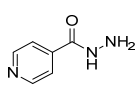
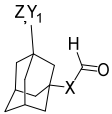
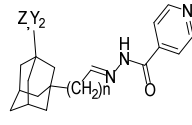
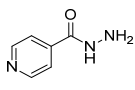
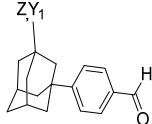
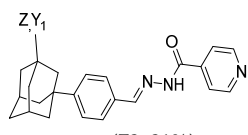
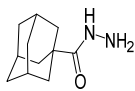
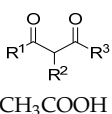
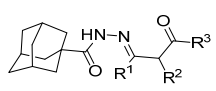
Ref.	Starting Material	Experimental Conditions	Purification Process	Hydrazone Compounds ($\eta\%$)
[98]	 8aax	RCHO (1 eq), EtOH, 78 °C, 4 h R = Ar	Recrystallization from acetonitrile or 70% ethanol	 52aa R = Ar (50–86%)
[37]	 8av	RCHO (2.1 eq) EtOH/DMF, reflux, 5 h R = Ar	Recrystallization from DMF/ethanol	 52ab R = Ar (72–80%)
[119]	 1 X = N, Y = CH 8abg.1 X = CH, Y = N 8abg.2 X = N ⁺ -O ⁻ , Y = CH 8abg.3 X = CH, Y = N ⁺ -O ⁻	 (n.s) EtOH or CH ₃ COOH, reflux	n.s.	 52ac (46–65%)
[119]	 1 X = N, Y = CH 8abg.2 X = N ⁺ -O ⁻ , Y = CH	 (n.s) EtOH or CH ₃ COOH, reflux R ¹ , R ² = alkyl	n.s.	 52ad R ¹ , R ² = alkyl (72–95%)
[53]	 8r	RCHO (1.1 eq), EtOH, reflux, 2 h R = Ar	Recrystallization from ethanol	 52ae R = Ar (10–93%)
[120]	 1 X = N, Y = CH 8abg.1 X = CH, Y = N	 (1 eq) EtOH, reflux, 5 h	Silica gel column chromatography	 52af R = R = H, OCH ₃ , F, Cl (89–94%)
[43]	 8al	 EtOH, CH ₃ COOH, 50 °C, 2 h	Silica gel column chromatography	 52p.12
[54]	 8s	R ¹ COR ² (1 eq) EtOH, acetic acid (~0.2 eq), reflux, 8 h	-	 52ag R ¹ = Ar, R ² = H or alkyl (62–92%)

Table 3. Cont.

Ref.	Starting Material	Experimental Conditions	Purification Process	Hydrazone Compounds (η %)
[121]	 1 X = N, Y = CH 8abh X, Y = C-Br, C-Cl, CH, N, C-Me, C-NO ₂	 (1 eq) EtOH, CH ₃ COOH (cat.), reflux, 3 h	Recrystallization from ethanol	 52ah (60–80%)
[122]	 8abi	 (1 eq) MeOH, reflux	Recrystallization from methanol	 52ai (78–95%)
[123]	 1	 (1 eq) MeOH, CH ₃ COOH (drops), reflux, 2 h	Recrystallization from ethanol	 52aj R ¹ = Ar (75–87%)
[78]	 8at	 (n.s.), 25 min	-	 52ak R = Ar (93%)
[79]	 8au	4-HOC ₆ H ₄ CHO (1 eq) EtOH, CH ₃ COOH (drops), r.t., 30 min	Recrystallization from ethanol	 52al (23%)
[125]	 8abh	RCHO (1 eq), EtOH, reflux, 1–2 h R = HetAr	Recrystallization from ethanol/water or ethanol	 52an R = HetAr (82–95%)
[126]	 1	 (1 eq), MeOH, Ar (g), reflux, 3–60 h; Y ₁ : CHO, Z: H, Ph, cyclopentyl	Recrystallization from a mixture of chloroform/ether or silica gel column chromatography	 52ao (40–86%) Y ₂ : CONH=CHPh; Z: H, Ph, cyclopentyl
[126]	 1	 (1 eq), MeOH, Ar (g), r.t., 18–48 h Y ₁ : CHO, Z: H, Ph, cyclopentyl	Recrystallization from a mixture of chloroform/ether or silica gel column chromatography	 52ap (78–81%) Y ₂ : CONH=CHPh; Z: H, Ph, cyclopentyl
[127]	 8abh	 (1 eq), EtOH, CH ₃ COOH (0.8 eq), reflux, 4–7 h R ¹ = Me or Ph; R ² = Me or H; R ³ = Me or OC ₂ H ₅	Recrystallization from ethanol	 52aq (73%)

n.s.—not specified by the authors.

3.1.2. Biological Activity of Hydrazone–Hydrazones

The new hydrazone–hydrazone derivatives represented in Figure 8 were evaluated as anticancer agents. Compounds **52a**, **52c.1**, **52d.1**, and **52e.1** showed good activity against human breast cancer cell lines, specifically against the MCF7 line, with IC_{50} values of 7.38, 59.81, 3.49, and 14.6 μ M, respectively [68,72,96,124]. Moreover, compound **52c.1** also showed promising anticancer activity, with IC_{50} = 22.42 μ M, against the human breast cancer cell line MDA-MB-231. Compound **52c.1** was tested in vivo and decreased the tumor volume in both low (60 mg/kg) and high (120 mg/kg) doses in mice [68]. Besides the activity against breast cancer, compound **52a** showed activity against the HepG2 cancer cell line with IC_{50} = 8.79 μ M [124]. In addition, derivatives **52d** were also tested against HCT-116 and SK-MEL-28 (melanoma) cancer cell lines. Compound **52d.1** displayed the highest activity with IC_{50} values of 6.82 and 10.39 μ M, respectively, with no relevant toxicity on non-malignant HaCaT (human keratinocyte) cells [96].

According to Halil et al. [97], natural compounds with bioactive properties, when combined with hydrazides, can lead to new active compounds with increased activity. Hence, Halil et al. [97] synthesized molecules with structure **52b** (Figure 8) starting from the natural product oleanolic acid. The in vitro anticancer activity was studied on the A549 (adenocarcinomic human alveolar basal epithelial) cell line. Of the thirteen compounds synthesized, compound **52b.1** showed the best activity with IC_{50} = 0.08 μ M and low cytotoxicity on the BEAS-2B cells (human non-tumorigenic lung epithelial cells).

The anticancer activity of combretastatin–oxindole **52d**, pyrimidine derivatives **52e**, and triazoles **52f** (Figure 8) was also evaluated against the A549 cell line. Compounds **52d.1** and **52e.1** were promising anticancer agents with IC_{50} values of 1.26 and 11.3 μ M, respectively [72,77,96]. Furthermore, Abba et al. [72] identified the derivative **52e.1** as a potent compound against DU145 (prostate cancer) using HeLa (cervical cancer) cell lines with IC_{50} values of 13.4 and 9.1 μ M, respectively [72].

According to Almehmadi et al. [77], molecules **52f** revealed an anticancer capacity, presenting a growth inhibition ranging from 55 to 90% at 400 μ g/mL against the A549 cell line.

Han et al. [95] described derivatives **52s.1** and **52s.2** with high anticancer activity against the human colorectal adenocarcinoma (Colo-205) cell line (IC_{50} = 50.0 and 20.5 μ M, respectively). On the other hand, compounds **52s.3**, **52s.4**, **52s.5**, **52t.1**, and **52t.2** displayed the great anticancer activity against the liver hepatocellular carcinoma HepG2 cell line with IC_{50} = 30.5, 35.9, 20.8, 42.4, and 37.4 μ M, respectively [66]. Derivatives **52t.1** and **52t.2**, reported by Han et al. [66] (Figure 8) exhibited lower activity than derivatives **52s**. Among the thirteen different hydrazones **52u**, described by Popiolek et al. [67], compound **52u.1** exhibited the best cytotoxicity with IC_{50} = 33.45 and 11.94 μ M against hepatocellular carcinoma (HepG2) and renal adenocarcinoma (769-P) cell lines, respectively, and additionally showed high selectivity, with low cytotoxicity against the normal Vero cell line, with IC_{50} = 320.54 μ M.

Among indole derivatives **52z** [34], compound **52z.1** was the most active against the A549 lung adenocarcinoma cell line with IC_{50} = 0.793 μ M. This compound also showed great activity against cervical HeLa and breast MCF-7 cancer cells with IC_{50} = 1.69 and 1.19 μ M. The authors studied the mechanisms of action of compound **52z.1** regarding different signaling pathways triggered in HeLa and MCF-7 cells, and it was verified that this compound induced cell apoptosis through the generation of reactive oxygen species and activation of many signal transduction pathways [34].

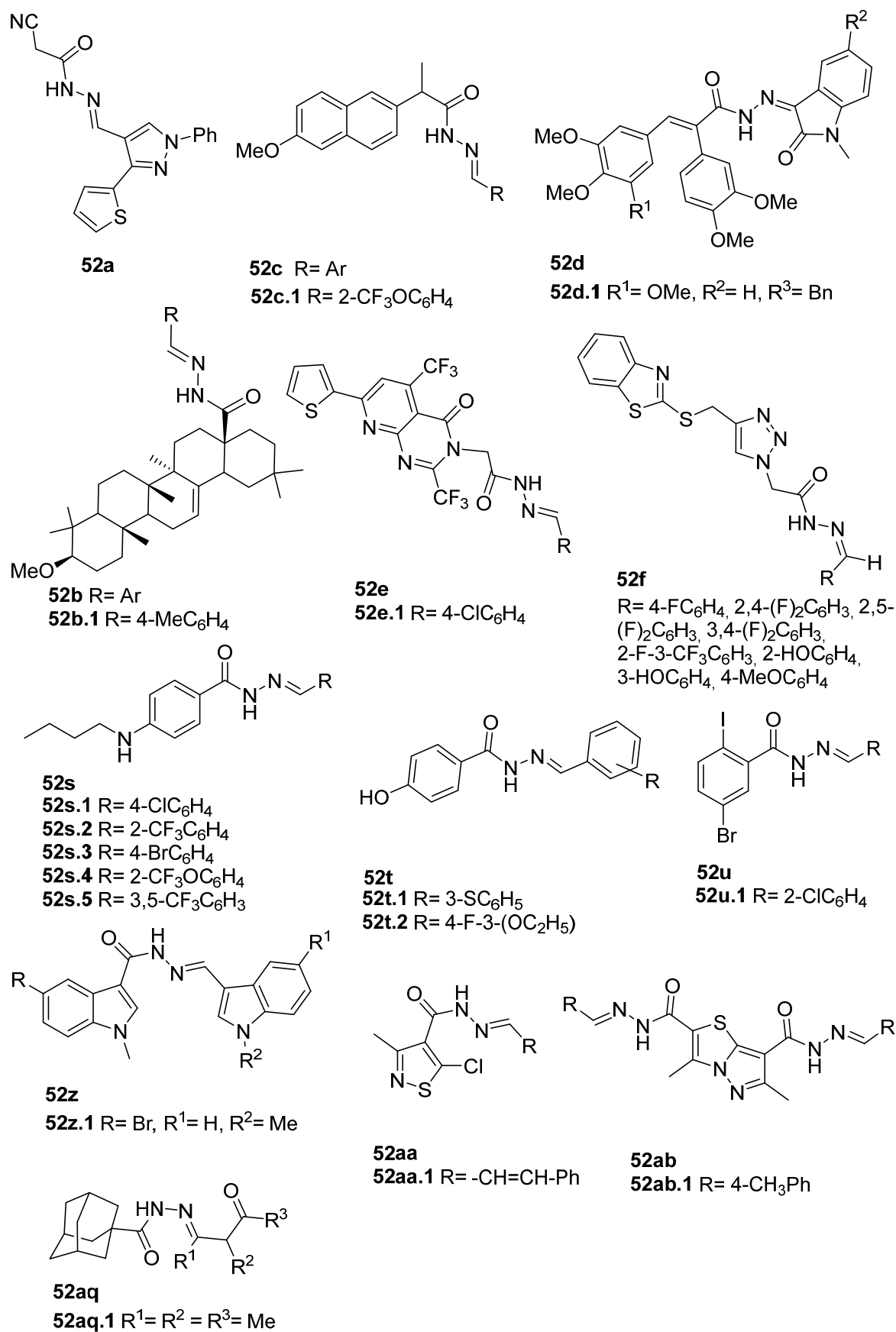


Figure 8. Hydrazide–hydrazones with anticancer activity.

Thiazole derivatives **52aa** (Figure 8) were screened towards various cancer cell lines, and **52aa.1** exhibited the highest antiproliferative activities with IC_{50} = 14, 25, 34.2, 39.3, and 68.6 μ M against human leukemia MV4-11 cells, colon LoVo and LoVo/DX, and breast MCF-7 and MCF-10A cancer cell lines, respectively [98].

Alsayari et al. [37] reported compounds **52ab** (Figure 8), from which **52ab.1** presented the highest activity towards HepG-2 and HCT-116 cell lines with IC_{50} = 30.5 and 86.9 μ g/mL, respectively.

Adamantane-1-carbohydrazone derivatives **52aq** were tested as anticancer agents for breast, liver, and lung cancers. Derivative **52aq.1** stood out with IC_{50} = 8.35, 7.82 and 4.39 μ M, for MCF-7, HepG-2 and A549 cell lines, respectively [127].

Compounds **52h** and **52g** (Figure 9) were evaluated for their antimicrobial activity against *Enterococcus faecalis*, *Staphylococcus aureus*, *Bacillus cereus*, and *Candida albicans*. Compounds **52h.1** presented an MIC of 12.5 μ M for the four strains, and **52h.2** presented IC_{50} values of 6.35 μ M, 6.77 μ M, 6.12 μ M, and 6.37 μ M against the same strains. Compounds **52g.1** and **52g.2** showed good inhibitory activity with IC_{50} values of 3.56 and 6.73 μ M against *Enterococcus faecalis* and 6.77 and 6.66 μ M against *Candida albicans*, respectively [57].

Pyrimidine derivatives **52j.1–52j.3** (Figure 9) also exhibited high antimicrobial activities with MIC = 0.05 μ g/mL against *St. aureus*, *Str. Pyogenes*, *P. vulgaris*, *K. pneumoniae*, *Ent. Aerogenes*, *P.S aeruginosa*, and *C. Albican* [75].

Compounds **52v** and **52w** (Figure 9) showed antibacterial potential against *S. aureus*, *E. Coli*, and *B. subtilis*. Specifically, compound **52v.1** was the best antibacterial agent against *S. aureus* with an MIC value of 0.625 μ g/mL. Compounds **52v.1–52v.4** had higher activity against *E. coli* with MIC = 0.625 μ g/mL. Moreover, compounds **52v.3** and **52v.4** displayed the best activities against *B. subtilis* with MIC = 0.312 μ g/mL [118]. Popiołek et al. [38] reported compounds **52w.1** and **52w.2** with MIC = 7.81 μ g/mL towards *B. subtilis* (ATCC 6633).

In 2020, furyl hydrazide–hydrazones **52ae** were also tested for their potential antimicrobial activity [53]. The assays of antibacterial and antifungal activity revealed that several of the synthesized compounds **52ae** (Figure 9) presented very strong bioactivity with MIC < 10 μ g/mL. Some compounds showed higher activity than the standard drugs (nitrofurantoin, cefuroxime, and ampicillin). For example, compound **52ae.1** was 130 times more active towards *Bacillus subtilis* ATCC 6633 (MIC = 0.48 μ g/mL) than ampicillin [53].

The novel derivatives **52af** (Figure 9) were evaluated for their inhibitory effects in several bacterial and fungal strains [120]. These compounds exhibited the maximum zone of inhibition ranging from 7 to 20 mm against *B. licheniformis* and *S. aureus*, as well as good antifungal activity against both *Asp. niger* and *C. albicans* with maximum zones of inhibition of 8–14 and 6–14 mm, respectively [120].

Adamantane hydrazide–hydrazone derivatives **52an.1** and **52an.2** presented by Al-Wahaibi et al. [125] also showed good antibacterial activity. Compound **52an.2** showed broad-spectrum antibacterial and antifungal activity with MIC = 1.5 μ M against *St. aureus* and *B. subtilis*, MIC = 3 μ M against *M. luteus*, and MIC = 6 μ M against *E. coli* and *P.S aeruginosa*. Compound **52an.1** only showed potent activity against the tested Gram-positive bacterial strains, with MIC = 3.53 μ M against *St. aureus* and *B. subtilis* and MIC = 7.06 μ M for *M. luteus* [125].

In the literature, simpler heteroaryl hydrazides, like isonicotinic hydrazide, or similar ones, have been employed to obtain compounds with a wide range of biological activities (Figure 10) [119,121,123,128]. A series of derivatives **52ad** that combine pyridine and indole moieties were reported, and the in vitro antimycobacterial activity was studied against strain *M. tuberculosis* H37Rv and against a clinical isolate of isoniazid-resistant *M. tuberculosis* strain, designated as CN-40 [119]. The hydrazide hybrid **52ad.1** (Figure 10) was the most promising compound with MIC = 0.05 μ g/mL and with a high selectivity index (SI = 300). Compared to isoniazid **1**, the new compound **52ad.1** had similar activity against *M. tuber-*

culosis H37Rv; still, the new compound showed higher activity than isoniazid against the isoniazid-resistant *M. tuberculosis* CN-40 strain [119]. Papageorgiou et al. [126] reported new isoniazid-based adamantane derivatives, **52ao.1** and **52ao.2**, with activity against *M. tuberculosis* H37Rv, MIC = 0.14 and 0.09 nM, respectively, and very low cytotoxicity against HepG2 (selectivity index ≥ 2500).

On the other hand, adamantane hydrazide–hydrazone derivative **52an.3** was also reported as an antituberculosis agent exhibiting MIC values of 0.2, 0.3, 1.5, 12.5, and 12.5 $\mu\text{g/mL}$ for *M. tuberculosis*, *M. bovis* BCG, *M. smegmatis*, *M. abscessus*, and *M. marinum*, respectively [129].

Antiviral activity was detected for hydrazide derivatives represented in Figure 11. Kassem et al. [73] obtained the 4-phenylcoumarin derivatives **52k**, and these proved to be potential inhibitors of the 3C protease of the hepatitis A virus. Compounds **52k.2** and **52k.1** presented the highest effects against viral adsorption and replication with $\text{IC}_{50} = 8.5$ and 10.7 $\mu\text{g/mL}$, respectively. Morsy et al. [101] reported derivative **52l** that showed 100% protection against Newcastle disease virus.

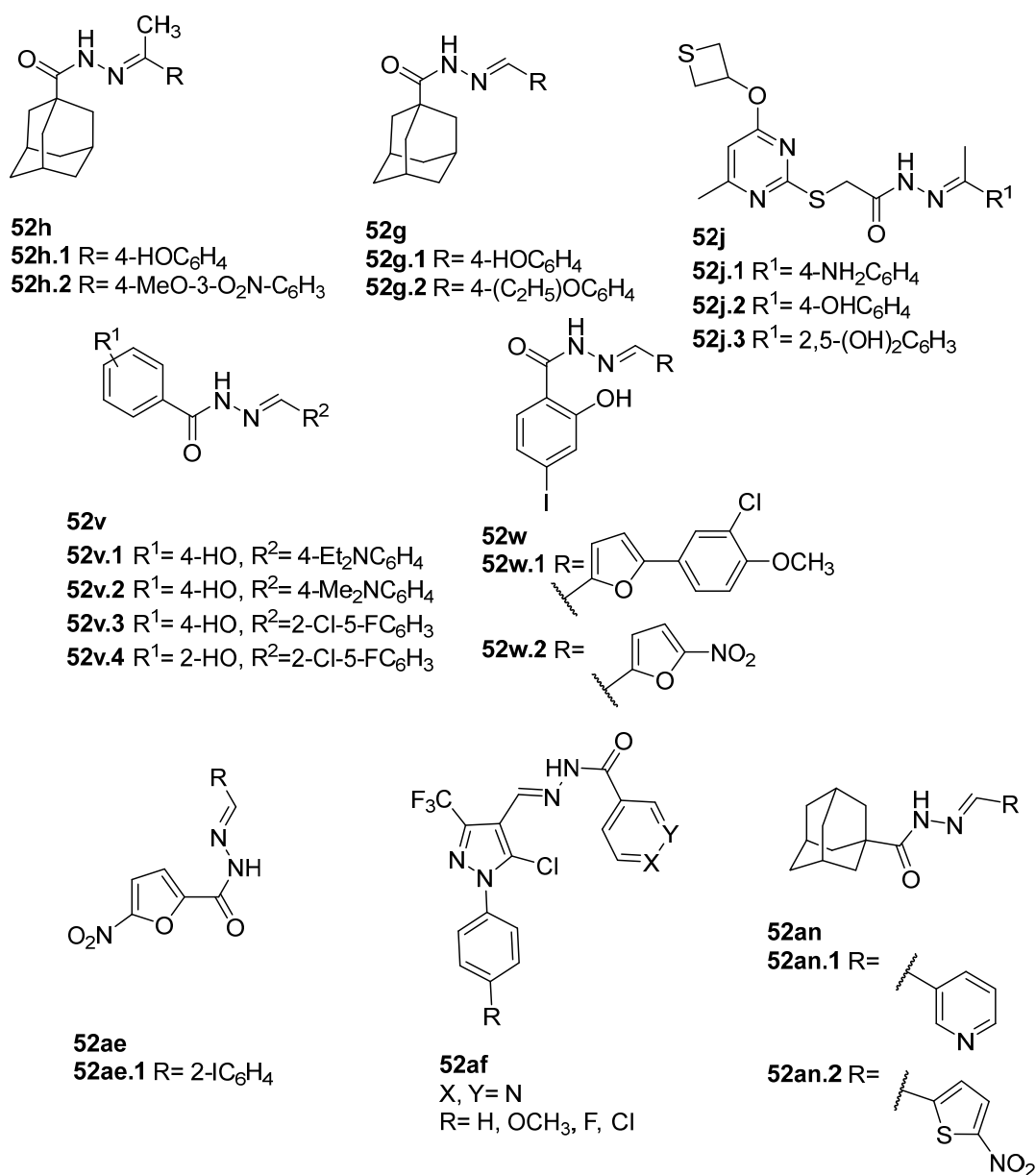


Figure 9. Hydrazide–hydrazones with antibacterial, antifungal, or antiparasitary activity.

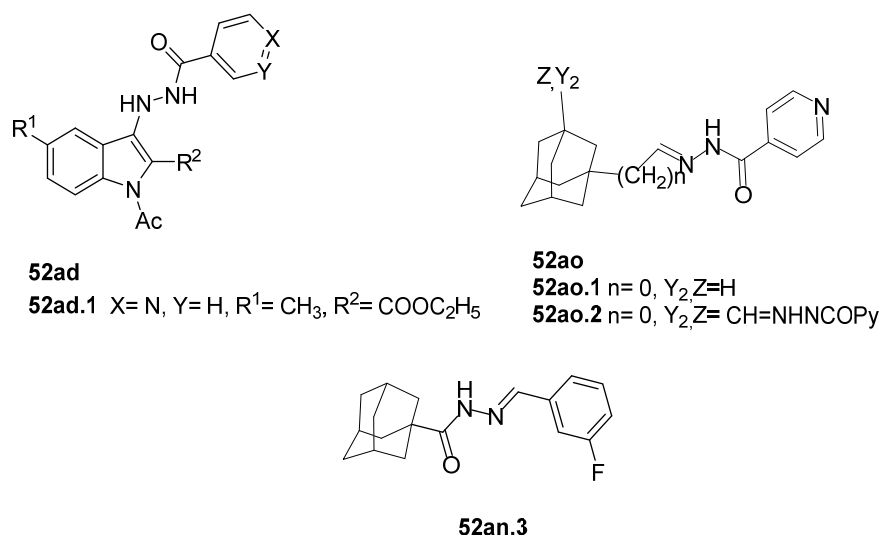


Figure 10. Hydrazide–hydrazones with antimycobacterial activity.

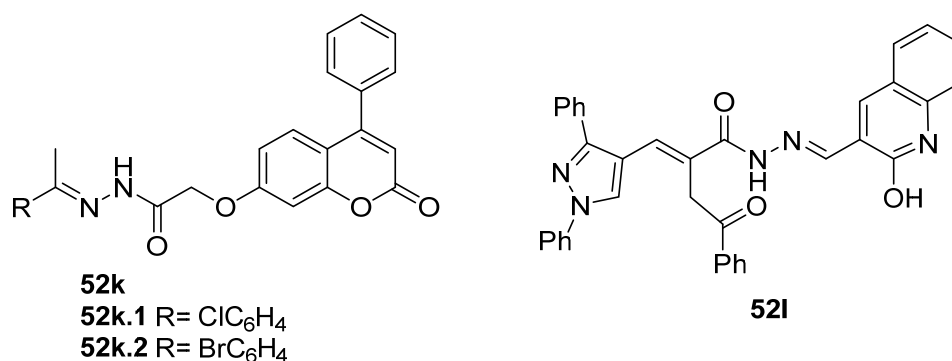


Figure 11. Hydrazide–hydrazones with antiviral activity.

A series of benzimidazole derivatives were synthesized and evaluated as cyclooxygenase-1(COX-1)/cyclooxygenase-2 (COX-2) inhibitors [76]. The results of the cyclooxygenase (COX) inhibition assay generally showed that the compounds **52m** and **52n.1** (Figure 12) exhibited low selectivity towards the COX-1 isozyme compared to those of reference drugs (indomethacin and celecoxib). Compounds **52m.1**, **52m.4**, **52n.1**, and **52n.2** showed selective inhibition of the COX-2 isozyme. Among all, compound **52m.1** exhibited the highest COX-2 inhibitory activity with an IC₅₀ = 0.10 μM and selectivity index SI = 134 [76]. Compounds **52m.1–4**, **52n.1**, and **52n.2** also exhibited good anti-inflammatory activity, reducing inflammation by more than 93%. Regarding the ulcerogenic liability, compound **52m.1** was the safest one with an Ulcer Index (UI) = 0.83 and a lower ulcerogenic effect than the reference drugs celecoxib (UI = 3.5) and indomethacin (UI = 13) [76].

Tumor Necrosis Factor alpha (TNF-α) is a pro-inflammatory cytokine that may trigger and amplify inflammatory signals via multiple signaling pathways [130]. The dysregulation of inflammation, particularly the dysregulation of TNF-α, has been associated with various diseases such as arthritis, atherosclerosis, neurodegenerative diseases, diabetes, and cancer [131]. Therefore, inhibition of TNF-α leads to higher control and better treatment of inflammatory diseases [117]. In 2019, Liang et al. [132] synthesized pyrazole–hydrazone **52am.1**, which showed excellent TNF-α inhibitory activity, and some displayed comparable anti-inflammatory activity to dexamethasone (reference drug) in vivo. In continuation of this work, Song et al. [117] discovered new pyrazole–hydrazone derivatives **52o** (Figure 12), particularly compound **52o.1**, which inhibited TNF-α in a dose-dependent manner with IC₅₀ = 5.56 μM. The authors also presented molecular docking results for **52o.1**, concluding

that the compounds' phenyl and hydrazide groups play an important role in binding to the target site [117].

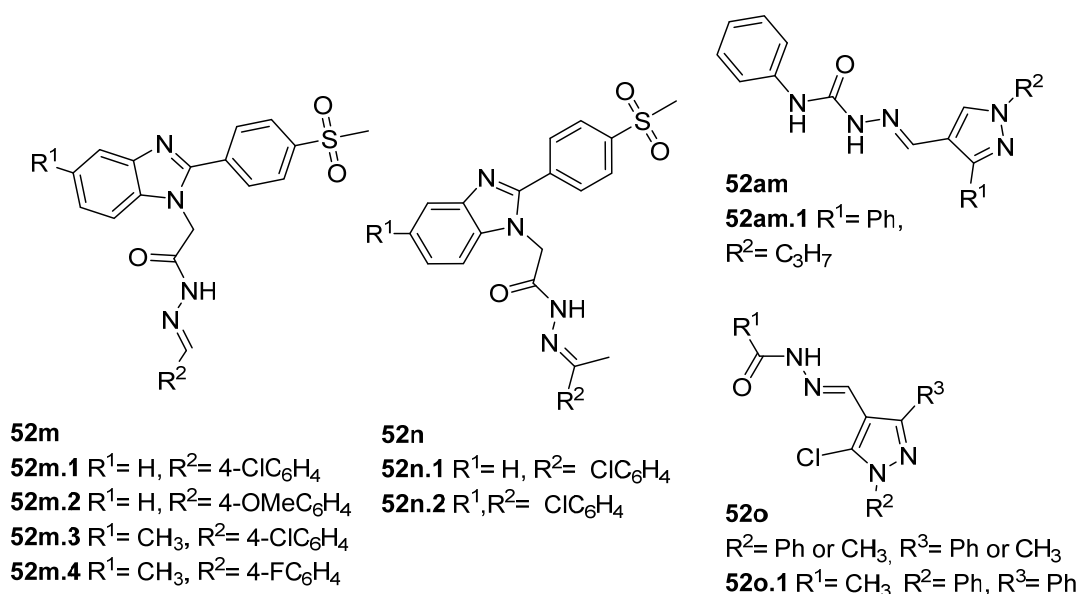


Figure 12. Hydrazide–hydrazones with anti-inflammatory activity.

Duong et al. [43] obtained the compounds **52p** (Figure 13) by reacting atranorin (natural product) with several hydrazides. The compounds were tested for the inhibition of α -glucosidase. Compounds **52p1–12** exhibited stronger activities than the natural product and acarbose, with IC_{50} values ranging from 6.67 to 54.7 μM . Compound **52p.1** exhibited the best activity, with $\text{IC}_{50} = 6.67 \mu\text{M}$. Additionally, the cytotoxicity of these compounds against the normal cell line HEK293 was evaluated, and they exhibited weak to no cytotoxicity [43].

New flavone derivatives **52ag** and indolone derivatives **52ah** also exhibited inhibitory activity against α -glucosidase (Figure 13). Compounds **52ag.1** ($\text{IC}_{50} = 1.02 \mu\text{M}$), **52ah.1** ($\text{IC}_{50} = 14.8 \mu\text{g/mL}$), and **52ah.2** ($\text{IC}_{50} = 14.5 \mu\text{g/mL}$) showed higher activity than the standard drug acarbose [54,121].

Additionally, Abbasi et al. [121] reported compounds **52ah** as inhibitors of the α -amylase enzyme. Compounds **52ah.1** and **52ah.2** were the most potent against the α -amylase enzyme with $\text{IC}_{50} = 19.6$ and $18.3 \mu\text{g/mL}$, respectively.

In addition, acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) are other critical enzymes in health care, and their inhibitors are used in the clinical management of Alzheimer's disease. AChE inhibitors include galantamine, donepezil, rivastigmine, and tacrine; however, these drugs have numerous side effects. So, Güngör [122] reported the synthesis of eleven new derivatives **52ai** (Figure 13) as potential inhibitors of AChE enzymes. Among these, compound **52ai.1** showed the best inhibitory activity with $\text{IC}_{50} = 2.01 \mu\text{M}$ against AChE, comparable to the control Galantamine ($\text{IC}_{50} = 2.60 \mu\text{M}$). In addition, compound **52ai.2** showed the best inhibitory effect with $\text{IC}_{50} = 2.83 \mu\text{M}$ against BChE, which was lower than the IC_{50} of control galantamine ($\text{IC}_{50} = 3.70 \mu\text{M}$) [122].

Hydrazides with aryl-substituted groups have also been used to obtain hydrazide–hydrazones with aggregation-induced emission (AIE) properties. Patil et al. [55] reported novel hydrazide–hydrazone **52q** with remarkable AIE properties. The study showed that compounds **52q.1** and **52q.2** behaved as aggregate-induced emission luminogens to illuminate and record images of subcellular organelles and targets in cancer cells (Figure 14) [55]. Moreover, the internalization of these compounds into the HeLa cervical cancer cells without showing any cytotoxicity was observed. On the other hand, Wu et al. [56] reported that

compound **52q.3** (the *E* isomer) exhibited photoisomerization to the *Z* isomer after light irradiation at 365 nm (Figure 14).

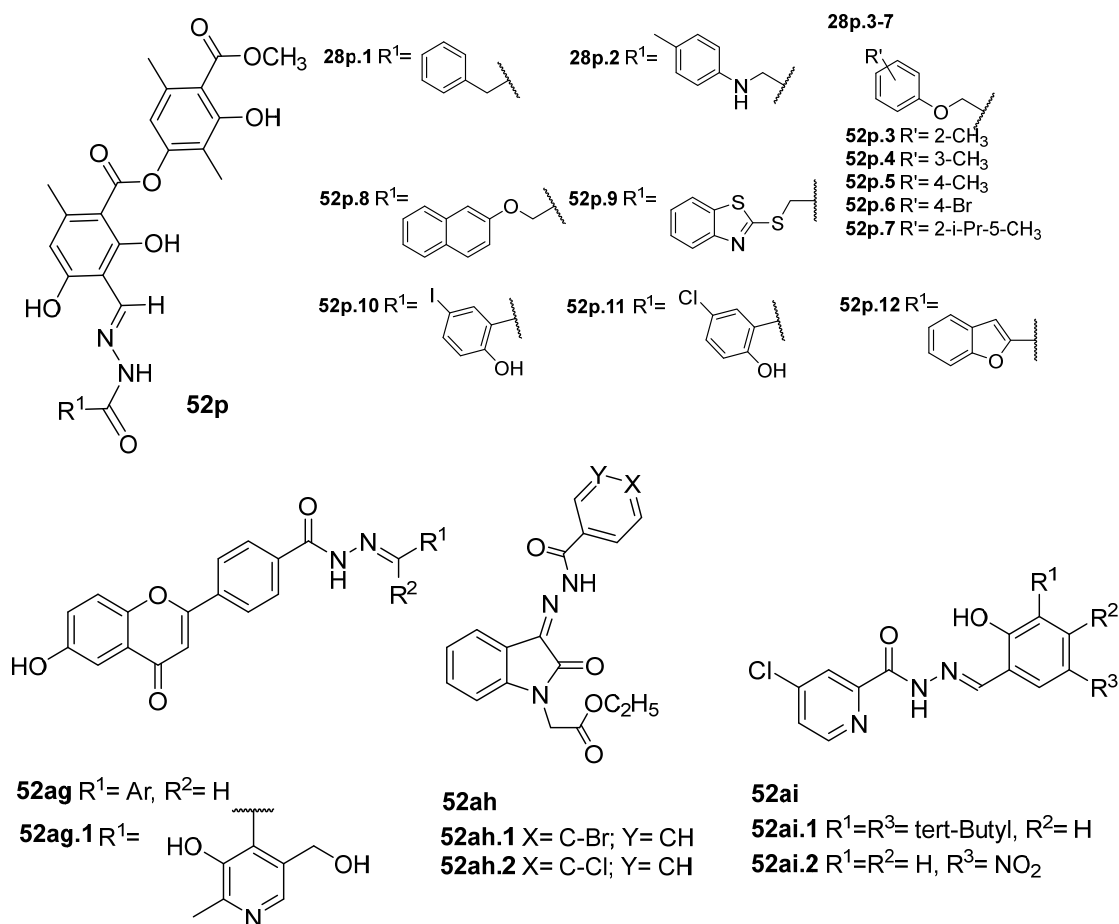


Figure 13. α -glucosidase, α -amylase, acetylcholinesterase, and butyrylcholinesterase inhibitors.

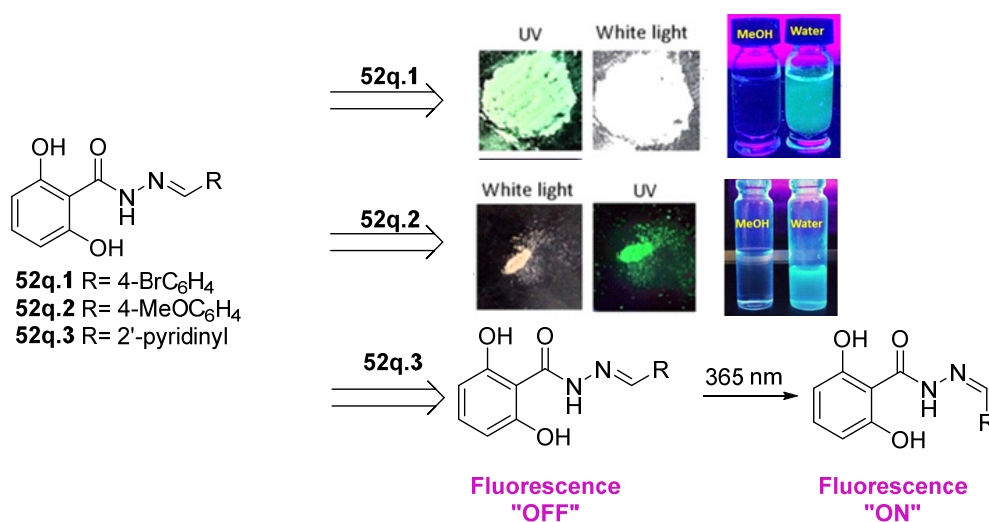


Figure 14. Hydrazone-hydrazones with aggregate-induced emission properties. Adapted with permission from Ref. [55] Copyright 2019 John Wiley & Sons, Inc., and Ref. [56] Copyright 2021 Royal Society of Chemistry.

Recently, the research of Fan et al. [13] highlighted a new fluorescent probe **52y** (Figure 15) capable of self-assembling into nanospheres in aqueous solution, and then,

when placed in the presence of human serum albumin (HSA), they disassemble and display an evident fluorescence signal.

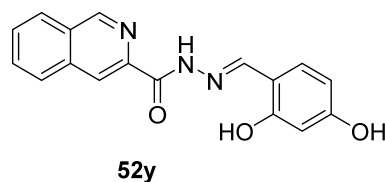


Figure 15. Hydrazone–hydrazone as potential probes.

Compounds **52aj**, **52ak**, and **52al** (Figure 16) were tested as potential antioxidants [78,79,123]. Among the twelve derivatives **52aj** tested in vitro, compound **52aj.1** showed the best activity according to the DPPH method ($SC_{50} = 0.03$ mg/mL) [123]. However, compound **52ak** showed antioxidant activity in vivo in rats according to Abdelhamid et al. [78]. Amongst the quinoline hydrazone–hydrazone derivatives synthesized by Cahyana et al. [79], compound **52al** showed the best antioxidant activity by DPPH assay with $IC_{50} = 843.52$ ppm, yet this was weak compared to ascorbic acid with $IC_{50} = 11$ ppm.

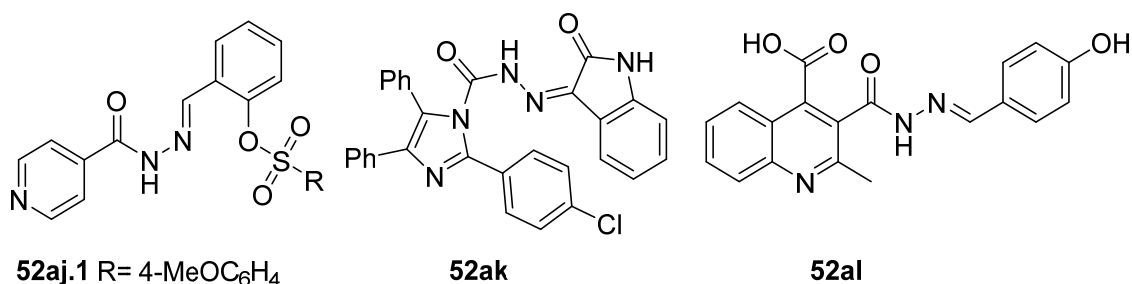


Figure 16. Hydrazone–hydrazone with antioxidant activity.

Apart from their biological importance, hydrazone–hydrazone compounds are occasionally mentioned in the following points as useful intermediate synthons for the synthesis of some heterocyclic rings [40,47].

3.2. Heterocycles from Hydrazides

Hydrazides are widely used as synthons in the synthesis of a variety of heterocycles via electrophilic reactions. After the cyclization process, the different heterocycles can also be further modified or not to obtain compounds with biological activity. Within the heterocycles generated from hydrazides, it has become possible to identify the synthesis of pyrrolones, pyrazoles, oxadiazoles, thiadiazoles, triazoles, and triazepinones in the recent literature, which will be discussed in the following sections. The biological activity of the synthesized compounds will also be presented.

3.2.1. Pyrrolones

Synthesis of Pyrrolones

Pyrrolones are five-membered heterocyclic lactams recognized as important scaffolds whose origin may be natural or synthetic, with a wide variety of pharmacological activities [133,134]. These compounds can present anticancer [27,135–137], antimalarial [138], anti-inflammatory [139], antiviral [28], and antioxidant activities [140]. In 2015, Pelkey et al. [141] reported different methods, including one-component intramolecular or two-component intermolecular cyclization approaches for pyrrolone synthesis that were reported through the end of 2014.

According to the literature mentioned in Table 4, from 2019 to 2024, [27,28,101,137,140], pyrrolones **53** and **54** can be formed from the reaction of hydrazides (compounds **8aax** or **8aba**) and electrophiles (e.g., acyl chlorides or aldehydes) (Scheme 12) [27,28,101,137,140]. The reactions with acyl chlorides occurred under reflux [27,28,140] or at room temperature [28,137], and in some cases, a base [28] was used. When the reaction occurred with aldehydes [28,101,140], the reactions were performed via the catalysis of acetic acid, in ethanol, under reflux conditions. The products were generally obtained in good yields.

Table 4. Reaction conditions for the synthesis and purification of pyrrolones from hydrazides.

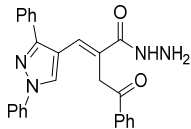
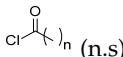
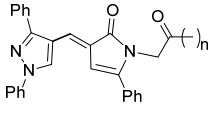
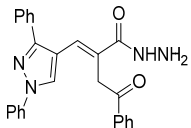
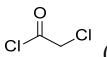
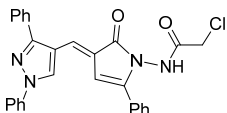
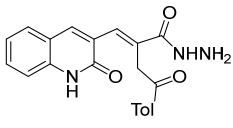
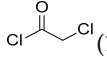
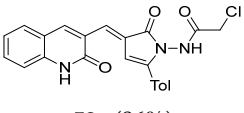
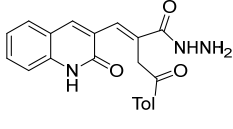
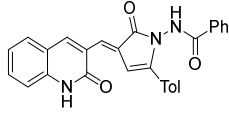
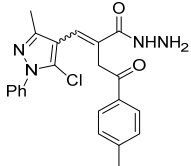
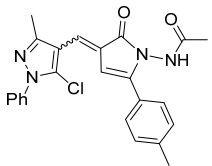
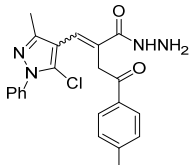
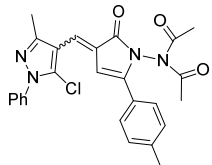
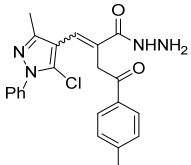
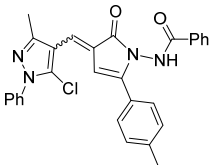
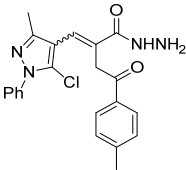
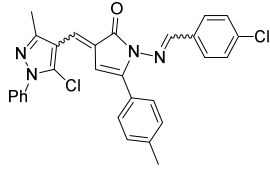
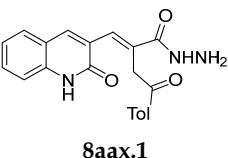
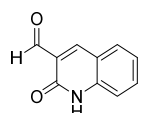
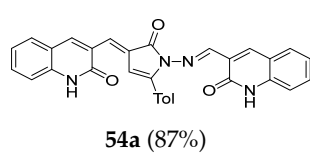
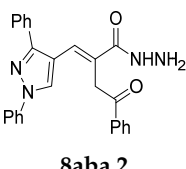
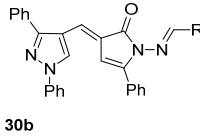
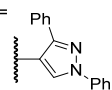
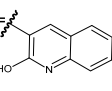
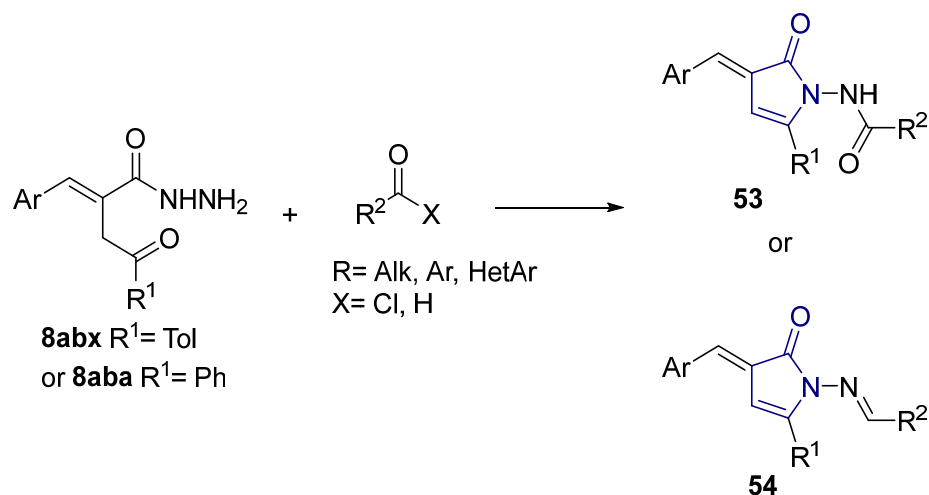
Ref.	Hydrazide	Experimental Conditions	Purification Process	Final Compounds (η %)
[27]	 8aba.2	 (n.s) Benzene, reflux	n.s.	 $n = 11$ 53a (78%)
[137]	 8aba.2	 (1 eq, dropwise) DMF, r.t., 4 h	Recrystallization from ethanol	 53b (78%)
[28]	 8aax.1	 (1 eq) Et ₃ N, dioxane, r.t., 1 h	Recrystallization from ethanol	 53c (86%)
[28]	 8aax.1	PhCOCl (1 eq) Benzene, reflux, 1 h	Recrystallization from ethanol	 53d (68%)
[140]	 8aax.2	CH ₃ COOCOCH ₃ (10.5 eq), r.t., 1 h	Recrystallization from benzene	 53e (65%)
[140]	 8aax.2	CH ₃ COOCOCH ₃ (10.5 eq), reflux, 4 h	Recrystallization from petroleum ether (60–80)	 53f (60%)
[140]	 8aax.2	PhCOCl, benzene, reflux, 3 h	Recrystallization from benzene	 53g (60%)

Table 4. Cont.

Ref.	Hydrazide	Experimental Conditions	Purification Process	Final Compounds ($\eta\%$)
[140]	 8aax.2	RCHO (1 eq), EtOH, CH ₃ COOH, reflux, 3 h	Recrystallization from dioxane	 54c (80%)
[28]	 8aax.1	 (1 eq), CH ₃ COOH, ethanol, reflux, 1 h	Recrystallization from ethanol/dioxane mixture (1:1)	 54a (87%)
[101]	 8aba.2	RCHO (1 eq) EtOH, CH ₃ COOH (cat.), reflux, 1 h	Recrystallization from ethanol/dioxane mixture	 30b 30b.1 R=  30b.2 R=  30b.3 R=  54b (80–84%)

n.s.—not specified by the authors.



Scheme 12. Representative scheme of pyrrolone synthesis from hydrazides.

Biological Activity of Pyrrolone Derivatives

The pyrrolone derivative **53a** exhibited great in vitro anticancer activity against HCT-116 and MCF-7 cell lines, with IC₅₀ = 7.49 and 8.51 μM [27], respectively (Figure 17). Also, compound **53b** showed IC₅₀ = 46.3 $\mu\text{g/mL}$ against HePG2 cell lines [137].

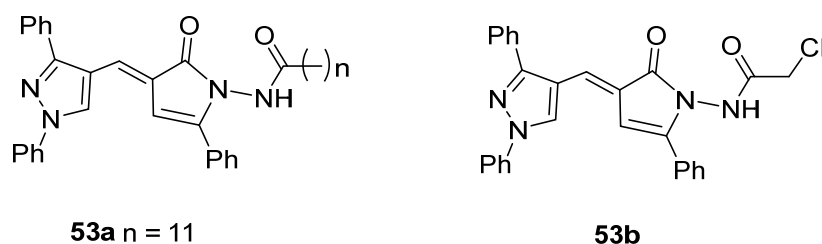


Figure 17. Pyrrolones with anticancer activity.

Compounds **53c** and **53d**, reported by El-Helw et al. [28], showed a high percentage of protection against the pathogenic avian influenza virus (H5N8) [28], higher than 80% of immunomodulators. Morsy et al. [101] reported on compounds **54b.2** and **54b.3**, which exhibited antiviral activity with 100% protection against Newcastle disease virus (Figure 18).

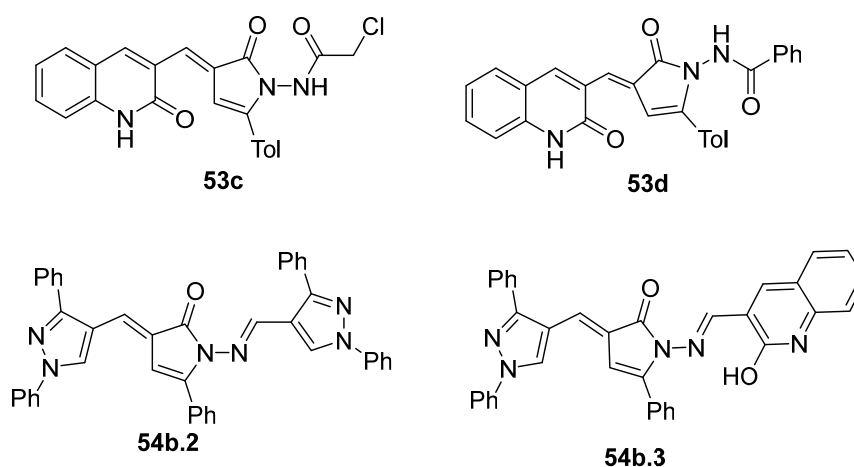


Figure 18. Pyrrolones with antiviral activity.

Moreover, Youssef et al. [140] used the phosphomolybdenum method to determine the antioxidant capacity of compounds **53e–g** and **54c** (Figure 19). The compounds showed good to moderate antioxidant capacity, presenting 163.0 to 262.27 mg of acid ascorbic equivalents per gram (AEE/g) of dry compound.

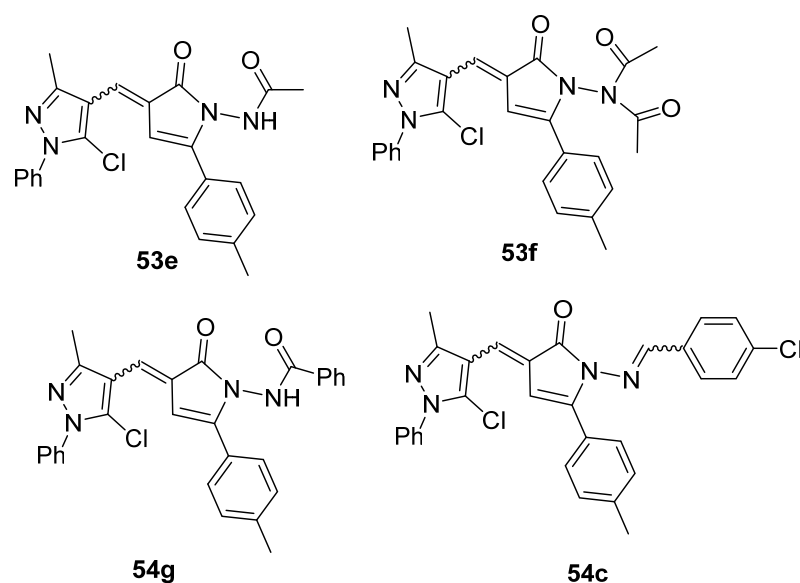


Figure 19. Pyrrolones with antioxidant activity.

3.2.2. Pyrazoles

Synthesis of Pyrazoles

Pyrazole derivatives are five-membered *N*-heterocycle compounds with two adjacent nitrogen atoms (1,2-positions) [29]. Unsubstituted pyrazole is a planar structure with three possible tautomeric forms (55-A, 55-B, and 55-C), as represented in Figure 20. However, it can also exist as a dimer (55-D), in concentrated solution, via hydrogen bonding [142].

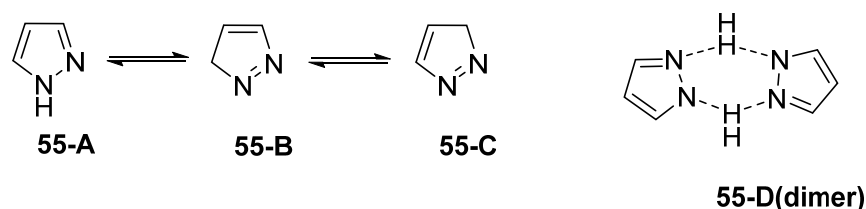


Figure 20. Tautomeric structures and dimer of pyrazole.

In the azole family, pyrazole derivatives are one of the most studied compounds, with a wide range of chemical and biological properties [29,143,144]. In clinical use, rimonabant, sildenafil, fomepizole, celecoxib, and ruxolitinib are some of the pyrazole-based drugs [142]. In the literature, pyrazoles have been described as antimicrobial [128,145,146], anti-inflammatory [147,148], and anticancer agents [149–151].

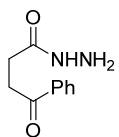
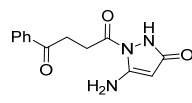
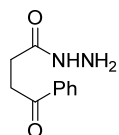
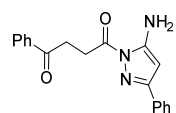
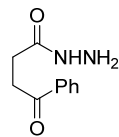
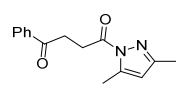
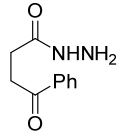
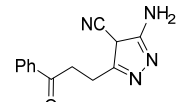
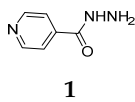
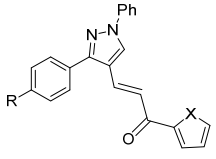
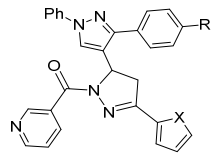
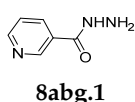
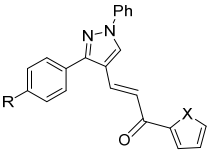
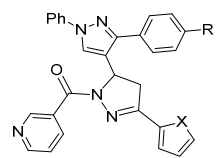
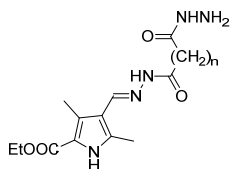
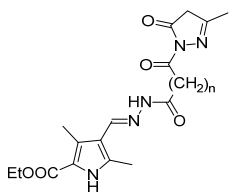
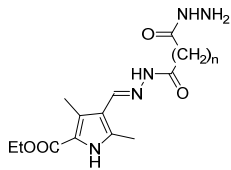
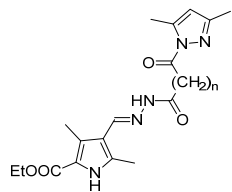
Hassani et al. [29] and Ríos et al. [143] compiled the works reporting the synthesis of pyrazole derivatives between 2013 and 2023 and between 2017 and 2022, respectively. Pyrazoles were obtained from the reaction between hydrazine and a carbon unit, such as 1,3-dicarbonyl, α,β -unsaturated carbonyl compounds, acetylenic ketones, or β -enaminones or similar compounds.

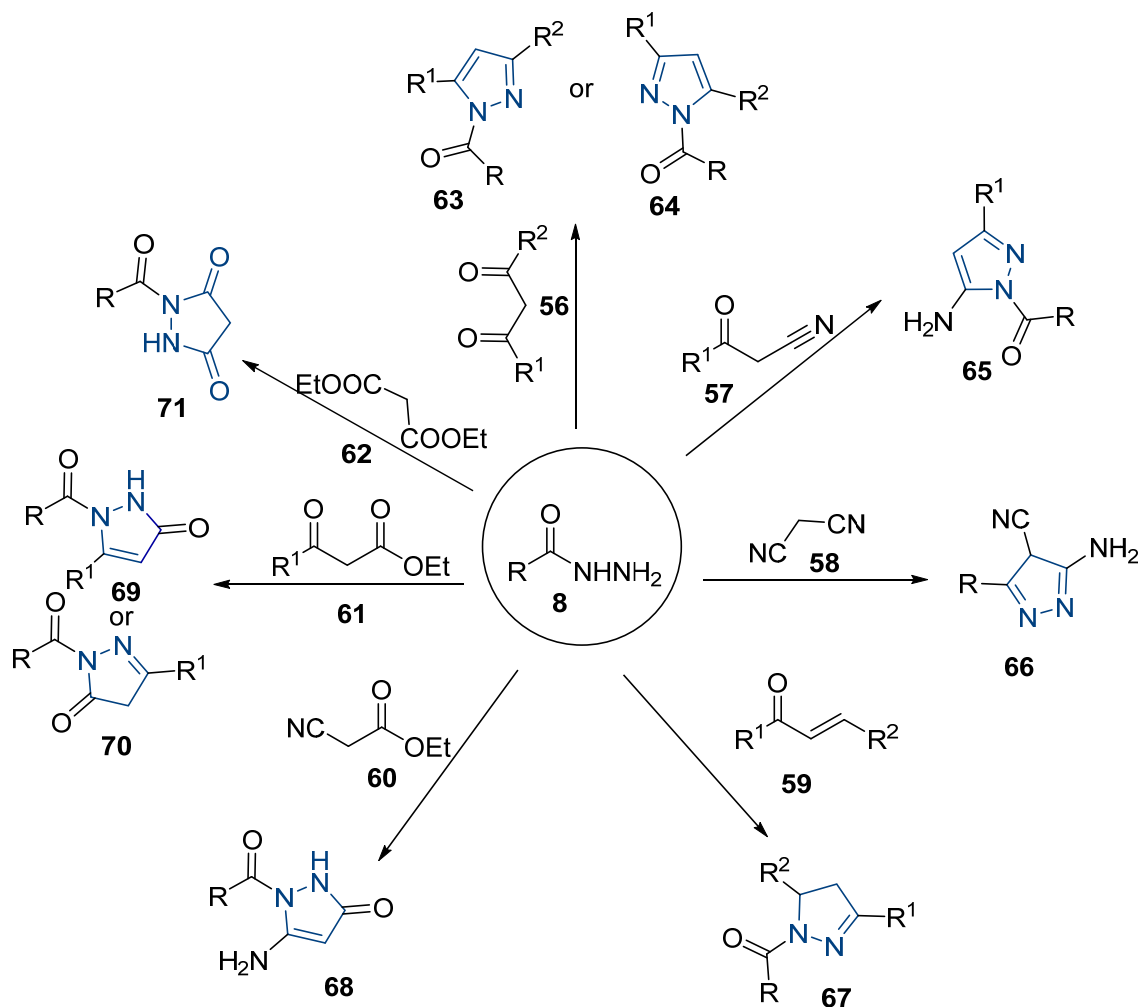
Although pyrazoles are usually obtained from hydrazine, in this review, we present hydrazides as precursors of pyrazoles, dihydropyrazoles, or pyrazolidine-diones (Table 5). The synthesis of these compounds occurred between hydrazides 8 and several carbonyl/nitrile compounds as represented in Scheme 13. Pyrazoles 63 to 66 were obtained in ethanol, under reflux, in the presence or not of an organic base [80,146]. Dihydropyrazoles 67–70 [80,128,146] or pyrazolidine-diones 71 [80] were generated from hydrazides and carbonyl/nitrile compounds in the presence of a strong inorganic base, in ethanol or DMF, at room temperature or under reflux. The products were usually obtained with good yields [80].

Table 5. Reaction conditions for the synthesis and purification of pyrazoles, dihydropyrazoles, and pyrazolidine-dione from hydrazides.

Ref.	Starting Material	Experimental Conditions	Purification Process	Pyrazole Compounds (η %)
[80]	 8ac	$\text{CH}_2(\text{COOC}_2\text{H}_5)_2$ $\text{C}_2\text{H}_5\text{ONa}/\text{EtOH}$ Reflux, 14–17 h	Recrystallization from dioxane	 71a (90%)
[80]	 8ac	$\text{CH}_3\text{COCH}_2\text{COOC}_2\text{H}_5$ DMF K_2CO_3 Reflux, 12–15 h	Recrystallization from methanol	 69a (85%)

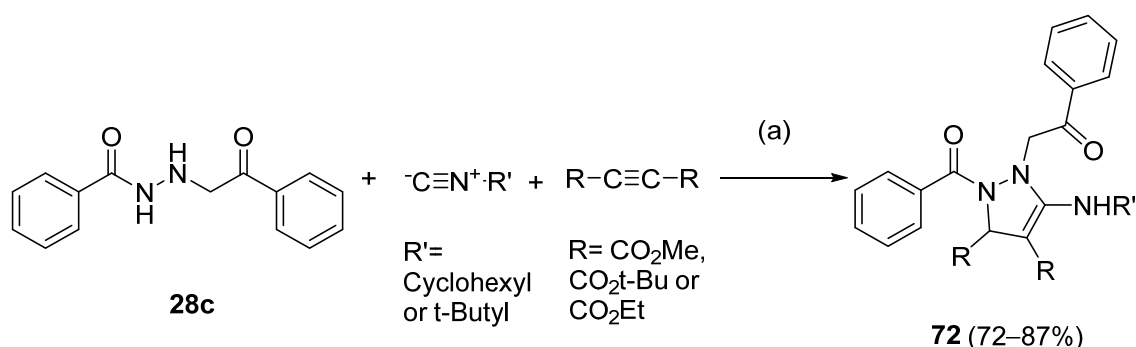
Table 5. Cont.

Ref.	Starting Material	Experimental Conditions	Purification Process	Pyrazole Compounds (η %)
[80]	 8ac	CNCH ₂ COOEt DMF K ₂ CO ₃ Reflux, 14–17 h	Recrystallization from methanol	 68a (77%)
[80]	 8ac	CNCH ₂ COPh EtOH Reflux, 6–9 h	Recrystallization from dioxane	 65a (72%)
[80]	 8ac	CH ₃ COCH ₂ COCH ₃ EtOH Piperidine (cat.) Reflux, 10–15 h	Recrystallization from methanol	 64a (95%)
[80]	 8ac	CNCH ₂ CN EtOH Piperidine (cat.) Reflux, 20–25 h	Recrystallization from DMF	 66a (70%)
[128]	 1	 NaOH/EtOH r.t. 8–9 min	Recrystallization from methanol	 67a (82–88%)
[128]	 8abg.1	 NaOH/EtOH r.t. 8–9 min	Recrystallization from methanol	 67b (82–87%)
[146]	 8abk	CH ₃ COCH ₂ COOC ₂ H ₅ DMF/EtOH CH ₃ COOH Reflux, 5 h	Column chromatography	 70a (62–67%)
[146]	 8abk	CH ₃ COCH ₂ COCH ₃ DMF/EtOH CH ₃ COOH Reflux 8 h	Column chromatography	 64b (61–72%)



Scheme 13. Representative scheme of pyrazoles, dihydropyrazoles, and pyrazolidine-dione synthesis from hydrazides.

Also, recently, Ardakani et al. [145] reported the synthesis of dihydropyrazole **72** by the reaction of substituted hydrazide **28c** with alkyl isocyanides and dialkyl acetylenedicarboxylates at room temperature, in 72–84% yields (Scheme 14).



Scheme 14. Synthesis of dihydropyrazole derivatives **48**: (a) acetone, -5°C , 10 min, r.t., 24 h.

Biological Activity of Dihydropyrazole and Pyrazole Derivatives

Compounds **67a,b** (Figure 21) were screened for their in vitro antibacterial and antifungal activities. Compound **67a.2**, with an MIC = 100 $\mu\text{g/mL}$ against Gram-positive *B. subtilis* and a stronger MIC = 50 $\mu\text{g/mL}$ against *C. tetani*, was equipotent or more potent than the reference drugs ampicillin (MIC 250 $\mu\text{g/mL}$) and ciprofloxacin (MIC 100 $\mu\text{g/mL}$).

Compound **67a.4** was more potent than ampicillin against *S. aureus* (MIC 62.5 µg/mL). In general, compounds **67a**, with isoniazid moieties, were more effective against all microorganisms than those with nicotinic hydrazide derivatives **67b** (Figure 21) [128].

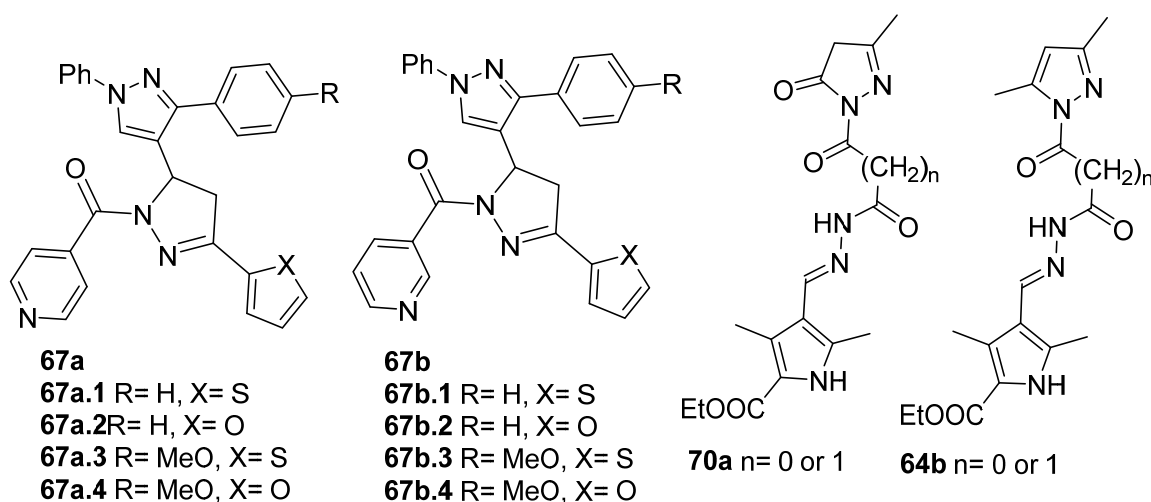


Figure 21. Pyrazole derivatives with antibacterial, antifungal, or anticancer activities.

Compounds **70a** and **64b** (Figure 21) demonstrated effective antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *E. coli*, and *Pseudomonas aeruginosa*, with MIC values ranging from 8 to 16 µg/mL, and good cytotoxicity in vitro against two human cancer cells, HCT-116 (colon) and HL-60 (leukemia), though it was less than the standard 5-fluorouracil [146].

3.2.3. Oxadiazoles

Synthesis of Oxadiazole Derivatives

Oxadiazoles are one of the most valuable five-membered heterocycles, holding one oxygen and two nitrogen atoms, with an extensive spectrum of applications [31]. From the oxadiazole isomers of 1,2,3-oxadiazole **73**, 1,2,4-oxadiazole **74**, 1,2,5-oxadiazole **75**, and 1,3,4-oxadiazole **76**, presented in Figure 22, 1,3,4-oxadiazole **76** stands among the most studied and used, due to its broad activity spectrum [152,153]. This isomer appears in some available drugs, such as Zibotentan, Furamizole, Raltegravir, and Nesapidil [83], but recently, new derivatives have been shown to have biological activities, including anticancer [82], antibacterial, antifungal [154], antimalarial [2], antileishmanial [40], antitubercular [81], antiviral [28], anti-inflammatory [41,85], antioxidant [105], and insecticidal activities [103].

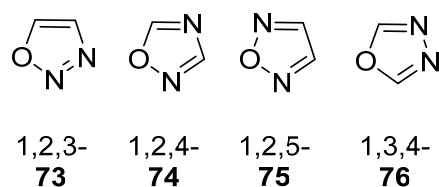


Figure 22. Structures of oxadiazole isomers.

Sharma et al. [31] collected and discussed the synthesis of 1,3,4-oxadiazoles in the past 15 years. The authors discussed dehydrogenative cyclization of 1,2-diacylhydrazines with phosphorus oxychloride (POCl₃), phosphoric acid (H₃PO₄), and thionyl chloride (SOCl₂); oxidative cyclization of hydrazide–hydrazones; and decarboxylative cyclization.

Here, we report the use of hydrazides in the synthesis of 1,3,4-oxadiazoles. According to Table 6, 1,3,4-oxadiazoles can be synthesized from the reaction between a hydrazide and carbon electrophilic reagents such as aldehydes, oxalyl chlorides, carboxylic acids, or carbon disulfide, as represented in Scheme 15. Some 2,3-dihydro-1,3,4-oxadiazol-2-yl derivatives **78** have been synthesized from hydrazides **8**, with hydrazide–hydrazones **52** as intermediates [40,82,154]. This method starts with the reaction of hydrazide and an aldehyde, and then the reaction follows in the presence of acetic anhydride under reflux. The oxadiazoles **78** obtained by this method were generally obtained in low to excellent yields. On the other hand, Paidi et al. [153] reported the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles **77** via one-pot NaOCl-mediated oxidative cyclization from hydrazide–hydrazones **52**, generated in situ from hydrazides **8** and aldehydes (Scheme 15). The best conditions reported by Paidi et al. [153] included hydrazide **8** in the presence of aldehydes and *t*-BuOH, under reflux, followed by a reaction with 10–12% aqueous NaOCl at room temperature. These reaction conditions were applied to hydrazides and aldehydes with both electron-donating and electron-withdrawing groups, and the desired products **77** were obtained in moderate to excellent yields. Compounds **77** were also generated directly from **8** by reaction with acetic anhydride [80].

Table 6. Reaction conditions for the synthesis and purification of 1,3,4-oxadiazoles and their derivatives.

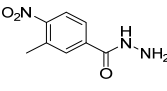
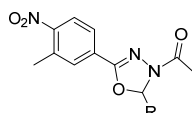
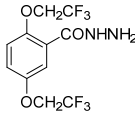
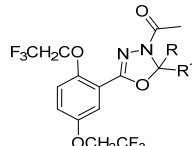
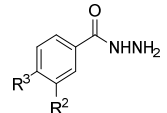
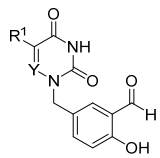
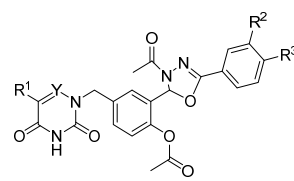
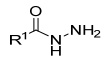
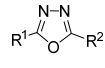
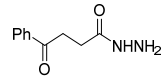
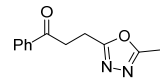
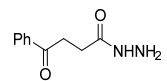
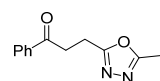
Ref.	Starting Material	Experimental Conditions	Purification Process	Oxadiazole Compounds (n%)
[154]	 8ab1	1. RCHO EtOH, reflux, 3 h 2. Ac ₂ O (32 eq), reflux, 3 h	Recrystallization from ethanol/acetone (3:1 v/v) mixture	 78a R = Ar (22–76%)
[82]	 8ax	1. RCOR ¹ 70 °C, 2 h 2. Ac ₂ O (10.5 eq), reflux, 8 h	Recrystallization from ethanol	 78b R = Ar, R ¹ = H, CH ₃ (n.s.)
[40]	 8o R ² = H, R ³ = H 8p R ² = Cl, R ³ = H 8q R ² = H, R ³ = Cl	 1. EtOH, CH ₃ COOH (cat.) 80 °C, 3 h 2. Ac ₂ O (10.5 eq), 155 °C, 90 min	Flash chromatography	 78c R ¹ = CH ₃ , H, F; Y = CH, N; R ² and R ³ = H, Cl (40–71%)
[153]	 8 R ¹ = Alk, Ar	1. R ² CHO, <i>t</i> -BuOH, reflux, 2–3 h 2. NaOCl, r.t., 1–2 h	Column chromatography	 77 R ¹ = Alk, Ar; R ² = Alk, Ar (50–93%)
[80]	 8ac	Ac ₂ O, 10–15 min, EtONa, 6–8 h;	Recrystallization from ethanol	 77a (88%)
[80]	 8ac	Ac ₂ O, reflux, 25–30 h	Recrystallization from methanol	 77b

Table 6. Cont.

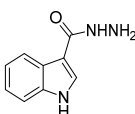
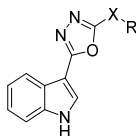
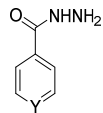
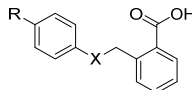
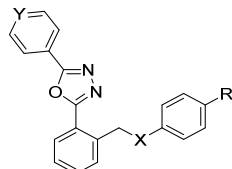
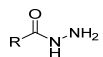
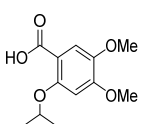
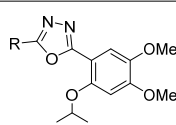
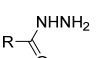
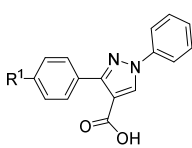
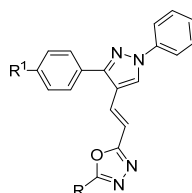
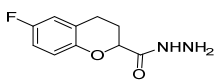
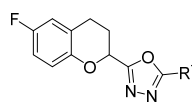
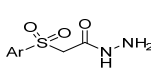
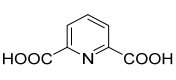
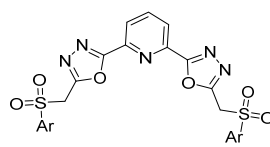
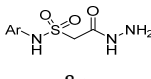
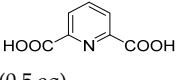
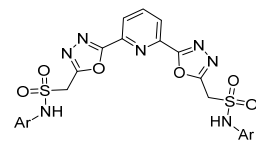
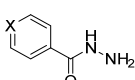
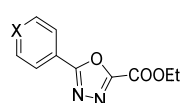
Ref.	Starting Material	Experimental Conditions	Purification Process	Oxadiazole Compounds (n%)
[84]	 8aab	R-X-CO ₂ H (1 eq) POCl ₃ (5 eq), 50 °C, 4 h X-R = CH ₂ O-Ar, CH ₂ -Ar or Ar	Recrystallization from ethanol	 77c X-R = CH ₂ O-Ar, CH ₂ -Ar or Ar (46–66%)
[152]	 1 Y = N or 8o Y = CH	 (1 eq) POCl ₃ (48 eq), reflux, 9 h	Recrystallization from an appropriate solvent	 77d X = S, SO ₂ ; R = H, CH ₃ , Cl; Y = N, CH (59–70%)
[83]	 8o R = C ₆ H ₅ 8ay R = 4-F-C ₆ H ₄ 8az R = 4-CH ₃ -C ₆ H ₄ 8aaa R = 2-Cl,4-Cl-C ₆ H ₃	 (1 eq), POCl ₃ (n.s.), reflux 6–7 h	Recrystallization from isopropanol	 77e R = Ar (80–88%) 77e.1 R = C ₆ H ₅ 77e.2 R = 4-F-C ₆ H ₄ 77e.3 R = 4-CH ₃ -C ₆ H ₄ 77e.4 R = 2-Cl,4-Cl-C ₆ H ₃
[2]	 R = Aryl, HetAr 8	 R ¹ = H, CH ₃ , F (1 eq), POCl ₃ (53 eq) 60–70 °C	Recrystallization from methanol	 77f R = Aryl, HetAr; R ¹ = H, CH ₃ , F (80–89%)
[59]	 8u	R ¹ CO ₂ H (1 eq), POCl ₃ (6.7 eq), reflux, 6–8 h	Recrystallization from methanol	 77g R ¹ = Ar (78–90%)
[105]	 8v	 (0.5 eq) POCl ₃ ultrasonication (35 kHz) 35–60 min	Recrystallization from 2-propanol	 77h (80–92%)
[105]	 8w	 (0.5 eq) POCl ₃ (53 eq) ultrasonication (35 kHz) 35–50 min	Recrystallization from 2-propanol	 77i (87–91%)
[81]	 1 X = N or 8o X = CH	1. CH ₂ Cl ₂ , 0 °C ClCOCOOEt (1.1 eq) Et ₃ N r.t., 8 h 2. <i>p</i> -TosCl (1 eq) r.t., 4 h	Recrystallization from ethanol	 79a X = N or CH (87, 83%)

Table 6. Cont.

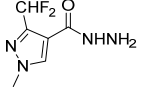
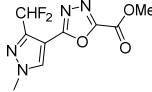
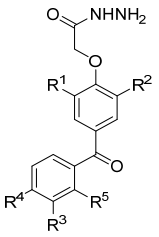
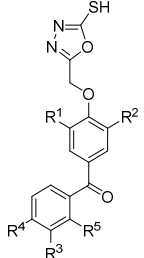
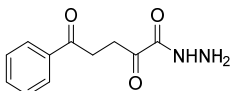
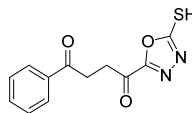
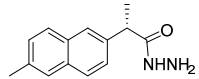
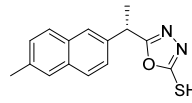
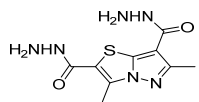
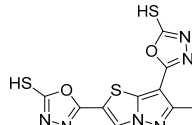
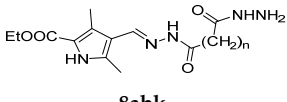
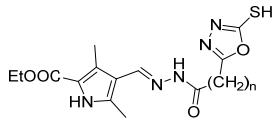
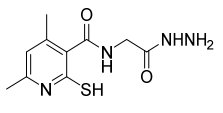
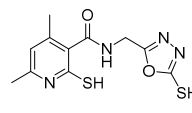
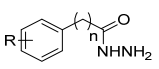
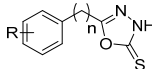
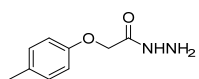
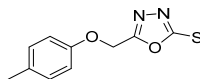
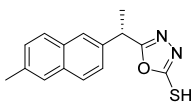
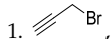
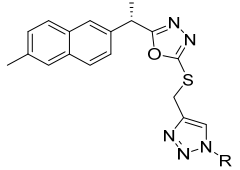
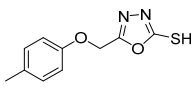
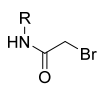
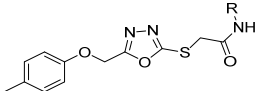
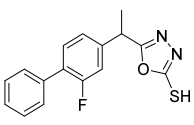
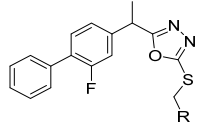
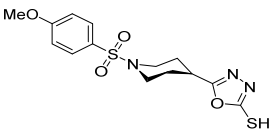
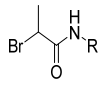
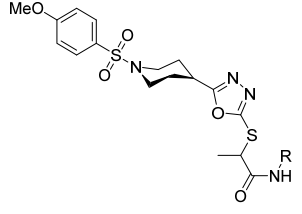
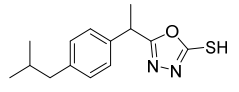
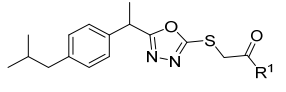
Ref.	Starting Material	Experimental Conditions	Purification Process	Oxadiazole Compounds (n%)
[39]	 8t	ClCOCOOCH ₃ (1.1 eq) POCl ₃ (10 eq), 85 °C 4–6 h	Recrystallization from ethanol	 79b (n.s.)
[86]	 8aaj	CS ₂ (17 eq) KOH (2 eq) EtOH, reflux, n.s. time HCl (pH ~3–4)	Recrystallization from acetone	 80a R ¹ = H, CH ₃ , F R ² = H, Cl R ³ = H, Cl R ⁴ = H, Cl, I R ⁵ = H, Cl (84% as an example)
[64]	 8ac	1. CS ₂ (5 eq) KOH (1.5 eq), reflux, 3 h 2. HCl (pH ~4)	Recrystallization from EtOH/DMF or EtOH	 80b (62%)
[36]	 8z	1. CS ₂ (n.s.) KOH (n.s.) EtOH, r.t., 24 h 2. 90–100 °C, 10 h	n.s.	 80c (n.s.)
[37]	 8v	CS ₂ (2.5 eq), KOH (2 eq) EtOH, reflux, 3 h 2. HCl	Recrystallization from ethanol/DMF	 80d (40%)
[146]	 8abk	KOH (2 eq), CS ₂ (2 eq) DMF, HCl (cat.), reflux, 30 min	Column chromatography	 80e (52–57%)
[63]	 8abm	1. CS ₂ (4 eq) KOH (2 eq) EtOH, reflux, 10 h 2. HCl	Recrystallization from ethanol	 80f (65%)
[41]	 8aa	1. CS ₂ (1.5 eq), KOH (1.5 eq), EtOH, r.t., 72 h 2. HCl	-	 80g (64–70%)
[85]	 8al	1. CS ₂ (2 eq), KOH (1 eq), EtOH, reflux, 4–5 h 2. HCl (pH ~5–6)	-	 80h (95%)

Table 6. Cont.

Ref.	Starting Material	Experimental Conditions	Purification Process	Oxadiazole Compounds (n%)
[36]	 80c	1.  , K_2CO_3 , acetone, 50–60 °C, 4 h 2. RN_3 , H_2O - t BuOH (1:1), $CuSO_4 \cdot 5H_2O$, $C_6H_7O_6 \cdot Na$, r.t., 4–12 h	-	 81d R = Ar (n.s.)
[85]	 80h	 KOH, EtOH, r.t., 4–5 h	-	 81e R = Alk, Ar (92–98%)
[61]	 80i	RCH_2Cl (1 eq), KOH (1 eq), H_2O , acetone	-	 81f R = Alk, Ar (67–76%)
[87]	 80j	 (1 eq) LiH, DMF, r.t. or with microwave irradiation	-	 81g R = Ar (84–96%)
[62]	 80k	 K_2CO_3 , EtOH, reflux, 5–6 h	-	 81h R^1 = Ar (58–79%)

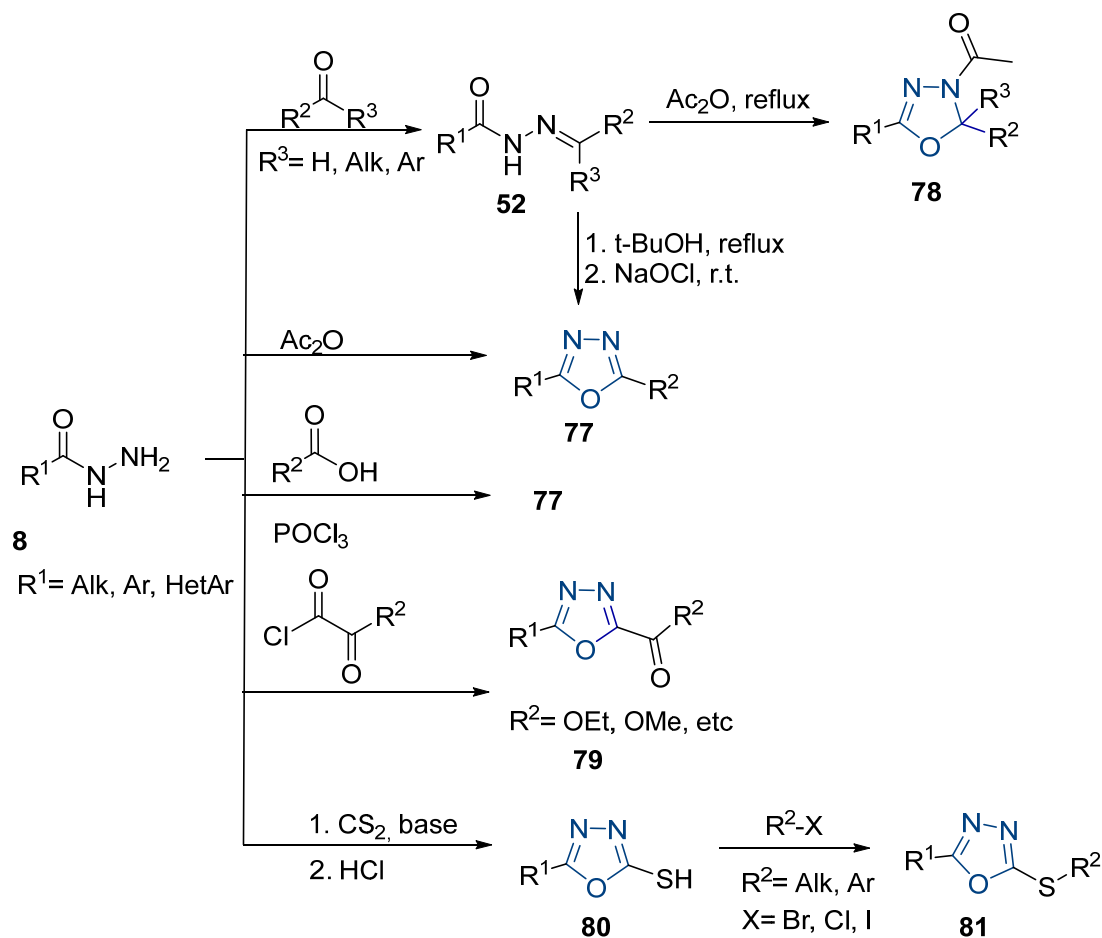
n.s.—not specified by the author.

The reaction of hydrazides with carboxylic acids is one of the most widely used processes to produce 2,5-substituted-1,3,4-oxadiazoles **77**. The reaction normally occurs in the presence of $POCl_3$ under high temperatures or reflux, yielding the products in reasonable to excellent yields [2,59,83,84,105,152].

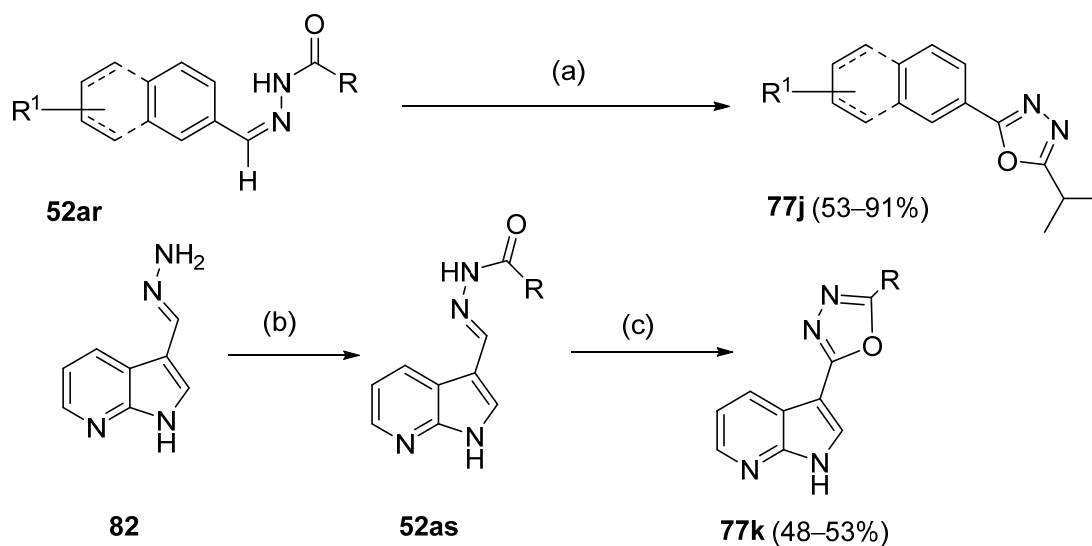
The reactions between hydrazides and oxalyl chlorides occur at room temperature in the presence of a base or at high temperatures in the presence of $POCl_3$ to produce compounds **79** [39].

Additionally, hydrazide derivatives **8** in the presence of carbon disulfide and a base (KOH, pyridine, or NaOH) are cyclized to produce different 1,3,4-oxadiazole-2-thiol derivatives **80** (Scheme 15) [28,36,37,41,61–64,86,87,103,146]. These reactions occurred generally under reflux, and the product **80** is isolated in good yield after neutralization of the reaction mixture with HCl (Table 6). Some of the compounds **80** were then alkylated with various alkyl/aryl halides to generate the new derivatives **81** (Table 6) [36,61,62,64,85–87].

On the other hand, 1,3,4-oxadiazoles **77** can also be obtained in reasonable to excellent yields by the iodine-mediated synthesis approach [155,156]. Chauhan et al. [155] reported the synthesis of oxadiazoles **77j** from **52ar** in the presence of isobutyraldehyde and *p*-anisoyl iodide under auto-oxidation conditions in the presence of molecular oxygen. The 2,5-disubstituted 1,3,4-oxadiazole **77k** was obtained from substituted carbohydrazides **52as** by the iodine-mediated synthesis approach represented in Scheme 16 [156].

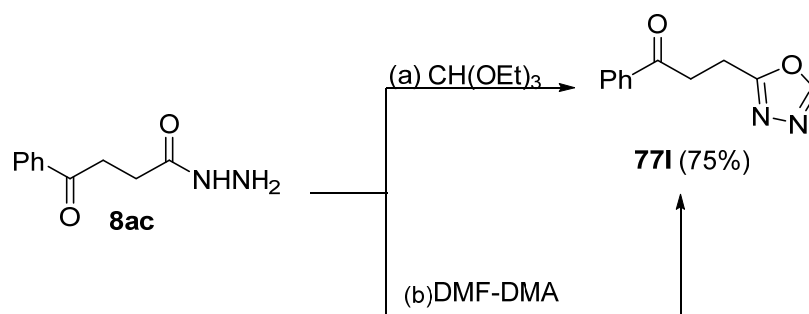


Scheme 15. Representative scheme of 1,3,4-oxadiazole synthesis from hydrazides.



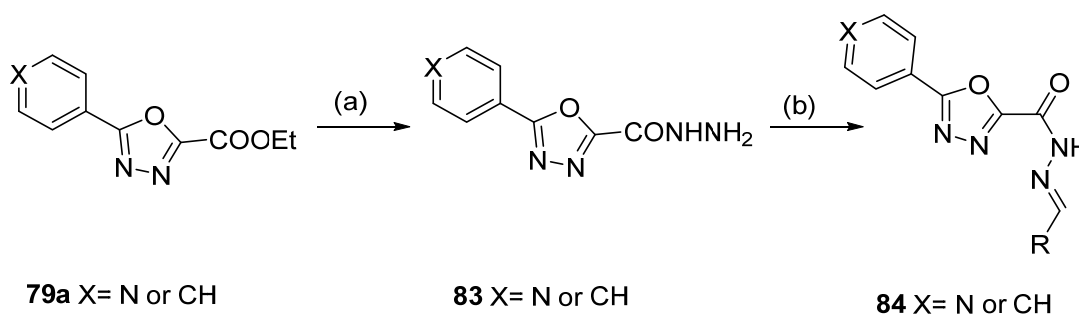
Scheme 16. Synthesis of oxadiazole derivatives: (a) Me₂CHCHO, p-anisolyliodide (0.1 eq), O₂, acetone, 35 °C, 6–8 h; (b) RCOCl, Et₃N, CH₃CN, r.t.; (c) DMSO, I₂, K₂CO₃, 110 °C, 24 h.

Moreover, Abu-Hashem et al. [80] reported the synthesis of 1,3,4-oxadiazoles **77i** (Scheme 17) starting from hydrazide **8ac** in the presence of triethyl orthoformate or dimethylformamide dimethyl acetal [80].



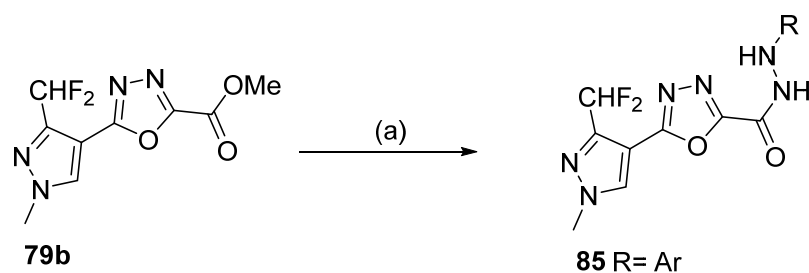
Scheme 17. Synthesis of 2-substituted 1,3,4-oxadiazole **77I**: (a) $\text{CH}(\text{OEt})_3$, reflux, 15–18 h; (b) DMF-DMA.

1,3,4-oxadiazoles **79a** were used to generate new derivatives **83** and **84**. Compounds **79a** reacted with hydrazine to generate the corresponding hydrazide **83**, which was converted to **84** by reaction with an aldehyde under acid catalysis [81] (Scheme 18).



Scheme 18. Synthesis of 2,5-disubstituted 1,3,4-oxadiazole derivatives: (a) H_2NNH_2 , EtOH, reflux; (b) RCOH (R = Ar, HetAr), EtOH, CH_3COOH (cat.), reflux.

Moreover, 1,3,4-oxadiazole derivatives **85** were obtained by reacting derivative **79b** with aryl hydrazines in an ionic liquid at 100 °C (Scheme 19) [39].



Scheme 19. Synthesis of 1,3,4-oxadiazole derivative **85**: (a) 1-butyl-3-methylimidazolium chloride, RNHNH_2 , Ar, 100 °C.

Biological Activity of Oxadiazole Derivatives

Hamdy et al. [84] reported the new series of 2-(1H-indol-3-yl)-5-substituted-1,3,4-oxadiazoles **77c** as inhibitors of the Bcl-2 anti-apoptotic gatekeeper protein. Compound **77c.1** (Figure 23) exhibited potent anticancer activity with $\text{IC}_{50} = 0.52$, 0.88, and 0.73 μM against MDA-MB-231, HeLa 2, and KG1a3 (Bcl-2-expressing) cell lines, respectively. Moreover, it showed no inhibitory effects in the Bcl-2-negative Jurkat cell line.

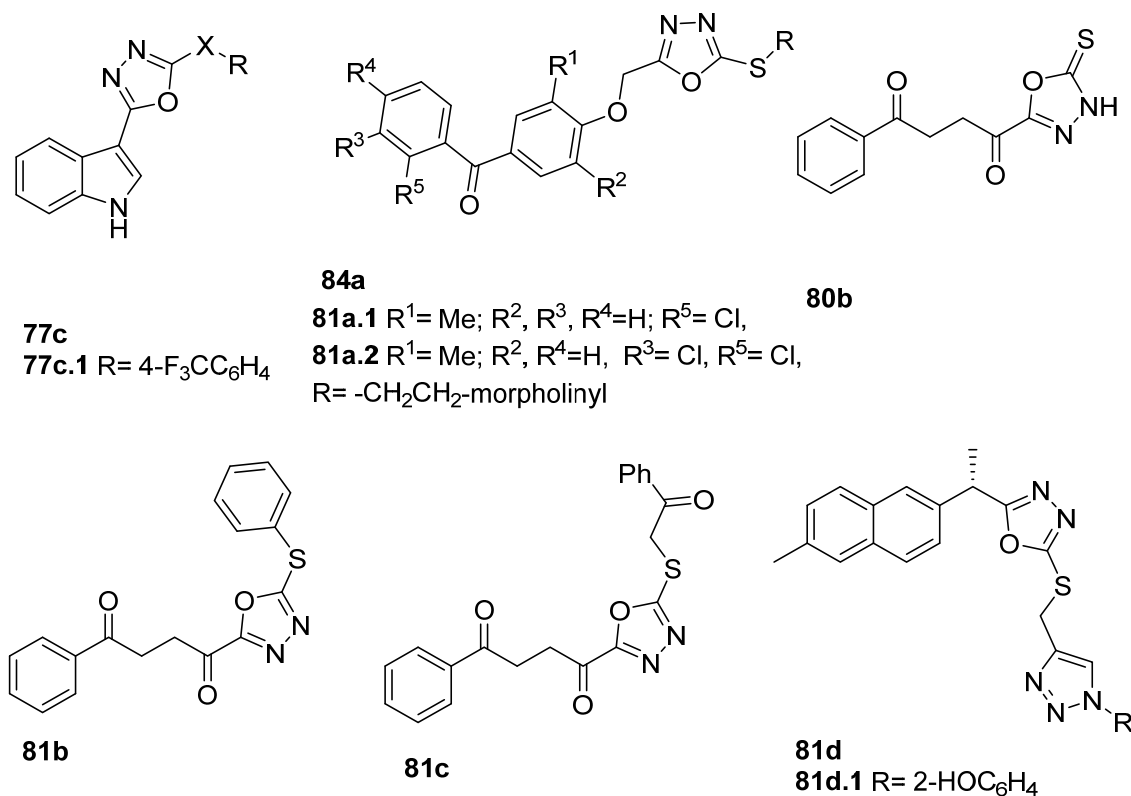


Figure 23. 1,3,4-oxadiazoles with anticancer activity.

Derivatives **81a.1** and **81a.2** (Figure 23) showed excellent activities against the MCF-7 cell line (breast cancer), with IC₅₀ = 127.0 and 126.7 µg/mL, respectively, and against KB (oral cancer) cell lines, with IC₅₀ = 113.8 and 112.6 µg/mL. Furthermore, these compounds revealed no toxicity against the normal cell line L929 at higher concentrations with IC₅₀ > 201 µg/mL [86].

Oxadiazole derivatives **80b**, **81b**, and **81c** (Figure 23) presented antiproliferative activities against MCF-7 breast cancer cells with IC₅₀ values between 8.2 and 8.8 µM, which were lower compared to doxorubicin (10.3 µM), and against hepatocellular HepG2 cells with IC₅₀ values between 26.9 and 29.8 µM, which were quite similar compared to doxorubicin (28.5 µM) [64].

Among the derivatives **81d**, oxadiazole **81d.1** showed the highest activity against MCF-7 and HepG2 cancer cell lines with IC₅₀ = 2.13 and 1.63 µg/mL, respectively. In addition, compound **81d.1** inhibited EGFR kinase with IC₅₀ = 0.41 µM [36].

Shankara et al. [82] evaluated the anticancer activity of compounds **78b** (Figure 24), and among them, compound **78b.1** was the most potent with an IC₅₀ = 8.14 µM against the LN229 Glioblastoma cell line. Also, derivative **80d** (Figure 24) showed good activities for HepG2 and HCT-116, with IC₅₀ = 6.9 and 13.6 µg/mL, respectively [37]. Rawat et al. [146] reported on compounds **80e.1** and **80e.2** (Figure 24), showing good cytotoxicity against HCT-116 and HL-60 (leukemia) cell lines, with the growth inhibition percentage being superior to 70% at 5 µg/mL, but less than the standard 5-fluorouracil (a growth inhibition percentage superior to 85% at the same concentration). Compounds **80e** also showed good antibacterial activity with MICs between 2 and 8 µg/mL against Gram-positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*) and Gram-negative bacteria (*E. coli*, *Pseudomonas aeruginosa*) [146].

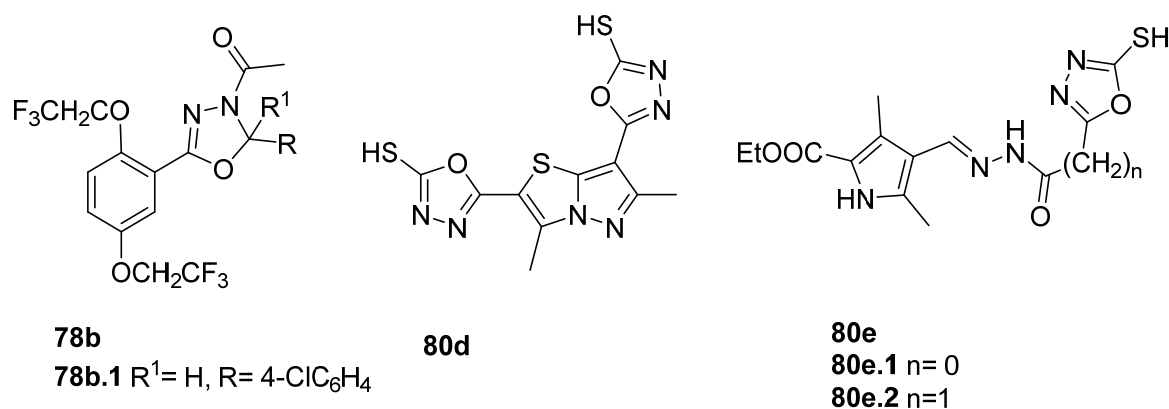


Figure 24. 1,3,4-oxadiazole-2-thiol derivatives with anticancer and/or antibacterial activities.

Compound **78a.1** (Figure 25) showed promising activity against *Staphylococcus epidermidis* with an MIC = 0.48 µg/mL, as well as low cytotoxicity against the L929 normal cell line [154].

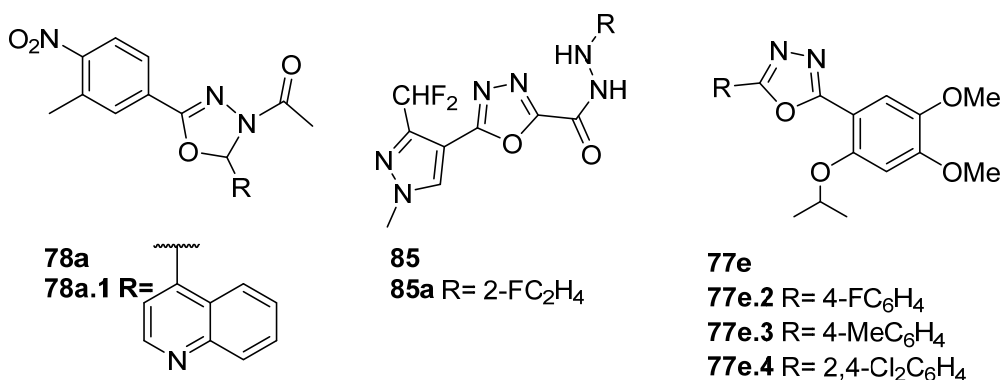


Figure 25. 1,3,4-oxadiazoles as antibacterial and antifungal agents.

Long et al. [39] designed, synthesized, and evaluated oxadiazole derivatives **85** (Figure 25) for their antifungal, antioomycete, and antibacterial activities. Compound **85a** showed the best in vitro antifungal activity against *Gibberella zeae* and antioomycete activity against *Phytophthora infestans*, with EC₅₀ = 0.47 µg/mL and 3.92 µg/mL, respectively. In the in vivo study against corn scab, compound **60a** showed protective and curative activities of 90.2 and 86.3% at 200 µg/mL, which were comparable to those of fungicides boscalid and fluopyram. These 1,3,4-oxadiazole-tailored pyrazole compounds with hydrazide functions in the middle as a linker are potential agricultural fungicides for controlling fungal diseases.

The 2,5-disubstituted 1,3,4-oxadiazoles **77e** (Figure 25) were evaluated for their in vitro antibacterial activity. Compound **77e.2** exhibited the best broad-spectrum antibacterial and antifungal activity, with MIC = 15.62, 7.81, 3.9, and 31.25, 62.5 µg/mL against *E. coli*, *S. typhi*, *B. subtilis*, *B. megaterium*, and *A. niger*, respectively [83].

Derivatives **84** (Figure 26) were evaluated for their in vitro antimycobacterial activity against the *M. tuberculosis* H37Ra-attenuated strain, H37Rv virulent strain, and several resistant strains. From the 5-phenyl-substituted oxadiazole subseries, derivatives **84a** and **84b** presented an MIC = 4 µM against pyrazinamide-resistant strains. Moreover, these compounds exhibited selectivity for mycobacteria and low cytotoxicity against human SH-SY5Y cells (CC₅₀ = 50 and 100 µM for **84a** and **84b**, respectively) [81].

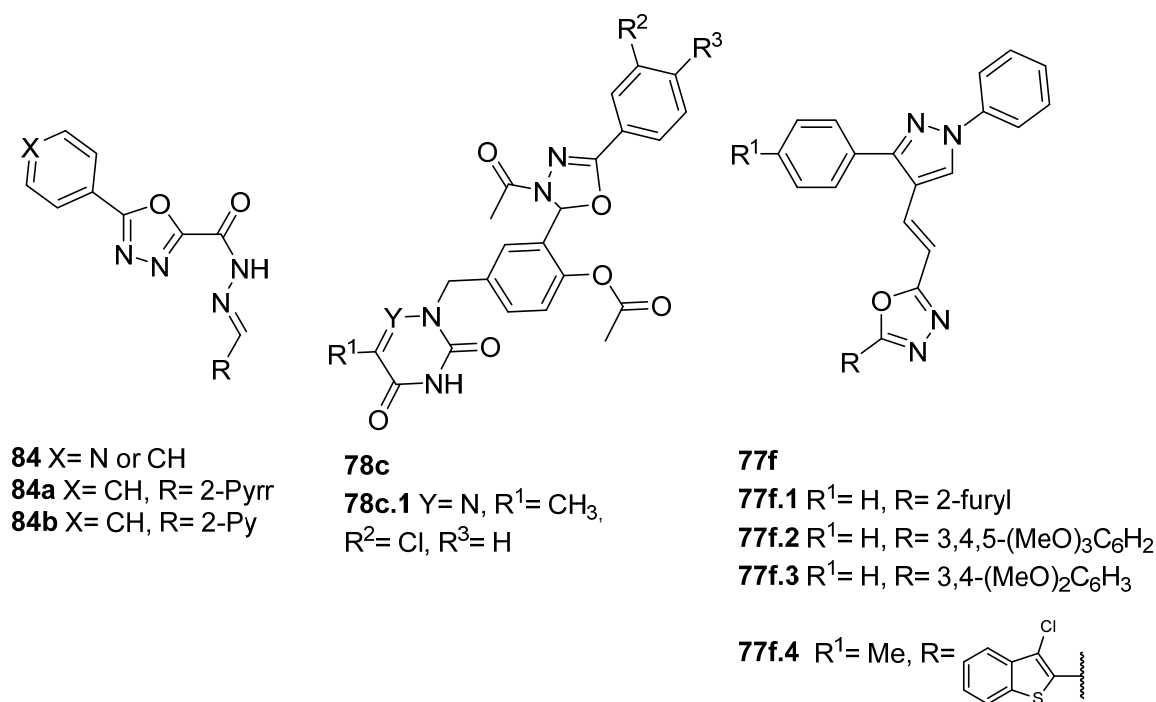


Figure 26. 1,3,4-oxadiazoles with antimycobacterial and antiparasitic activities.

Also, *N*³-acetyl-1,3,4-oxadiazoline derivatives **78c** (Figure 26) were screened against *Leishmania donovani*, and compound **78c.1** exhibited an antileishmanial activity with IC₅₀ = 8.98 µM on *L. donovani* intramacrophage amastigotes [40].

Moreover, Verma et al. [2] synthesized the hybrid compounds **77f** and evaluated their activity against *P. falciparum* 3D7 (chloroquine-sensitive) and RKL 9 (chloroquine-resistant) strains. Among the evaluated compounds **77f** (Figure 26), compound **77f.1** exhibited the best activity with an IC₅₀ = 0.25 µg/mL against the 3D7 (chloroquine-sensitive) strain and 0.86 µg/mL against the RKL 9 (chloroquine-resistant) strain of *P. falciparum*. Moreover, the antileishmanial activity of compounds **77f** against *L. donovani* promastigotes was also evaluated. Compounds **77f.2**, **77f.3**, and **77f.4** exhibited IC₅₀ = 33.3, 40.1, and 19.0 µg/mL, respectively. The same compounds (**77f.2**, **77f.3**, and **77f.4**) also had effects on amastigote infectivity with IC₅₀ = 44.2, 66.8, and 73.1 µg/mL, respectively. Among the tested compounds, the most promising were **77f.1** and **77f.4** for their good antimalarial and antileishmanial activity, respectively; hence, their cytotoxicity was studied, as well as their safety profile.

El-Helw et al. [28] reported compound **80l** (Figure 27) as an immunomodulator against the highly pathogenic avian influenza virus (H5N8), with the high potency of 100% protection, and Ramadan et al. [103] reported compound **80m** (Figure 27) as an insecticide with low LC₅₀ = 9.67 and 1.07 mg/mL against lab and field strains of the third larval instar of *Culex pipiens*.

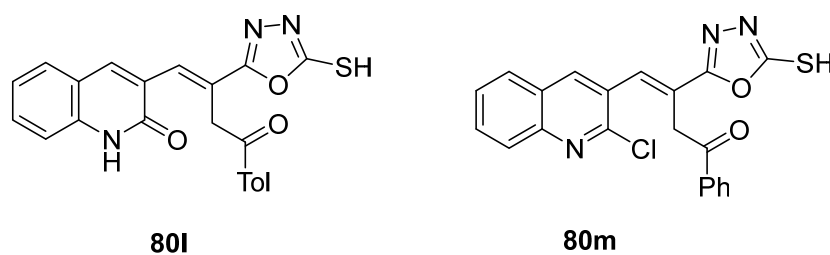


Figure 27. 1,3,4-oxadiazole-2-thiol derivatives with antiviral (**80l**) or insecticidal activity (**80m**).

New derivatives of novel 2,5-disubstituted 1,3,4-oxadiazole (Figure 28) were also synthesized as potential anti-inflammatory and antioxidant agents. Kashid et al. [59] reported compounds **77g** (Figure 28) with great anti-inflammatory and antioxidant activities, of which compounds **77g.1**, **77g.2**, and **77g.3** showed better anti-inflammatory activities with IC_{50} = 45.69, 58.54, and 56.70 μ M, respectively, compared to the standard drug diclofenac sodium that presents an IC_{50} = 90.21 μ M. According to the DPPH assay, compound **77g.4** exhibited good antioxidant activity with IC_{50} = 17.15 μ M, which was better than the reference antioxidant ascorbic acid (IC_{50} = 44.18 μ M). Also, a molecular docking study showed that these compounds can recognize the active site and accomplish significant bonded and non-bonded interactions with main residues in the anti-inflammatory target cyclooxygenase-2 (COX-2) [59]. Gunthanakkala et al. [105] reported compounds **77h** and **77i** (Figure 28) as potential antioxidants with IC_{50} values between 32.95 and 121.12, 29.90 and 117.73, and 31.34 and 106.42 μ g/mL, for DPPH, NO, and H_2O_2 assays, respectively. Among them, compound **77h.2** stood out with IC_{50} values = 32.95, 31.64, and 32.42 μ g/mL, and compound **77i.2** with IC_{50} values = 32.01, 29.90, and 31.34 μ g/mL for DPPH, NO, and H_2O_2 assays, respectively.

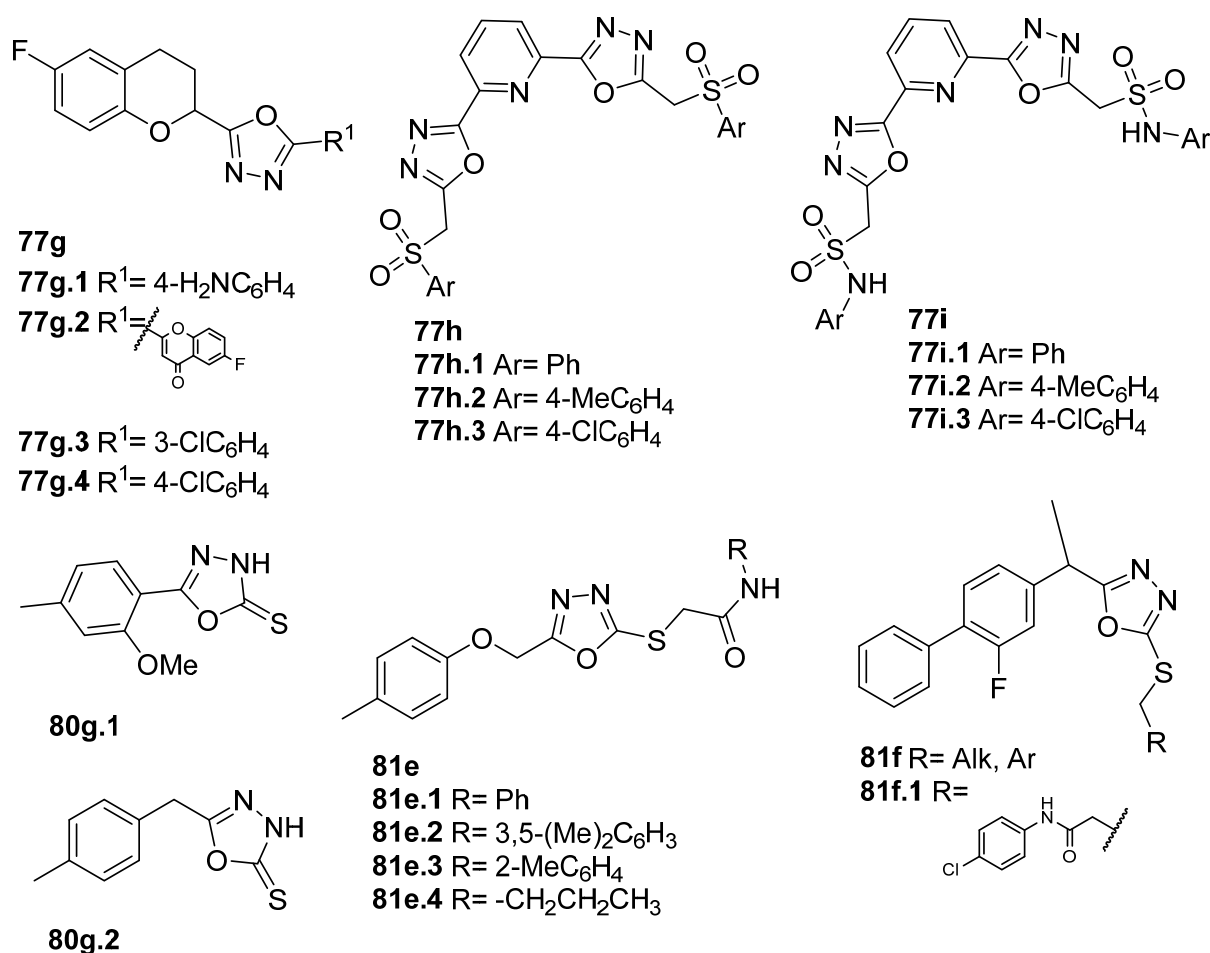


Figure 28. 1,3,4-oxadiazole derivatives as potential anti-inflammatory and antioxidant agents.

Some oxadiazole-2-thiol derivatives **80g** (Figure 28) also presented anti-inflammatory activity as inhibitors of COX or lipoxygenase (LOX) enzymes [41,85]. Munir et al. [41] identified derivatives **80g** with good in vitro cyclooxygenase inhibition activity, with IC_{50} values ranging from 31.5 to 39.5 μ M for COX-2 and from 43.91 to 27.55 μ M for COX-1. On the other hand, Bashir et al. [85] identified oxadiazoles **81e.1–4**, which showed good LOX inhibitory activities with IC_{50} values of 21.5, 29.1, 31.3, and 24.3 μ M, respectively.

Rana et al. [61] reported new derivatives **81f** (Figure 28) incorporating the flurbiprofen moiety. Compound **81f.1** showed the highest anti-inflammatory activity of the series, displaying 74.16% activity at 200 µg/mL, which is slightly lower than standard ibuprofen (84.31% activity). The same compound also showed antioxidant activity in the DPPH assay, with an IC_{50} = 25.35 µg/mL, while for ascorbic acid, the IC_{50} value was 6.13 µg/mL.

Furthermore, both derivatives **81g** and **81h** (Figure 29) showed good inhibition against α -glucosidase. Compound **81g.1** had the inhibition potential of 72.13% at 500 µM, which was higher than that of the standard drug acarbose (65.73% at 500 µM) [87]. Additionally, Daud et al. [62] identified compound **81h.1** with IC_{50} = 56.01 µM as more active than acarbose, the standard drug, which presents an IC_{50} = 375.82 µM, in the same assay. Compound **77k.1** also showed good α -glucosidase inhibition activity with an IC_{50} = 460 µM [156].

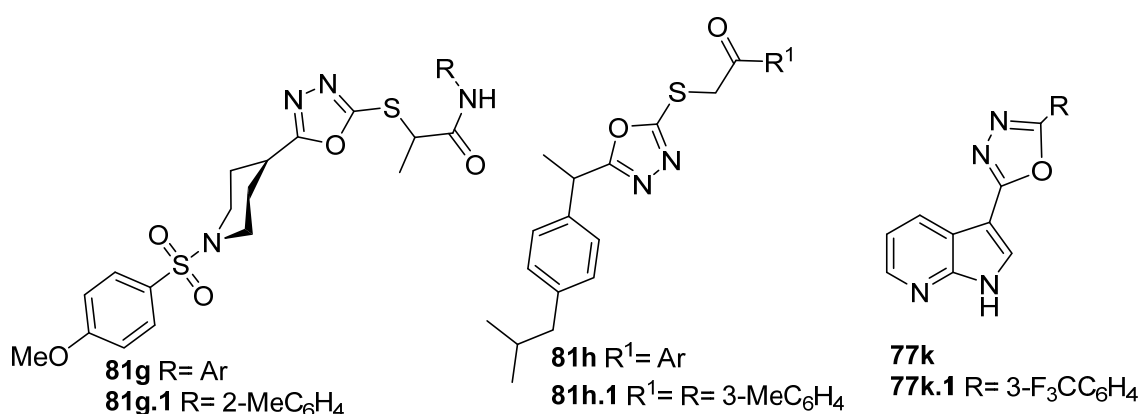


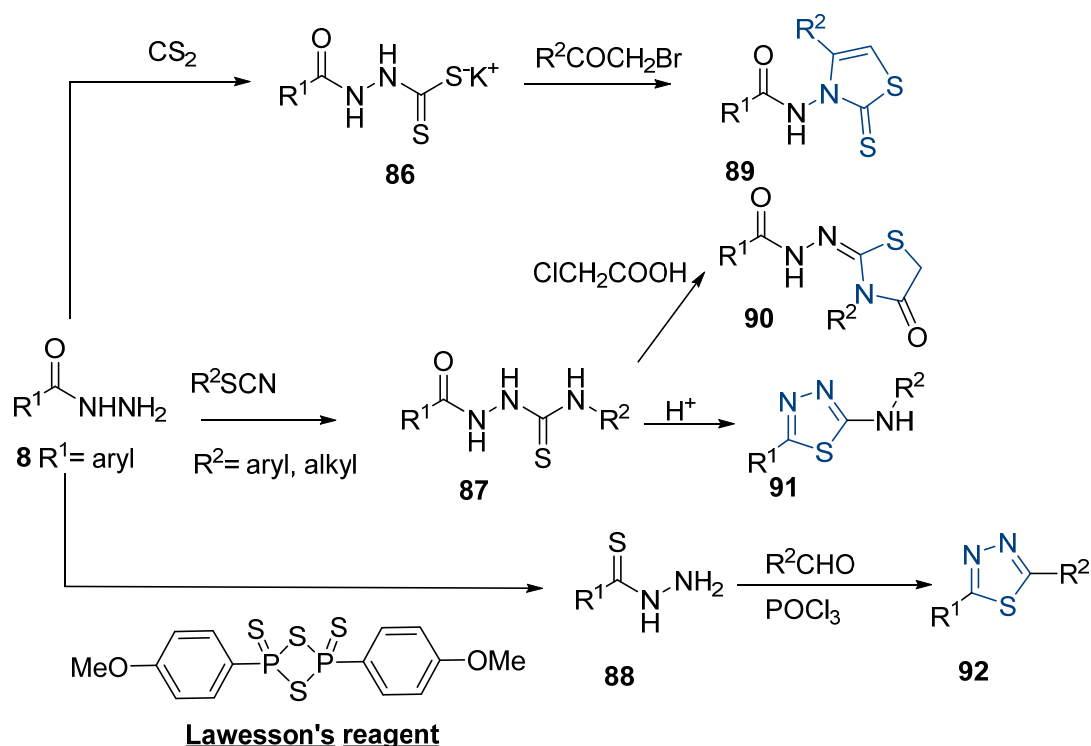
Figure 29. Oxadiazole derivatives as α -glucosidase inhibitors.

3.2.4. Thiazoles and Thiadiazoles

Synthesis of Thiazole and Thiadiazole Derivatives

Thiazole and thiadiazole are five-membered N,S- and N,N,S-heterocycles with important biological applications that foster the search for new derivatives. Recently, Babalola et al. [157] and Ahmad et al. [158] collected and discussed recent synthetic methodologies and the biological activity of thiadiazoles. Babalola et al. [157] discussed the synthesis of thiadiazoles over the last 10 years using heterogeneous catalysts, microwave-assisted synthesis, ultrasound-aided techniques, solvent-free synthesis, or complex catalyzed reactions; Ahmad et al. [158] discussed the synthesis of thiadiazoles, since 2008, from hydrazides, thiosemicarbazide, acylhydrazines, thioacylhydrazones, dithiocarbazates, and isothiocyanate. Scheme 20 presents the general approaches to obtain these heterocycles from hydrazides **8**, and Table 7 describes the reaction conditions to obtain the different derivatives from the reactions between hydrazides and carbon disulfide, isothiocyanate reagents, or Lawesson's reagent.

Tolan et al. [64] reported the synthesis of compounds **89** in a two-step approach (Scheme 20). The reaction of hydrazide **8** with carbon disulfide produced intermediary **86**, which reacted with an acyl bromide reagent in ethanol and was refluxed to generate the thiazole ring of derivative **89**. Abumelha et al. [44] synthesized thiazole derivatives **90** (Scheme 20). The synthetic approach involved the conversion of hydrazide **8** into intermediate **87**, by reaction of **8** with isothiocyanate, under heating. The reaction of intermediate **87** with chloroacetic acid promoted the formation of thiazole ring **90**. Moreover, intermediary **87** was converted to 1,3,4-thiadiazoles **91** by treatment with sulfuric acid under reflux [94,159].

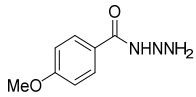
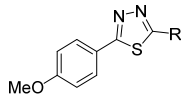
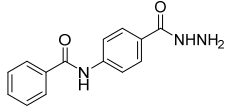
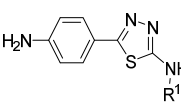


Scheme 20. General approaches to 1,3-thiazole and 1,3,4-thiadiazole synthesis from hydrazides.

Table 7. Reaction conditions for the synthesis and purification of 1,3-thiazole and 1,3,4-thiadiazole derivatives from hydrazides.

Ref.	Starting Material	Experimental Conditions	Purification Process	Products ($\eta\%$)
[64]	 8ac	CS ₂ , KOH (aq.), reflux, 3 h	-	 86a (86%)
[64]	 86a	PhCOCH ₂ Br, EtOH, reflux, 3 h	Recrystallization from ethanol	 89a (67%)
[44]	 8aaq	PhNCS, EtOH, reflux, 4 h	-	 87a (64%)
[44]	 87a	ClCH ₂ COOH, EtOH, AcONa, reflux, 6 h	-	 90a (74%)
[108]	 29d	Lawesson reagent (1.7 eq) toluene, 110 °C, 6 h	Silica gel column chromatography	 92a (36–49%)

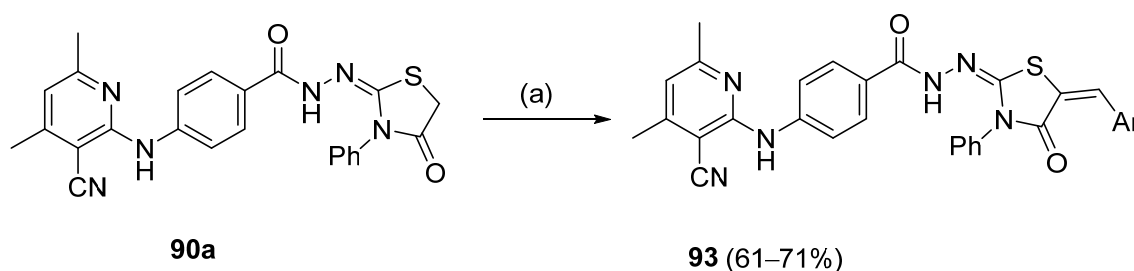
Table 7. Cont.

Ref.	Starting Material	Experimental Conditions	Purification Process	Products (η %)
[93]	 8aar	1. Lawesson's reagent (1 eq) toluene, reflux, 8 h 2. RCHO (1 eq), POCl ₃ (107 eq) reflux, 4–6 h	Recrystallization from methanol	 92b (n.s.)
[94]	 8aas	1. R ¹ NCS, EtOH, 2 h 2. H ₂ SO ₄ , reflux, 5 h	1. Recrystallization from ethanol 2. Recrystallization from ethanol	 91a (n.s.)

n.s.—not specified by the authors.

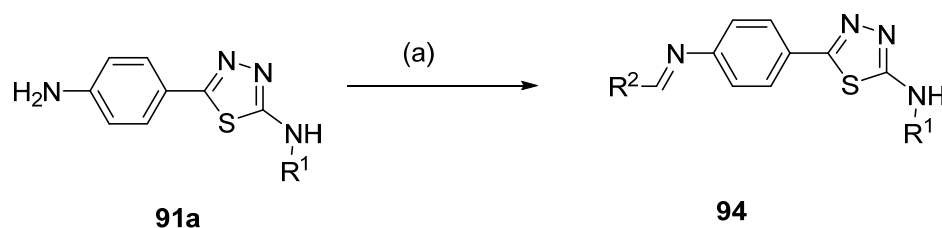
Hydrazides **8**, in the presence of Lawesson's reagent, generated the corresponding thio-derivatives **88**, which generated 1,3,4-thiadiazole derivatives **92** in the presence of phosphoryl chloride and an aldehyde, under heating (Scheme 20) [93].

Abumelha et al. [44] synthesized thiazole derivatives **93** as precursors of antioxidant agents. Compound **90a** was converted to the hybrids **93** by reaction with aldehydes under reflux, in an acidic medium. Products **93** were obtained in good to moderate yields (Scheme 21).



Scheme 21. Synthesis of thiazole derivative **93**: (a) ArCHO, CH₃COOH/AcONa, reflux, 4 h.

Compounds **94** (Scheme 22) were yielded from thiadiazole derivative **91a** and aldehydes under reflux conditions, in methanol [94].



Scheme 22. Synthesis of thiadiazole derivative **94**: (a) R²CHO, MeOH, reflux.

Biological Activity of Thiazole and Thiadiazole Derivatives

Compound **89a** (Figure 30) was evaluated for anticancer activity and showed good antiproliferative activities against MCF-7 breast cancer cells and against hepatocellular HepG2 cells with IC₅₀ = 8.0 and 28.2 μ M, respectively. These IC₅₀ values are better or similar to those of doxorubicin, which has IC₅₀ = 10.3 and 28.5 μ M, for the same cell lines [64].

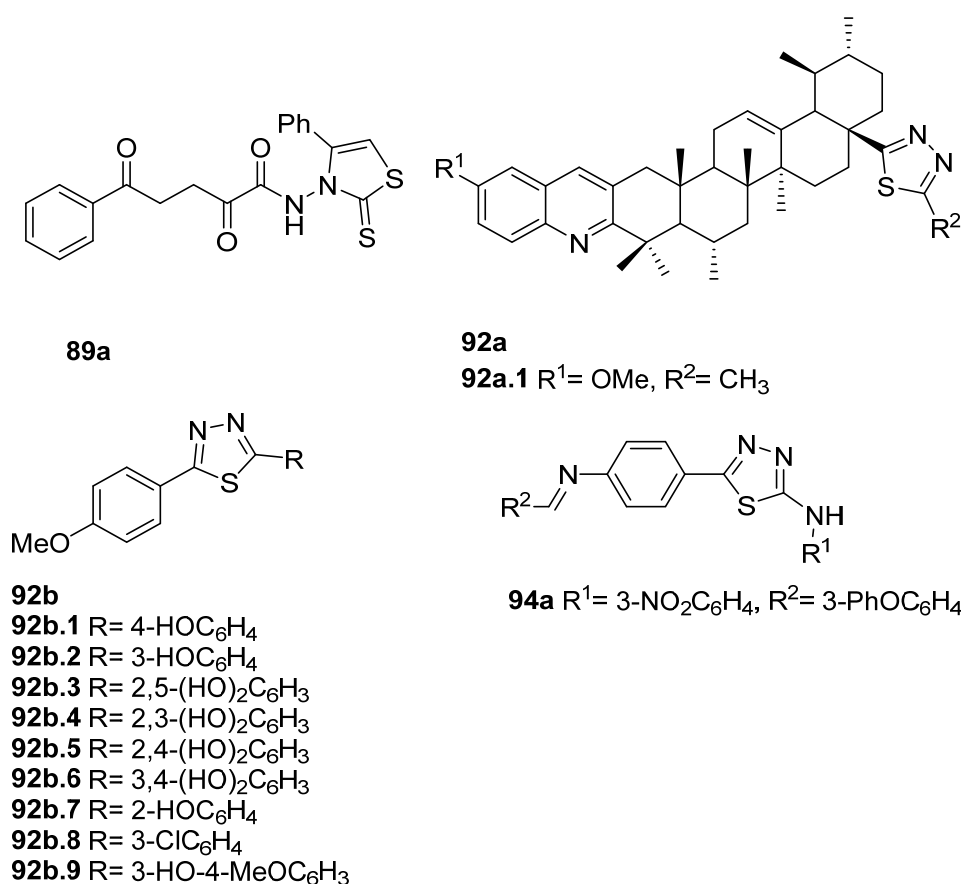


Figure 30. Thiazole and 1,3,4-thiadiazole derivatives with anticancer and antimycobacterial activity.

Compounds with structure **92a** (Figure 30) were screened against cancer cell lines MDA-MB-231 and HeLa. Compound **92a.1** (Figure 30) exhibited good anticancer activity with $\text{IC}_{50} = 15.75$ and $12.82 \mu\text{M}$ against cancer cell lines MDA-MB-231 and HeLa, respectively, although it had a lower activity than the positive control etoposide [108]. Taha et al. [93] reported the 2,5-disubstituted thiadiazoles **92b** (Figure 30) as potent β -glucuronidase inhibitors presenting IC_{50} values between 6.74 and $52.36 \mu\text{M}$, revealing higher or equivalent activity to the standard *D*-saccharic acid-1,4-lactone ($\text{IC}_{50} = 48.4 \mu\text{M}$). Among these, compound **92b.5** was the most potent, with $\text{IC}_{50} = 6.74 \mu\text{M}$.

On the other hand, thiazoles **94** (Figure 30) were screened against *Mycobacterium tuberculosis* H₃₇Rv, and compound **94a** was the most potent with an inhibitory activity of 80% at $6.25 \mu\text{g/mL}$ [94].

3.2.5. Triazoles

Synthesis of Triazole Derivatives

Triazole, also known as pyrroldiazole, is a five-membered heterocyclic ring system containing three nitrogen atoms, existing in two isomeric forms, 1,2,3- **95** or 1,2,4-triazoles **96** (Figure 31) [160]. Both isomers present a wide range of pharmacological activities.

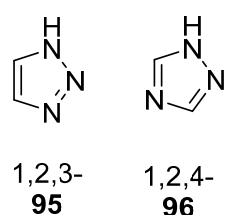


Figure 31. Isomeric forms of the triazole ring.

In a recent review, Hassani et al. [161] reported the advances in the synthesis of triazole derivatives. The authors presented multiple methods to obtain 1,2,3- or 1,2,4-triazoles, including metal-free and metal-catalyzed reactions. Among them are the cycloaddition of azides and terminal alkynes; the reaction between two nitriles and hydroxylamine hydrochloride; the reaction of formamide reagents and hydrazide; the reaction of acylhydrazines with carbon disulfide, followed by the reaction with hydrazine monohydrate; and others [161]. Ren et al. [162] recently reported a different approach for the synthesis of 1,2,3-triazoles, involving an iodine-mediated condensation–cyclization reaction from α -azido acetophenones and *p*-toluenesulfonyl hydrazide. Moreover, Clark et al. [163] developed the synthesis of substituted 1,2,3-triazoles from α -ketoacetals, tosyl hydrazide, and a primary amine. On the other hand, Patterson et al. [164] presented the synthesis of 1,2,3-triazoles from tosylhydrazide, aldehydes, and a primary amine, as an alternative to azides.

Here, in this review, we present the synthesis of 1,2,4-triazole (Table 8), in which hydrazides are often combined with thiocyanate or isothiocyanates, carbon disulfide, or nitrile derivatives (Scheme 23). Hydrazides **8**, in the presence of isothiocyanates and under reflux conditions, generate the intermediates **87** (in a neutral or acidic medium), which cyclize in a basic medium under reflux, to give **97** [35,42,80,88,89,91,165]. Several derivatives of **100** were obtained by the condensation of **97** with electrophiles [42,88–91]. The reaction with carbon disulfide took place in a basic medium with reflux, followed by cyclization with hydrazine hydrate to obtain compounds **98** [41]. Reflux or high temperatures are also used when nitrile derivatives are used as reagents to obtain compounds **99** [166,167]. The products **97**, **98**, and **99** were typically isolated in good to excellent yields. The experimental conditions for the synthesis of 1,2,4-triazole-3-thione derivatives are presented in Table 8. The 1,2,4-triazole-3-thione compounds were sometimes just intermediates to obtain the compounds **100** or others with potential biological activity [110].

Table 8. Reaction conditions for the synthesis and purification of 1,2,4-triazole derivatives from hydrazides and their derivatives.

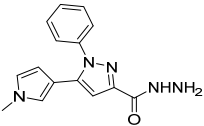
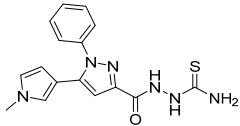
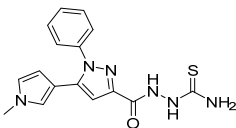
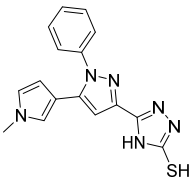
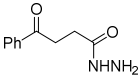
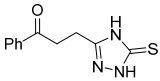
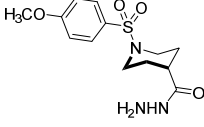
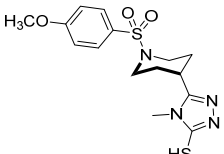
Ref.	Starting Material	Experimental Conditions	Purification Process	Intermediates or Triazoles (η %)
[35]	 8ad	NH ₄ SCN (1 eq) HCl, EtOH, reflux, 6 h	Recrystallization from DMF/ethanol	 87a (82%)
[35]	 87a	KOH EtOH, reflux, 6 h	Recrystallization from DMF/ethanol	 97a (78%)
[80]	 8ac	KSCN (1 eq), 10% HCl, reflux, 6–9 h	Recrystallization from dioxane	 97b (77%)
[42]	 8aal	1. MeNCS (1 eq) EtOH, reflux, 1 h 2. KOH (1 eq), reflux, 1 h 3. HCl	-	 97c (n.s.)

Table 8. Cont.

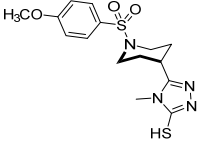
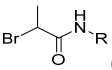
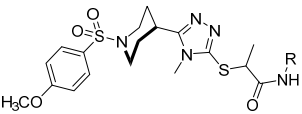
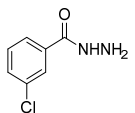
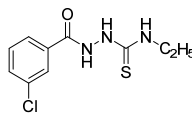
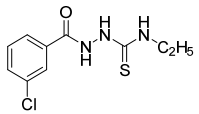
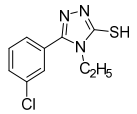
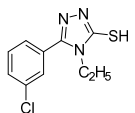
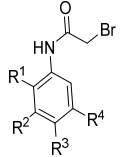
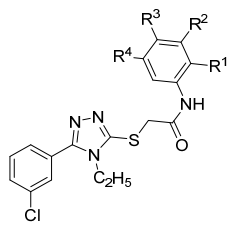
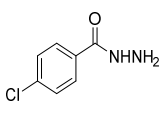
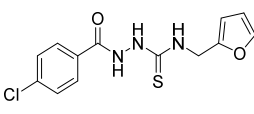
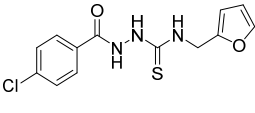
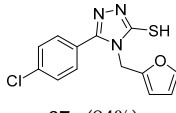
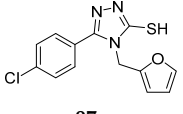
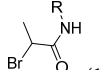
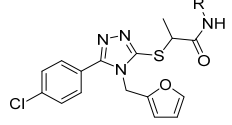
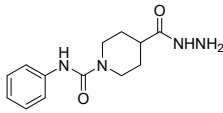
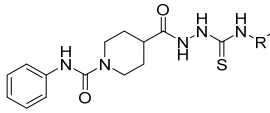
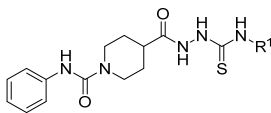
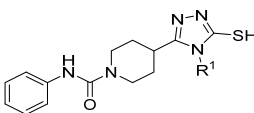
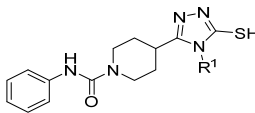
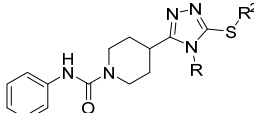
Ref.	Starting Material	Experimental Conditions	Purification Process	Intermediates or Triazoles (η %)
[42]	 97c	 (1 eq) LiH, DMF, r.t, 6–17 h or LiH, DMF, microwave, 33–90 s	-	 100a R = Ar (85–90%)
[88]	 8p	EtNCS (1 eq) EtOH, reflux 3–4 h	-	 87d (98%)
[88]	 87d	10% NaOH, reflux, 4 h HCl	-	 97d (96%)
[88]	 97d	 (1 eq) DMF, NaH, 30 min, r.t.	-	 100b (62–77%)
[89]	 8q	furfuryl isothiocyanate (1 eq) MeOH, reflux, 8–10 h	-	 87e (97%)
[89]	 87e	10% NaOH reflux, 6–8 h HCl	-	 97e (94%)
[89]	 97e	EtOH, KOH(1 eq)  (1 eq), reflux, 4–5 h	-	 100c R = Ar (89–95%)
[90]	 8aao	EtNCS or PhNCS (1 eq) EtOH, reflux 3–4 h	-	 87f (97%)
[90]	 87f	1. 10% NaOH, reflux 4 h 2. HCl	-	 97g (98%)
[90]	 97g	KOH, EtOH, r.t., 30 min, alkyl halides (1 eq), reflux, 4–5 h	-	 100d R ¹ = Ar, R ² = Alk (70–99%)

Table 8. Cont.

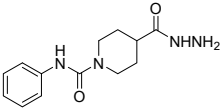
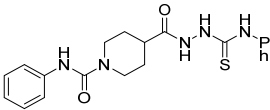
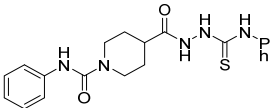
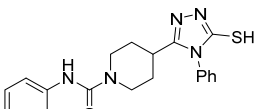
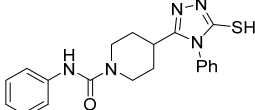
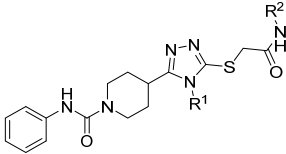
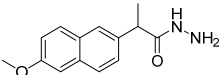
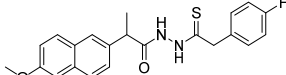
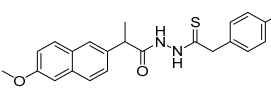
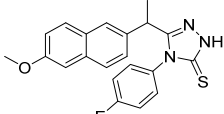
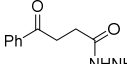
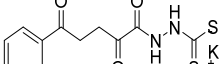
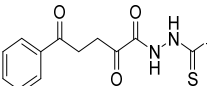
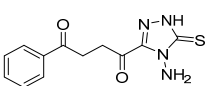
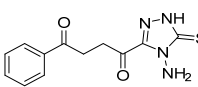
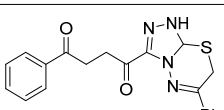
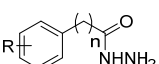
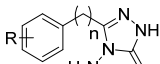
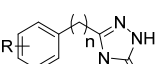
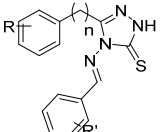
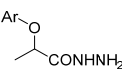
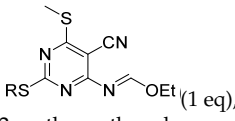
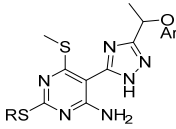
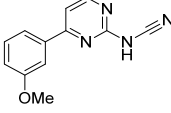
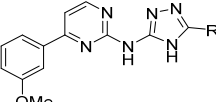
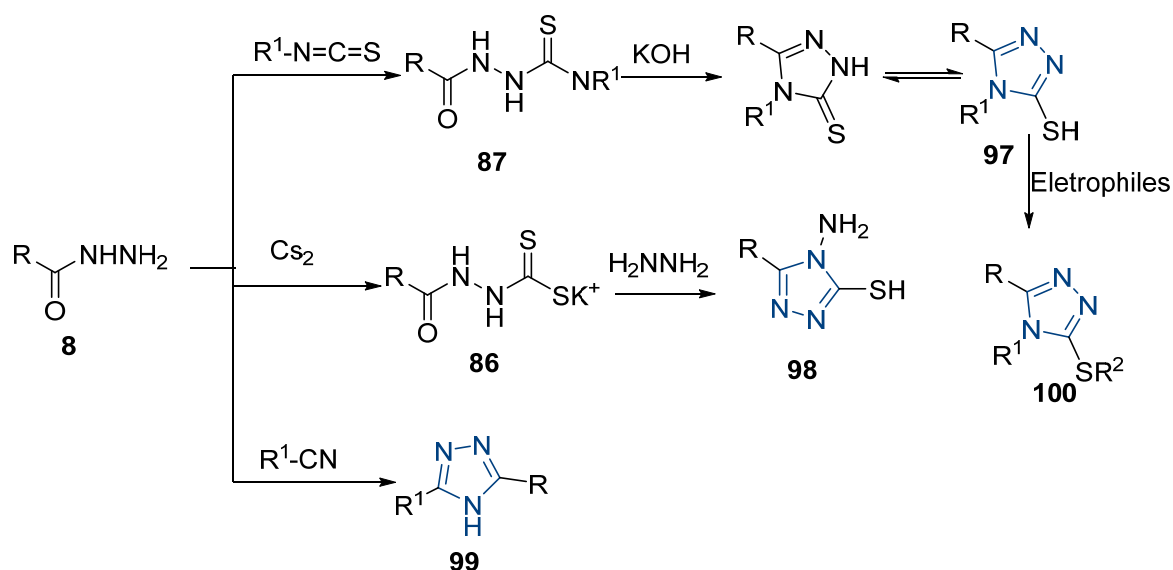
Ref.	Starting Material	Experimental Conditions	Purification Process	Intermediates or Triazoles (η %)
[91]	 8aao	PhNCS MeOH, reflux 3–4 h	-	 87h (98%)
[91]	 87h	1.10% NaOH, reflux, 4 h 2. HCl	-	 97h (95%)
[91]	 97h	KOH MeOH, r.t., 30 min  , reflux 4–5 h	-	 100e $R^1 = \text{Ar}$, $R^2 = \text{Ar}$ (88–96%)
[165]	 8abn	4-FC ₆ H ₄ NCS (1 eq), CH ₃ (CH ₂) ₃ OH, 65 °C, 4 h	Recrystallization from ethanol	 87h (75%)
[165]	 87h	4 N NaOH, heat under Radley, 16 h, CH ₃ COOH	Recrystallization from ethanol	 97i (60%)
[64]	 8ac	CS ₂ KOH (aq.), reflux, 3 h	-	 86a (86%)
[64]	 86a	H ₂ NNH ₂ ·H ₂ O, reflux 2 h	Recrystallization from EtOH/DMF	 98a (43%)
[64]	 98a	PhCOCH ₂ Br (1 eq), Et ₃ N (1 eq), EtOH, reflux, 2 h	Recrystallization from DMF/H ₂ O	 101 (60%)
[41]	 8aa	KOH CS ₂ water/ethanol (1:1) H ₂ NNH ₂ ·H ₂ O 64% (1 eq), reflux	-	 98b (52–65%)
[41]	 98b	RCHO (1 eq), CH ₃ COOH (cat.), MeOH, reflux, 12 h	-	 102 (72–89%)

Table 8. Cont.

Ref.	Starting Material	Experimental Conditions	Purification Process	Intermediates or Triazoles ($\eta\%$)
[166]	 8a	 2-methoxyethanol TFA (cat.) reflux, 8–10 h	Recrystallization from DMSO	 99a (70–84%)
[167]	 8 R = Ar	 (1 eq) DMF, 90 °C, 5 h HCl (0.05 N)	Recrystallization from dioxane	 99b R = Ar (73–81%)

n.s.—not specified by the authors.



Scheme 23. Representative scheme of 1,2,4-triazoles from hydrazides.

Biological Activity of Triazole Derivatives

According to the literature [35,41,42,64,80,88–91], 1,2,4-triazole derivatives showed enzymatic inhibition (α -glucosidase, 15-lipoxygenase, acetylcholinesterase, and butyrylcholinesterase enzymes), as well as anticancer or anti-inflammatory activity.

Derivative **97a** (Figure 32) was tested against the human colon carcinoma cell line HCT-116 and showed moderate cytotoxic effects with $IC_{50} = 12.05 \mu\text{g/mL}$ [35]. Both compounds **98a** and **101** (Figure 32) presented antiproliferative activities against MCF-7 breast cancer cells with IC_{50} values of 8.2 and 9.2 μM , respectively, which were lower than the IC_{50} of the reference drug doxorubicin (10.3 μM). They were also active against hepatocellular HepG2 cells with IC_{50} values of 33.7 and 30.8 μM , which were quite similar compared to doxorubicin (28.5 μM) [64]. Moreover, Abu-Hashem et al. [80] evaluated compound **97b** against human gastric carcinoma (MGC-803), nasopharyngeal carcinoma (CNE2), oral carcinoma (KB), and breast adenocarcinoma (MCF-7) cell lines. The compound showed IC_{50} values in the range of 12.8 to 14.2 μM .

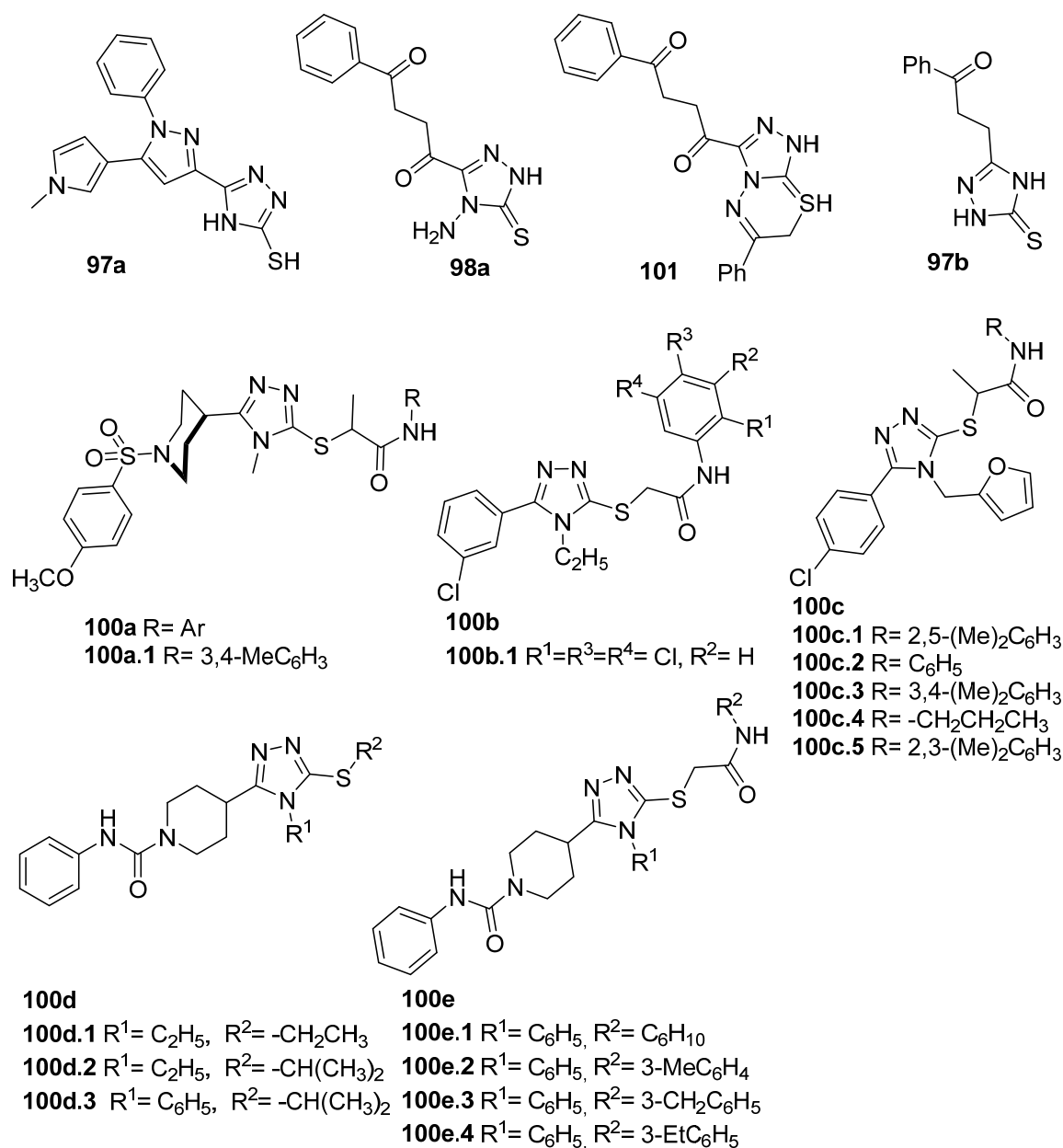


Figure 32. 1,2,4-triazole derivatives with anticancer and enzymatic (α -glucosidase, acetylcholinesterase, butyrylcholinesterase, and 15-lipoxygenase) inhibition activity.

Virk et al. [42] and Riaz et al. [88] evaluated the biological potential of compounds **100a** (Figure 32) against AChE. Derivative **100a.1** showed good inhibition against α -glucosidase (IC_{50} = 27.52 mM) compared to acarbose (IC_{50} = 375.82 mM) and lower inhibition against AChE (IC_{50} = 407.24 mM) in comparison with the standard drug eserine (IC_{50} = 0.19 mM) [42]. On the other hand, compound **100b.1** showed activity against AChE and BChE with IC_{50} values of 5.41 and 7.52 μ M, respectively [88]. Compounds **100c–e** (Figure 32) were tested as potential lipoxygenase inhibitors. Among these [89], compounds **100c.1–5** demonstrated good activity as inhibitors of 15-lipoxygenase with IC_{50} values of 17.43, 19.35, 23.59, 26.35, and 27.53 μ M, respectively. The 1,2,4-triazole thioethers **100d.1–3** also showed very good inhibitory profiles against the same enzyme, with IC_{50} values ranging from 12.52 to 35.64 μ M [90].

Muzaffar et al. [91] reported on derivatives **100e.1–4** (Figure 32), which displayed inhibitory potential against the 15-lipoxygenase enzyme with IC_{50} values between 9.25 and 21.82 μ M.

Munir et al. [41] obtained 1,2,4-triazole derivatives **98b** and **102** (Figure 33), and compounds **98b.1** and **102a** displayed excellent and good activity for the COX-2 isozyme with IC_{50} values of 1.76 and 23.47 μ M, respectively. Other compounds **102** of this series showed COX-2 inhibition in the range of 12.56–26.58 μ M. In vivo anti-inflammatory studies, by using the carrageenan-induced paw edema test, showed that after 5 h, the maximum percentage inhibition was 29.4% for compound **98b.1** and 17.6% for compound **102a** [41].

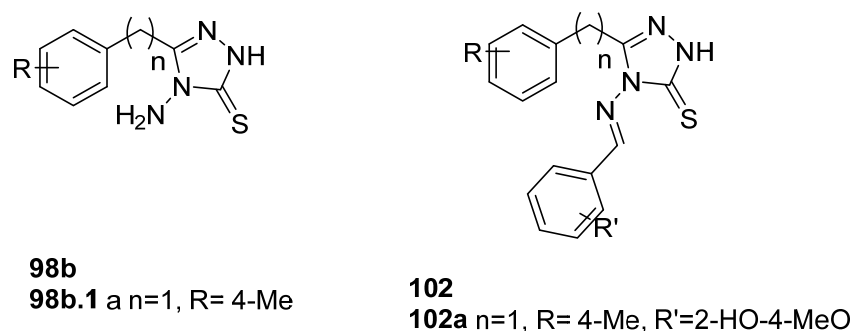


Figure 33. 1,2,4-triazole derivatives with anti-inflammatory activity.

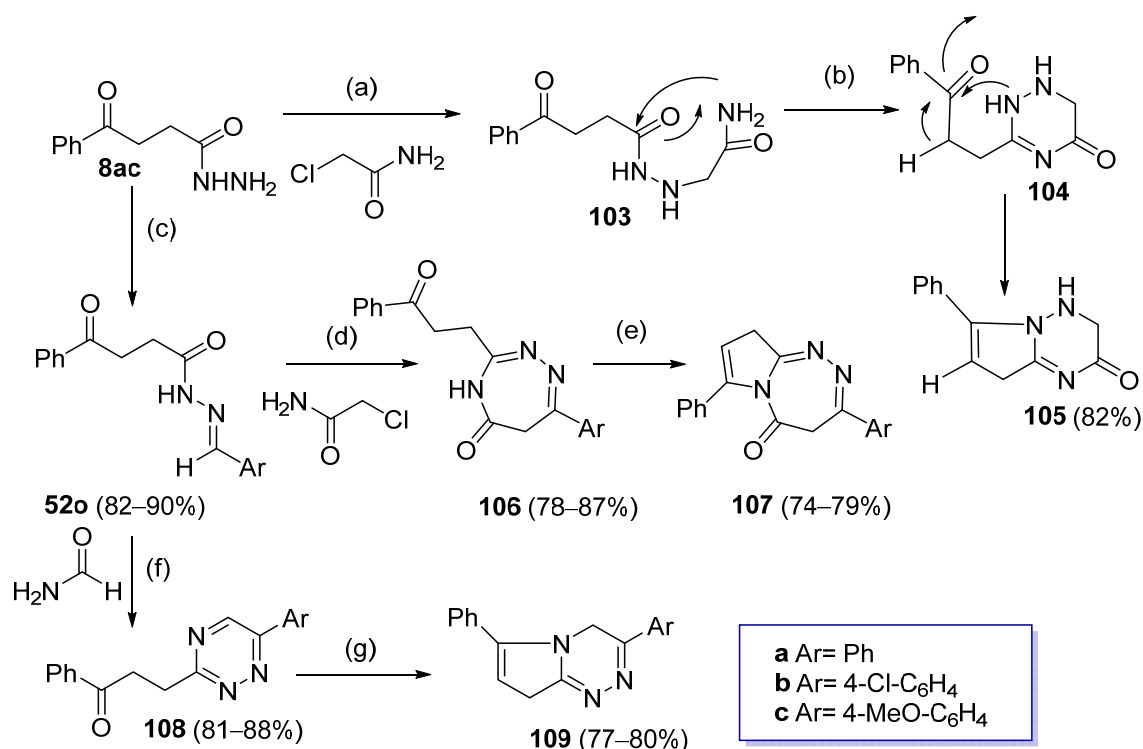
4. Miscellany

In the literature, hydrazides are also mentioned as reagents to generate triazine or triazepine rings [80], coating agents of nanoparticles [168], or even ligands for complexes [169,170].

Abu-Hashem et al. [80] synthesized triazine or triazepine derivatives from hydrazide **8ac** (Scheme 24). Intermediate **103** was synthesized from hydrazide **8ac** and chloroacetamide under reflux. It was converted to **104** by reflux under basic medium. The latter further suffered an intramolecular cyclization, generating pyrrolotriazinones **105**. This hydrazide was also the starting material of hydrazide–hydrazone derivatives **52o**, which were used to obtain new compounds such as 1,2,4-triazepinones **106**, pyrrolotriazepinones **107**, 1,2,4-triazines **108**, and pyrrolotriazines **109**. Derivatives **106** were obtained from intermediate **52o** in the presence of chloroacetamide, which can undergo a posterior cyclization in the presence of a base and reflux to form compound **107**. Compound **52o** in the presence of formamide and reflux generated 1,2,4-triazines **108**, which under reflux led to the formation of pyrrolotriazines **109**. Compounds **107a–c**, **106a–c**, **109a–c**, and **105** displayed activities against human gastric carcinoma (MGC-803), nasopharyngeal carcinoma (CNE2), oral carcinoma (KB), and breast adenocarcinoma (MCF-7) lines with IC_{50} values ranging from 11.1 to 14.2 μ M.

Umapathi et al. [168] prepared gold nanoparticles with a surface corona of curcumin and isonicotinic acid hydrazide for improved anticancer activity, since gold nanoparticles can carry and stabilize these molecules. The isonicotinic acid hydrazide was used due to its biological importance. The resulting nanoparticles with the isonicotinic hydrazide at a 5 ppm concentration showed good anticancer activity towards human lung squamous carcinoma (LK-2) through ROS generation (Figure 34).

To improve the water solubility and stability of bisdemethoxycurcumin (BDMC), Guo et al. [169] obtained pillar[5]arene complexes of this compound (Figure 35). They synthesized hydrazide–pillar[5]arene (HP5A) and the complex of the two (BDMC and HP5A) self-assembled into fibers. Regarding the IC_{50} of free BDMC ($IC_{50} = 50.6 \mu\text{g/mL}$) and in complex ($IC_{50} = 32.4 \mu\text{g/mL}$), this complex showed greater antiproliferative activity in vitro against hepatocellular carcinoma HepG2 cells and, at the same time, reduced the undesirable side effects on normal cells.



Scheme 24. Synthesis of other heterocyclic rings from hydrazides: (a) ClCH₂CONH₂, DMF, reflux, 24–48 h; (b) DMF, K₂CO₃, reflux, 13–16 h; (c) ArCHO, EtOH, piperidine (cat.), reflux, 5–8 h; (d) H₂NCOCH₂Cl, DMF; (e) DMF, K₂CO₃, reflux, 17–20 h; (f) H₂NCOH, DMF, reflux, 9–24 h; (g) DMF, K₂CO₃, reflux, 15–18 h.

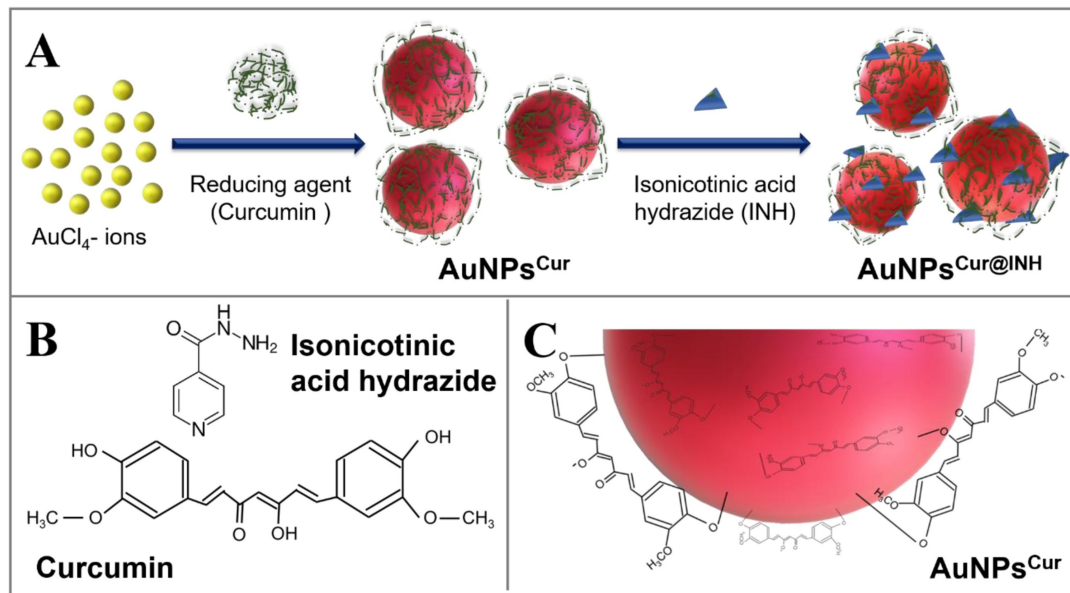


Figure 34. Representation of the synthesis of curcumin-coated gold nanoparticles with surface modification with isonicotinic acid hydrazide. (A) Schematic representation of the formation of curcumin (Cur) coated AuNPs^{Cur}, and their sequential surface modification with isonicotinic acid hydrazide (INH) to develop AuNPs^{Cur@INH}; (B) The chemical structures of curcumin and isonicotinic acid hydrazide (INH); (C) The phenolic and enolic hydroxide groups of curcumin are involved in the reduction of AuCl₄[−] ions, and orientation of oxidized moieties of curcumin on the surface of AuNPs. Reprinted with permission from Ref. [168] Copyright 2020 Elsevier.

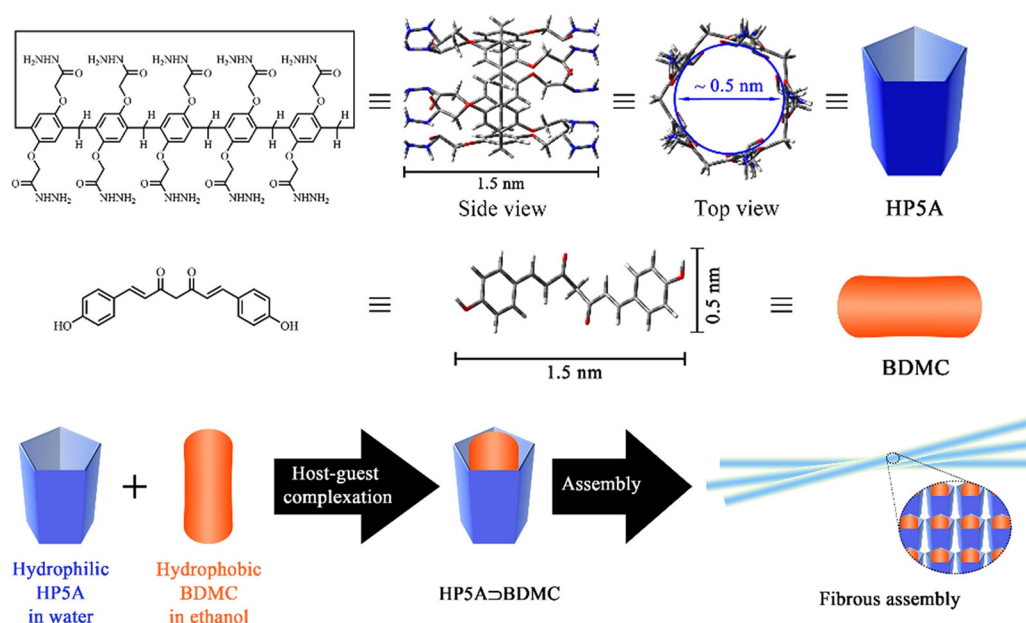


Figure 35. Representation of hydrazide-pillar[5]arene (HP5A), the complex of these with bis-demethoxycurcumin (BDMC), and the self-assembly into fibers. Reprinted with permission from Ref. [169] Copyright 2021 Elsevier.

In 2022, new 1,3,4-oxadiazole (odt) derivatives and hydrazides (hz) were used as ligands for Pd(II) complexes, aiming to generate inhibitors of lipoxygenase (LOX) and butyrylcholinesterase (BChE). The Pd(II)-hz complexes (**P1–P3**) and six new Pd(II)-odt complexes (**P'2–P'7**), shown in Figure 36, were obtained via the reaction of the ligands with Pd(II) in a 1:2 metal/ligand molar ratio in acetonitrile or ethanol at room temperature [170].

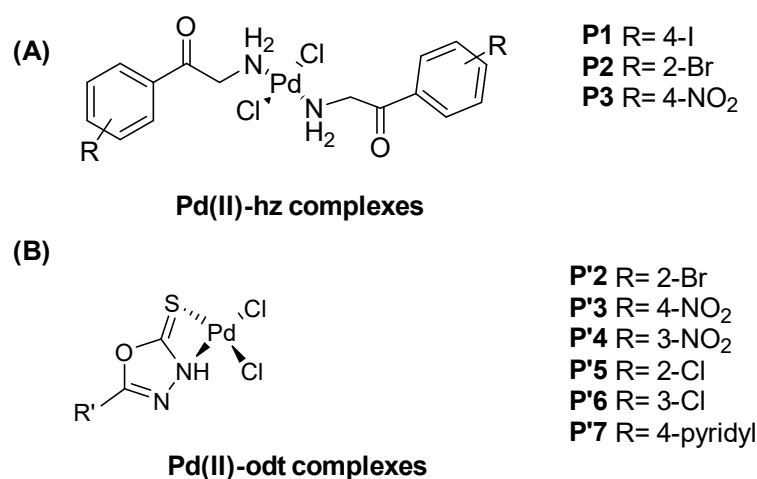


Figure 36. (A) New Pd(II)–hydrazide (Pd(II)-hz) complexes (**P1–P3**) and (B) new Pd(II)–oxadiazole (Pd(II)-odt) complexes (**P'2–P'7**).

All compounds synthesized exhibited moderate BChE inhibition with IC₅₀ values ranging between 21.5 and 95.6 μM, which were lower than the IC₅₀ of the reference drug eserine (IC₅₀ = 7.3 μM). The most active complexes were **P1** and **P'2** with IC₅₀ values of 21.5 and 23.4 μM, respectively [170].

5. Conclusions

Many diseases (infections, cancers, diabetes, parasitic diseases, Alzheimer's disease, dementia, etc.) have concerned the scientific community due to the high mortality, high

toxicity, and lack of effective drugs, as well as the presence of drug resistance to the available treatments. Aiming for new therapeutic solutions, the scientific community has synthesized the simplest to the most complex hydrazides to obtain new compounds with different biological activities. Most of the reported hydrazides in the last five years have been synthesized from acids or acid derivatives by reactions with hydrazine. A few new methods were also reported to synthesize hydrazides, such as the transamidation of N-substituted amides with hydrazine, the alkylation of hydrazides promoted by ruthenium catalysts, N-N cross-coupling reactions between hydroxamates and amines catalyzed by nickel complexes, nickel-catalyzed photochemical C-N coupling reactions between hetero(aryl) halides and hydrazides, photochemical reactions between azodicarboxylates and aryl or heteroaryl acylsilanes, and via hydrazine insertion into the β -position of benzoyl acrylates. The newly developed methods mostly generated substituted hydrazides, except for transamidation, which allowed the synthesis of non-substituted hydrazides in high yield. A wide variety of hydrazides have been used as synthons and precursors to hydrazide-hydrazones or heterocyclic derivatives. From hydrazides, hydrazide-hydrazone derivatives, oxadiazoles, and pyrazoles are among the most synthesized compounds. In addition, pyrrolones, thiazoles, thiadiazoles, and triazoles were also synthesized. Overall, the synthesis methods allow for obtaining these compounds in reasonable to excellent yields from hydrazides. The purification methods include silica gel column chromatography and recrystallization, with the latter being the most common. Hydrazides and their derivatives showed many biological activities, such as anticancer, antidiabetic (as α -glucosidase inhibitors), antibacterial, antifungal, antiparasitic, antiviral, anti-inflammatory (as COX inhibitors), and cholinesterase inhibition activity (neurodegenerative diseases), among others. This review represents a convenient tool for those aiming to explore the synthesis of new hydrazides or their derivatives to generate different scaffolds with biological activity.

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