

Review

# Amidoalkyl Naphthols as Important Bioactive Substances and Building Blocks: A Review on the Current Catalytic Mannich-Type Synthetic Approaches

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**Abstract:** Currently, 1-amidoalkyl-2-naphthol derivatives are of increasing interest due to their biological activities and further use in the preparation of other important bioactive molecules, such as aminoalkyl naphthols and oxazines. The synthesis of 1-amidoalkyl-2-naphthol moiety is usually achieved by employing one-pot multicomponent Mannich reactions. This review covers the recent reports on 1-amidoalkyl-2-naphthols' preparation with the use of different catalysts and summarizes the available published data for the period of the last 3 years. It also puts emphasis on the structure, synthetic transformation and biological importance of this class of products.

**Keywords:** multicomponent reaction; Mannich reaction; 1-amidoalkyl-2-naphthol; bioactivity; aminoalkyl naphthol; oxazine



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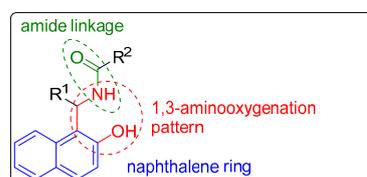


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## 1. Introduction

The 1,3-aminoxygenated functional motif exists in a variety of natural products [1–4] as well as in a number of marketed drugs [5–10]. Sedridine, allosedridine, febrifugine, nikkomyacin Z, and negamycin, bearing 1,3-aminoxygenated moiety, are naturally occurring compounds some of which possess antifungal and antibacterial properties [1–4]. Ritonavir and lopinavir, approved antiretroviral drugs against HIV/AIDS [5,6]; haloperidol, an antipsychotic drug [7]; venlafaxine and desvenlafaxine, antidepressant medications [8]; vildagliptin, an antidiabetic drug [9]; and tramadol, a synthetic analgesic [10], are marketed drugs which also feature the 1,3-aminoxygenated motif. As can be seen, the list of bioactive molecules containing the 1,3-aminoxygenation pattern is fairly long, which justifies and encourages the search for other valuable and pharmaceutically interesting compounds bearing this functional motif.

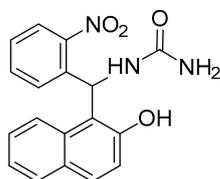
Naphthalene compounds are known to exhibit diverse biological activities. They possess anti-inflammatory [11], antibacterial [12–14], cardiovascular [15], antiproliferative [16], and antiviral [17] properties. A pharmaceutically interesting class of substances is the 1-amidoalkyl-2-naphthols, which possess the important 1,3-aminoxygenated moiety in their molecular structures, as well as an amide linkage, along with a naphthalene ring (Figure 1).



**Figure 1.** General structure of 1-amidoalkyl-2-naphthols.

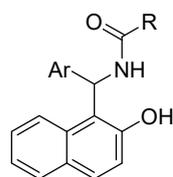


Another study by Manavi et al., revealed the in vitro anti-*Helicobacter pylori* activities of various amidoalkyl naphthols [20]. The obtained results illustrated that many of them show promising potency with compound **11** (Figure 4) being the most active against this bacteria.

**11**

**Figure 4.** Promising anti-*Helicobacter pylori* agent from the amidoalkyl naphthol class.

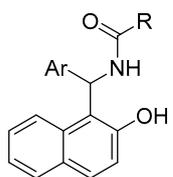
Rahimizadeh et al., used different benzaldehydes and long-chain amide derivatives to prepare a number of amidoalkyl naphthols, and examined their antibacterial properties in vitro [21]. The results indicated that compounds **12–18** (Figure 5) were the most potent against *Staphylococcus aureus*, exhibiting better activity than the reference, gentamicin.

**12-18**

- 12**, Ar=C<sub>6</sub>H<sub>5</sub>, R=C<sub>3</sub>H<sub>7</sub>
- 13**, Ar=C<sub>6</sub>H<sub>5</sub>, R=C<sub>4</sub>H<sub>9</sub>
- 14**, Ar=4-ClC<sub>6</sub>H<sub>4</sub>, R=C<sub>4</sub>H<sub>9</sub>
- 15**, Ar=3-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, R=C<sub>5</sub>H<sub>11</sub>
- 16**, Ar=4-ClC<sub>6</sub>H<sub>4</sub>, R=C<sub>9</sub>H<sub>19</sub>
- 17**, Ar=4-ClC<sub>6</sub>H<sub>4</sub>, R=C<sub>11</sub>H<sub>23</sub>
- 18**, Ar=3-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, R=C<sub>15</sub>H<sub>31</sub>

**Figure 5.** Amidoalkyl naphthols potent against *Staphylococcus aureus*.

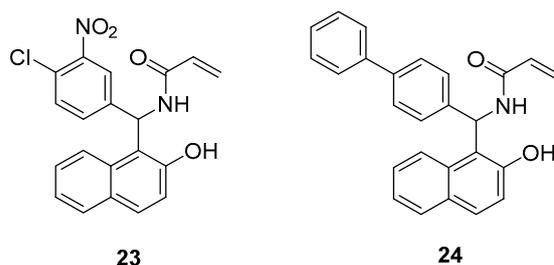
Rode and co-authors reported the antiparasitic activity of a series of 23 amidoalkyl naphthol derivatives [22]. As a result of an in vitro screening against *Leishmania donovani*, followed by a molecular docking study and an in silico study of the ADME (absorption, distribution, metabolism, and excretion) properties of the molecules, four of them (compounds **19–22**, Figure 6) were distinguished as the most promising anti-leishmanial agents possessing good drug-like characteristics.

**19-22**

- 19**, Ar=4-ClC<sub>6</sub>H<sub>4</sub>, R=CH<sub>3</sub>
- 20**, Ar=4-FC<sub>6</sub>H<sub>4</sub>, R=CH<sub>3</sub>
- 21**, Ar=4-ClC<sub>6</sub>H<sub>4</sub>, R=C<sub>6</sub>H<sub>5</sub>
- 22**, Ar=4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, R=C<sub>6</sub>H<sub>5</sub>

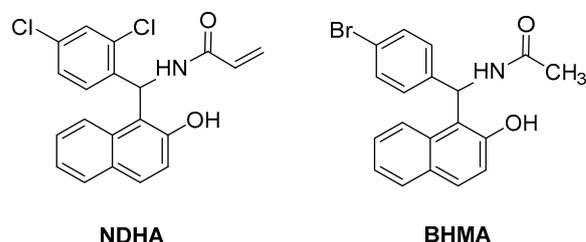
**Figure 6.** Amidoalkyl naphthols with antiparasitic properties.

Boudebous et al., synthesized 19 amidoalkyl naphthols and evaluated their cholinesterase and  $\alpha$ -glucosidase inhibitory activities [23]. The results of the in vitro assays were backed by a docking study of selected derivatives. The properties of compounds **23** and **24** (Figure 7) were found to be very promising since both substances showed better inhibition on cholinesterase than the reference drug galantamine. Derivative **24** was also the most potent one in the  $\alpha$ -glucosidase assay and exhibited a greater inhibitory effect than quercetin and acarbose, which were used as standards.



**Figure 7.** Amidoalkyl naphthols proven as potent cholinesterase and  $\alpha$ -glucosidase inhibitors.

In vitro and in silico studies by Boudebous et al., aimed to estimate the biological potential of another two amidoalkyl naphthol derivatives—**NDHA** [24] and **BHMA** [25] (Figure 8). Both compounds exhibited promising antioxidant properties, and in addition, **NDHA** was proven to be a potent acetylcholinesterase and  $\alpha$ -glucosidase inhibitor.

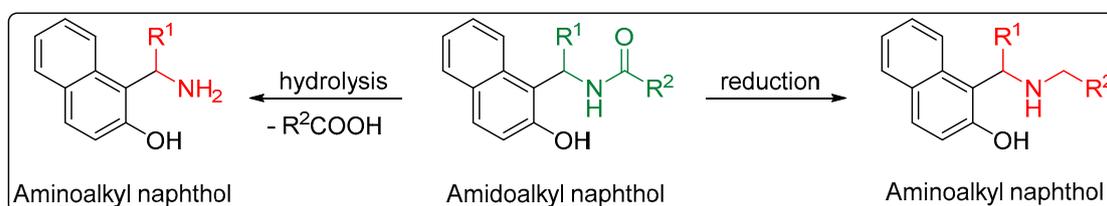


**Figure 8.** Amidoalkyl naphthols with promising antioxidant properties.

Based on the pronounced biological activities that amidoalkyl naphthols exhibit, it can be concluded that this class of compounds has the potential to become an important starting point for the pharmaceutical industry. However, more in-depth studies are needed in order to evaluate the physiological effect of these substances.

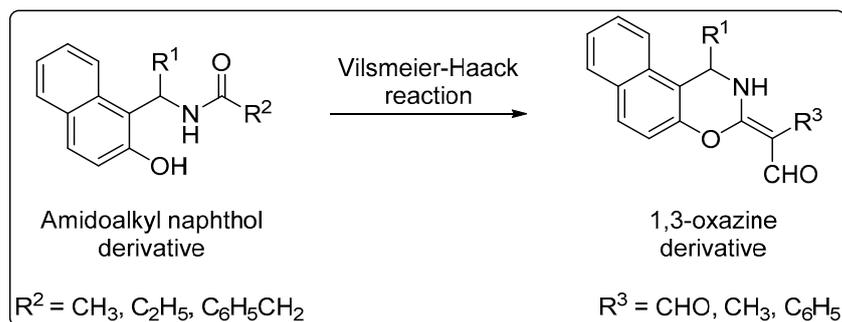
### 3. Amidoalkyl Naphthols as Building Blocks

As well as possessing interesting properties, amidoalkyl naphthols are valuable building blocks for the preparation of other bioactive molecules. They can be easily converted to aminoalkyl naphthols, the so-called *Betti* bases, via hydrolysis or reduction [23,26–29] (Scheme 1). These are of great importance because of their biological activities, such as enhancing antitumor agents' cytotoxicity [30], and hypotensive and bradycardiac effects [31]. In addition, these compounds can be used as ligands to chelate with organometallic reagents in asymmetric synthesis and catalysis [32–34].



**Scheme 1.** Hydrolysis and reduction of amidoalkyl to aminoalkyl naphthols.

Furthermore, the intramolecular cyclization of amidoalkyl naphthols produces 1,3-oxazines via the Vilsmeier–Haack reaction (Scheme 2). These compounds have also attracted interest because of their potential as antibiotics, antitumor agents, analgesics, and anticonvulsants [35].



**Scheme 2.** Intramolecular cyclization of amidoalkyl naphthols to 1,3-oxazines.

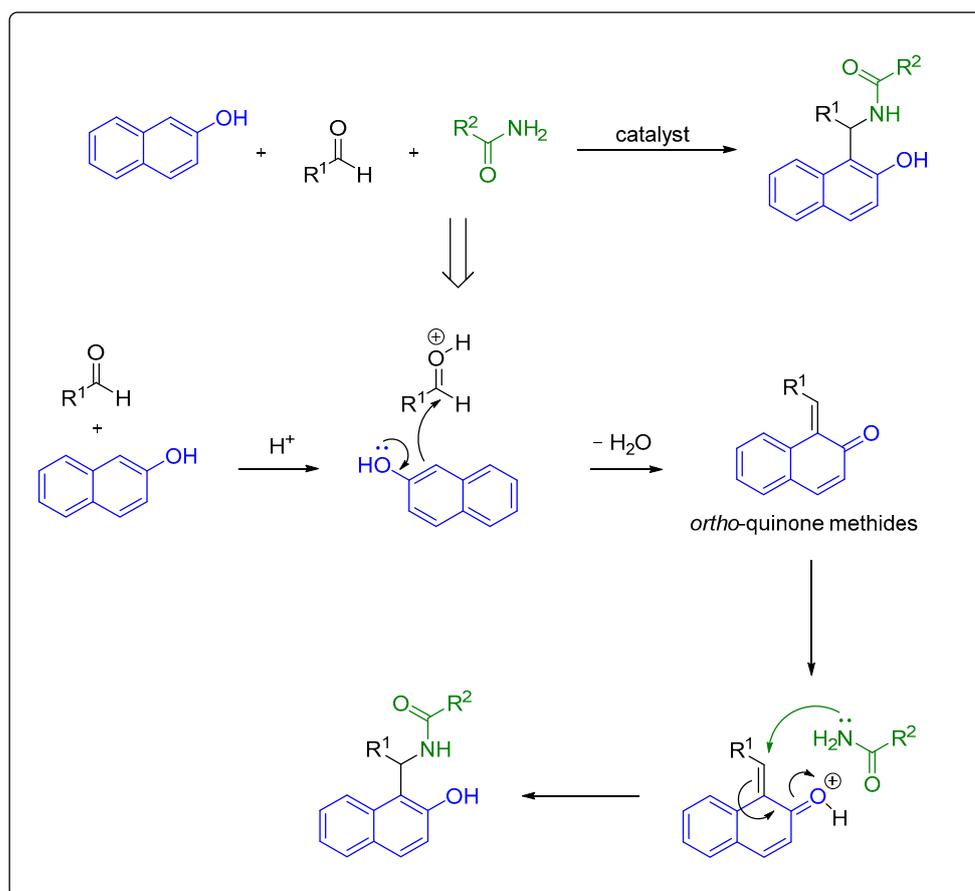
The above-mentioned considerations encouraged the extensive research in this area. Consequently, two review articles, covering the literature data until 2019, have been published [36,37]. This review is an update of the existing literature precedents and covers the reported catalytic synthetic methods for the one-pot preparation of 1-amidoalkyl-2-naphthol derivatives in the period of 2020–2022.

#### 4. Synthesis of Amidoalkyl Naphthols via Multicomponent Mannich Condensation

Although many routes to obtain similar structures including phenols and naphthols, e.g., via transition-metal catalysis, have been reported [38–41], multicomponent Mannich condensation continues to be the primary way to achieve the synthesis of amidoalkyl naphthols.

Multicomponent reactions are of increasing importance in organic synthesis for the preparation of complex and diverse molecules through the formation of carbon–carbon and carbon–heteroatom bonds. These reactions involve three or more compounds mixed simultaneously in one vessel that react with each other and give the final target product without having to isolate the intermediates. Hence, one-pot multicomponent synthesis is in accordance with the principles of green chemistry, which require the development of new substances and reaction conditions that have the potential to provide benefits to chemical synthesis to meet certain requirements regarding resource and energy efficiency, operational simplicity, and product selectivity, as well as including environmental and health protections through reducing toxic solvent use and amount of waste produced as much as possible [42–46]. An example of such a reaction is the Mannich condensation of 2-naphthol with aldehydes and amide derivatives, in the presence of a catalyst, which is used as a practical synthetic route towards 1-amidoalkyl-2-naphthols [47] (Scheme 3). The same reaction is applicable to the synthesis of 1-carbamatoalkyl-2-naphthols when carbamates are used as reaction partners [48–53]. However, the reports on the synthesis of 1-carbamatoalkyl-2-naphthols over the last 3 years are limited [54,55]. The generally accepted reaction mechanism of the acid-promoted three-component Mannich condensation of 2-naphthol with aldehydes and amides proceeds with the initial formation of highly reactive *ortho*-quinone methides. These intermediates react with an amide via nucleophilic conjugate addition to form 1-amidoalkyl-2-naphthol (Scheme 3) [56–58].

A number of different catalytic systems that effectively promote this reaction have been reported. These catalytic systems could be generally classified as homogeneous (Bronsted acids, Table 1, and ionic liquids/deep eutectic solvents, Table 2) and heterogeneous (nanomaterials and others, Table 3).



**Scheme 3.** Synthesis of amidoalkyl naphthols via multicomponent Mannich condensation and plausible mechanism.

#### 4.1. Homogeneous Catalysis

##### 4.1.1. Bronsted Acids as Catalysts

Bronsted acid catalysts play an important role in modern organic synthesis due to their ability to activate a wide range of functional groups. These catalysts are relatively easy to store and generally stable toward oxygen and water. Their metal-free nature also makes them an alternative to the metal catalysts used in the pharmaceutical industry, as traces of toxic metal impurities are often very hard to remove from the desired products [59]. In several instances this class of catalysts has been reported to promote the synthesis of amidoalkyl naphthols via multicomponent Mannich reaction (Table 1).

Boudebbois et al., developed an efficient green synthesis of 1-amidoalkyl-2-naphthol derivatives via three-component one-pot condensation of 2-naphthol with a wide range of functionalized aromatic aldehydes and acetamide/acrylamide at 120 °C under solvent-free conditions in the presence of 15 mol% phenylboronic acid as a catalyst. The synthesis of 19 amidoalkyl naphthols was achieved in 60–92% yields in the range of 1–7 h [23]. Darbandi et al., made use of 10 mol% adipic acid as a catalyst in a similar three-component condensation of 2-naphthol under solvent-free conditions and 120 °C. Yields of up to 96% for 21 amidoalkyl naphthols have been achieved in shorter reaction times that lay in the range of 9 to 76 min [60]. Another efficient solvent-free method was reported by Sadeghi and Moradi. The presence of only 8.5 mol% of the readily available natural ascorbic acid rendered a range of 13 amidoalkyl naphthols in good to high yields (75–96%) in very short reaction times of only 4–12 min. Notably, the easy work-up was stated to be one of the advantages of this method [61]. Govindhan and Nagarajan achieved the synthesis of 1-amidoalkyl-2-naphthol derivatives in the presence of 10 mol% 2,6-pyridinedicarboxylic acid (dipicolinic acid) as a reusable catalyst. High yields of up to 96% in reaction times

of a few hours were reported [62]. However, this method requires the use of refluxing toluene as a reaction medium. Rezaei-pour et al., used *p*-toluenesulfonic acid (10 mol%) for the preparation of these derivatives. The highest yields (65–91%) were obtained when polyethylene glycol 400 (PEG-400) was utilized as an environmentally friendly solvent. The reaction times varied from 20 min to 4 h [63].

**Table 1.** Summarized data on the recent homogeneous Bronsted-acid-catalyzed amidoalkyl naphthols' synthesis via multicomponent Mannich reaction (Scheme 3).

| Refs. | Type of Catalyst (mol%)                               | Reusability (Cycles) | Substituents (Number of Products)                                              | Reaction Medium | T, °C  | Reaction Time | Yield, % |
|-------|-------------------------------------------------------|----------------------|--------------------------------------------------------------------------------|-----------------|--------|---------------|----------|
| [23]  | Phenylboronic acid (15)                               | No                   | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl, Vinyl (19)                   | Solvent-free    | 120    | 1–7 h         | 60–92    |
| [60]  | Adipic acid (10)                                      | No                   | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl, Phenyl (21)                  | Solvent-free    | 120    | 9–76 min      | 83–96    |
| [61]  | Ascorbic acid (8.5)                                   | No                   | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl, Phenyl (13)                  | Solvent-free    | 100    | 4–12 min      | 75–96    |
| [62]  | 2,6-pyridinedicarboxylic acid (dipicolinic acid) (10) | Yes (3)              | R <sup>1</sup> = Propyl, Aryl<br>R <sup>2</sup> = Methyl, NH <sub>2</sub> (17) | Toluene         | reflux | 3.5–4.5 h     | 79–96    |
| [63]  | <i>p</i> -Toluenesulfonic acid (10)                   | No                   | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Aryl (12)                            | PEG-400         | 100    | 20 min–4 h    | 65–91    |

#### 4.1.2. Ionic Liquids and Deep Eutectic Solvents as Catalysts

Ionic liquids are often proposed as alternative green reaction media due to their distinctive physical and chemical characteristics, but they have since surpassed this threshold and demonstrated their significance in reaction control [64]. The same is valid for the deep eutectic solvents, with their non-toxicity, biodegradability, and easy and low-cost preparation, which gives them additional benefits as catalysts for many organic reactions [65]. The application of these catalysts to the synthesis of amidoalkyl naphthols is summarized in Table 2.

Hadadianpour and Pouramiri successfully performed a one-pot synthesis of amidoalkyl naphthols using triethylammonium hydrogen sulfate ([Et<sub>3</sub>NH][HSO<sub>4</sub>]) as a green and reusable catalyst. The reported yields, using 20 mol% of catalyst at 70 °C, varied from 65 to 85% when the reaction times were in the range of 2–25 min [66]. N,N,N',N'-tetramethylethylene-diaminium-N,N'-disulfonic acid chloride ([TMEDSA][Cl]<sub>2</sub>) has been found to be another efficient catalyst under solvent-free conditions. High yields (92–95%) of amidoalkyl naphthols were achieved within minutes using only 7.5 mol% of the catalyst at 70 °C. Notably, this method was applicable to the preparation of 1-carbamatoalkyl-2-naphthol derivatives in excellent yields [54].

Torabi et al., prepared the magnetic phosphonium ionic liquid (SO<sub>3</sub>H)(*n*-Bu)<sub>3</sub>P<sup>+</sup>FeCl<sub>4</sub><sup>−</sup> that proved efficient as a catalyst in the synthesis of one-pot amidoalkyl naphthols. High to excellent yields of a number of amidoalkyl naphthols were obtained under solvent-free conditions at 45 °C in short reaction times using only 1 mol% of the catalyst [67].

Keshtibanian et al., synthesized a novel acidic magnetic dicationic ionic liquid [C<sub>6</sub>BIM] (SO<sub>3</sub>H)<sub>2</sub> (FeBr<sub>3</sub>Cl)<sub>2</sub> and utilized it as a catalyst in a solvent-free synthesis of amidoalkyl naphthols. The authors made use of 0.1 g/1 mmol of catalyst/substrate ratio and achieved good to excellent yields in up to 20 min reaction time. However, in this case a higher temperature of 100 °C was required [68].

Tetradentate acidic catalyst (tetrakis(N-methylimidazolium-1-ylmethyl)methane tetra(hydrogen sulfate)) was shown to exhibit high catalytic activity in the synthesis of amidoalkyl naphthols under solvent-free conditions. Only 1.25 mol% of the catalyst was sufficient to promote the reaction at 90 °C, and this rendered excellent yields of 90–96% in very short reaction times (3–15 min) [69].

Manavi et al., utilized triethanolammonium acetate ionic liquid as a green and reusable catalyst for solvent-free synthesis of a series of compounds, using 2-naphthol, (hetero)aromatic aldehydes, and urea/acetamide at 90 °C. Although relatively high catalyst loading of 20 mol% was required, the authors successfully prepared the targeted derivatives in moderate to high yields of 76 to 91% in up to 85 min reaction times. Furthermore, the synthesized products were tested for in vitro anti-*Helicobacter pylori* activity and it was found that they exhibited promising potency [20].

Numerous amidoalkyl naphthol derivatives have been synthesized by Rode et al., using 10 mol% prolinium dihydrogen phosphate as a green catalyst under solvent-free conditions at 120 °C. The synthesis of the remarkable number of 23 derivatives has been achieved in 79–92% yield. However, the recyclability of this catalytic system was not revealed. All of the obtained compounds were screened for their anti-leishmanial activity against *L. donovoni*. Four of the prepared molecules showed good bioactivity and were further subjected to a molecular docking study. Furthermore, the in silico study of the ADME (absorption, distribution, metabolism, and excretion) properties of the synthesized compounds showed good drug-like characteristics [22].

A green method for the synthesis of amidoalkyl naphthols that utilizes 20 mol% [CholineCl][ZnCl<sub>2</sub>] deep eutectic solvent as a recyclable catalyst was reported. Moderate to high yields of 45–95% were achieved [70].

Nakhate and colleagues successfully prepared a series of amidoalkyl naphthols in water as a green solvent. In this work, 81 to 96% yields in 1–2.5 h were achieved using 10 mol% quaternary ammonium compound cetrimonium bromide as a catalyst at 100 °C [71].

**Table 2.** Summarized data on the recent synthesis of amidoalkyl naphthols via multicomponent Mannich reaction, catalyzed by homogeneous ionic liquids and deep eutectic solvents (Scheme 3).

| Refs. | Type of Catalyst (mol%)                                                                                  | Reusability (Cycles) | Substituents (Number of Products)                                                              | Reaction Medium | T, °C | Reaction Time | Yield, % |
|-------|----------------------------------------------------------------------------------------------------------|----------------------|------------------------------------------------------------------------------------------------|-----------------|-------|---------------|----------|
| [66]  | [Et <sub>3</sub> NH][HSO <sub>4</sub> ] (20)                                                             | Yes (3)              | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl, NH <sub>2</sub> (12)                         | Solvent-free    | 70    | 2–25 min      | 65–85    |
| [54]  | Tetramethylethylene diaminium disulfonic acid chloride (7.5)                                             | No                   | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Alkoxy, Alkyl, Aryl (13)                             | Solvent-free    | 70    | 15–25 min     | 92–95    |
| [67]  | (SO <sub>3</sub> H)( <i>tert</i> -Bu) <sub>3</sub> P <sup>+</sup> FeCl <sub>4</sub> <sup>−</sup> (1)     | No                   | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl, Phenyl (17)                                  | Solvent-free    | 45    | 5–30 min      | 75–94    |
| [68]  | [C <sub>6</sub> BIM] (SO <sub>3</sub> H) <sub>2</sub> (FeBr <sub>3</sub> Cl) <sub>2</sub> (0.1 g/1 mmol) | Yes (4)              | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl, Phenyl (12)                                  | Solvent-free    | 100   | 10–20 min     | 84–90    |
| [69]  | Tetrakis(N-methylimidazolium-1-ylmethyl)methane tetra(hydrogen sulfate) (1.25)                           | No                   | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl (10)                                          | Solvent-free    | 90    | 3–15 min      | 90–96    |
| [20]  | Triethanolammonium acetate ionic liquid (20)                                                             | Yes (4)              | R <sup>1</sup> = Aryl, Heteroaryl<br>R <sup>2</sup> = Methyl, NH <sub>2</sub> (>10)            | Solvent-free    | 90    | 40–85 min     | 76–91    |
| [22]  | Prolinium dihydrogen phosphate (10)                                                                      | No                   | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl, Phenyl (23)                                  | Solvent-free    | 120   | 2 h           | 70–92    |
| [70]  | [CholineCl][ZnCl <sub>2</sub> ] <sub>3</sub> (20)                                                        | Yes (3)              | R <sup>1</sup> = Aryl, Furyl, Propyl, Cyclohexyl<br>R <sup>2</sup> = Phenyl, Chloromethyl (16) | Solvent-free    | 60    | 40–80 min     | 45–95    |
| [71]  | Cetrimonium bromide (10)                                                                                 | No                   | R <sup>1</sup> = Aryl, Heteroaryl<br>R <sup>2</sup> = Methyl, Phenyl, NH <sub>2</sub> (24)     | Water           | 100   | 1–2.5 h       | 81–96    |

## 4.2. Heterogeneous Catalysis

### 4.2.1. Nanomaterials as Catalysts

Nanocatalysts are a rapidly emerging field of research. They find numerous applications in catalytic reactions due to their large surface area, easy separation, and reusability [72]. A large number of nanocatalysts have been reported to efficiently catalyze the

formation of amidoalkyl naphthols via multicomponent Mannich reaction. The recent literature precedents are summarized in Table 3, Refs. [73–92].

A nanostructured cobalt-containing complex was successfully employed as a catalyst under solvent-free conditions. Excellent yields of 85–95% were achieved in the presence of 5 mol% of the catalyst. However, the recyclability of this catalyst was not revealed [73].

Two magnetic-nanoparticle-supported 2-(((4-(1-iminoethyl)phenyl)imino)methyl) phenols, namely Cu(II) and Zn(II) complexes, represented another class of reusable catalysts for the multicomponent synthesis of amidoalkyl naphthols. Yields of up to 97% have been achieved under solvent-free conditions in 0.1 g/1 mmol catalyst/substrate ratio [74].

A series of amidoalkyl naphthols was prepared by Hakimi et al., via a reaction of 2-naphthol, various aldehydes, and amides in the presence of nickel nanoparticles as a catalyst under solvent-free conditions at 100 °C. The reported yields ranged from 35 to 95% and the reaction times were between 12 and 40 min [75].

Phosphotungstic acid supported on functionalized graphene oxide nanosheets (GO-SiC<sub>3</sub>-NH<sub>3</sub>-H<sub>2</sub>PW) exhibited good catalytic activity and recyclability in a catalyst/substrate ratio of only 0.03 g/1 mmol. The reactions were carried out in refluxing ethanol and rendered 80 to 94% yields in 10–20 min [76].

Rohaniyan and colleagues also prepared functionalized graphene oxide nanosheets containing a phosphomolybdc counterion. In contrast with the previous work, this catalyst operated under solvent-free conditions and shorter reaction times (2–10 min), while maintaining a similar level of recyclability [77]. Another example of a recyclable graphene oxide catalyst for the preparation of amidoalkyl naphthols was that reported by Rostami et al., [78], in which graphene oxide was simultaneously functionalized with 2-aminobenzothiazole and phosphoric acid. This method provided several advantages such as short reaction times (15–35 min), solvent-free conditions, simple work-up, and high yields (86–97%). The stability and recoverability of the catalyst were also examined in five cycles which showed no considerable loss of activity.

Several Fe<sub>3</sub>O<sub>4</sub>-based nanocatalysts have been shown to exhibit good catalytic activity towards the synthesis of amidoalkyl naphthols under solvent-free conditions. In all instances the amidoalkyl naphthols were isolated in good to excellent yields in short reaction times. Notably, this class of catalysts exhibited a very good level of recyclability [21,79–84]. Furthermore, the biological activity of some of the obtained products was examined against *Staphylococcus aureus* and *Escherichia coli*. Seven of the synthesized compounds showed better activity against *S. aureus* than the standard (gentamicin) [21].

Baghernejad and Ashoori used tin(IV) oxide nanoparticles (nano-SnO<sub>2</sub>) as a reusable catalyst for the preparation of several derivatives in refluxing aqueous medium. The targeted amidoalkyl naphthols were isolated in high yields (90–96%) within minutes using only 0.02 g/1 mmol catalysts/substrate ratio [85].

Sulfonic acid implemented on a silica-coated cobalt ferrite core was applied as a recyclable catalyst for the preparation of amidoalkyl naphthols under solvent-free conditions at 80 °C. The use of 0.05 g/1 mmol catalyst/substrate ratio rendered good to excellent yields in 10–20 min [86].

Mazraati et al., explored bis(benzoyl acetone ethylene diimine) complex of nickel(II) supported on magnetite silica nanoparticles as a catalyst under solvent-free conditions. Although relatively long reaction times (3.5–4 h) were required compared with other classes of nanocatalysts, the authors achieved the synthesis of 11 amidoalkyl naphthols in very good yields using only 1.5 mol% of catalyst [87].

A reusable bifunctional SBA-amino-amido-carboxylic acid rendered 12 amidoalkyl naphthols in high yields (85–91%) in a very short reaction time (10 min). However, this catalyst required the use of refluxing ethanol as a reaction medium [88]. CdCl<sub>2</sub>-containing filamentous silica nanoparticles [89] and CuFe<sub>2</sub>O<sub>4</sub>/KCC-1/PMA [90] also provided access to very high yields of a similar scope to amidoalkyl naphthols. In comparison with the bifunctional SBA-amino-amido-carboxylic acid, these catalysts operated under solvent-free conditions and lower catalyst loadings.

Mansouri and co-workers made use of phenyltetrazolethiol-based Ni complex as a recyclable heterogeneous nanocatalyst. The synthesis of 10 amidoalkyl naphthols in 74–93% yields was achieved using a catalyst/substrate ratio of only 0.01 g/1 mmol [91]. The same number of amidoalkyl naphthols was prepared in the presence of a pine-cone-derived nanocatalyst. Very high yields of 90–96% were achieved in 20–30 min [92].

#### 4.2.2. Other Types of Heterogeneous Catalysts

The application of other heterogeneous catalysts to the multicomponent Mannich reaction leading to the formation of amidoalkyl naphthols is summarized in Table 3, Refs. [93–96].

A procedure for the synthesis of amidoalkyl naphthols using a biodegradable and reusable polymeric catalyst, chitosan-SO<sub>3</sub>H (CTSA), was developed by Patil and colleagues. Their method operates under solvent-free conditions at 80 °C using a 0.02 g/1 mmol catalyst/substrate ratio and renders high yields in short reaction times [93]. Similar results have been reported for natural hydroxyapatite derived from waste bovine bone and further loaded with zinc chloride. Notably, the remarkable number of 22 amidoalkyl naphthols have been prepared [94]. Perci et al. reported the synthesis of a series of pyrazole-containing amidoalkyl naphthols by using silica-supported sodium hydrogen sulfate (NaHSO<sub>4</sub>·SiO<sub>2</sub>). Although in some instances the targeted amidoalkyl naphthols were obtained in very high yields, this method requires longer reaction times and the use of acetic acid as a solvent [95]. Dipake et al. prepared a zeolite catalyst, zirconium silicate, and utilized it for the preparation of amidoalkyl naphthols. Excellent yields have been obtained; however, this catalyst operates at higher temperature and catalyst loading [96].

**Table 3.** Summarized data on the recent heterogeneously catalyzed synthesis of amidoalkyl naphthols via multicomponent Mannich reaction (Scheme 3).

| Refs. | Type of Catalyst (Catalyst/Substrate Ratio)                                                                   | Reusability (Cycles) | Substituents (Number of Products)                                                            | Reaction Medium | T, °C  | Reaction Time | Yield, % |
|-------|---------------------------------------------------------------------------------------------------------------|----------------------|----------------------------------------------------------------------------------------------|-----------------|--------|---------------|----------|
| [73]  | <b>Nanomaterials</b><br>Nano-Co-[4-chlorophenyl-salicylaldehyde-methylpyranopyrazole]Cl <sub>2</sub> (5 mol%) | No                   | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl (15)                                        | Solvent-free    | 100    | 5–15 min      | 85–95    |
| [74]  | Nanoparticle-supported 2-((4-(1-iminoethyl)phenyl)imino)methylphenol Cu(II) or Zn(II) complex (0.1 g/1 mmol)  | Yes (4)              | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl, Chloromethyl, Phenyl, NH <sub>2</sub> (22) | Solvent-free    | 80     | 40–100 min    | 73–97    |
| [75]  | Nickel nanoparticles (6 mg/1 mmol)                                                                            | Yes (not reported)   | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl (15)                                        | Solvent-free    | 100    | 12–40 min     | 35–95    |
| [76]  | Phosphotungstic acid supported on functionalized graphene oxide nanosheets (0.03 g/1 mmol)                    | Yes (5)              | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl (10)                                        | Ethanol         | reflux | 10–20 min     | 80–94    |
| [77]  | Phosphomolybdic acid supported on functionalized graphene oxide nanosheets (3.33 mol%)                        | Yes (5)              | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl (11)                                        | Solvent-free    | 100    | 2–10 min      | 80–94    |
| [78]  | Graphene oxide functionalized with 2-aminobenzothiazole and phosphoric acid (0.02 g/1 mmol)                   | Yes (5)              | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl, NH <sub>2</sub> (15)                       | Solvent-free    | 70     | 15–35 min     | 86–97    |
| [21]  | Sulfonic acid functionalized silica-coated Fe <sub>3</sub> O <sub>4</sub> -nanoparticles (0.34 mol%)          | Yes (6)              | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Alkyl (17)                                         | Solvent-free    | 120    | 15 min–8 h    | 80–96    |

Table 3. Cont.

|               |                                                                                                                     |                    |                                                                                              |              |        |           |        |
|---------------|---------------------------------------------------------------------------------------------------------------------|--------------------|----------------------------------------------------------------------------------------------|--------------|--------|-----------|--------|
| [79]          | Nano-Fe <sub>3</sub> O <sub>4</sub> @TiO <sub>2</sub> -Pr-2AB@Cu (0.02 g/1 mmol)                                    | Yes (7)            | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl, Phenyl, NH <sub>2</sub> (12)               | Solvent-free | 80     | 15–25 min | 89–94  |
| [80]          | Fe <sub>3</sub> O <sub>4</sub> @enamine-B(OSO <sub>3</sub> H) <sub>2</sub> (0.015 g/1 mmol)                         | Yes (6)            | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl, Phenyl, NH <sub>2</sub> (18)               | Solvent-free | 90     | 10–40 min | 84–96  |
| [81]          | Dodecylbenzenesulfonic acid supported on Fe <sub>3</sub> O <sub>4</sub> -nanoparticles (0.15 g/1 mmol)              | Yes (5)            | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl, Phenyl, NH <sub>2</sub> (15)               | Solvent-free | 80     | 10–15 min | 88–92  |
| [82]          | Nano-[Fe <sub>3</sub> O <sub>4</sub> @SiO <sub>2</sub> @RNHMe <sub>2</sub> ][HSO <sub>4</sub> ] (0.048 g/1 mmol)    | Yes (3)            | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl, Phenyl (14)                                | Solvent-free | 90     | 15–35 min | 89–97  |
| [83]          | Pistachio-peel-derived magnetic nanoparticles (Fe <sub>3</sub> O <sub>4</sub> @C-SO <sub>3</sub> H) (0.04 g/1 mmol) | Yes (6)            | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl, Phenyl, NH <sub>2</sub> (12)               | Solvent-free | 70     | 15–40 min | 90–100 |
| [84]          | Nano-Fe <sub>3</sub> O <sub>4</sub> -hexamine (0.04 g/1 mmol)                                                       | Yes (7)            | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl, Phenyl, NH <sub>2</sub> (10)               | Solvent-free | 60     | 5–20 min  | 92–96  |
| [85]          | Nano-SnO <sub>2</sub> (0.02 g/1 mmol)                                                                               | Yes (5)            | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl (7)                                         | Water        | reflux | 15–60 min | 90–96  |
| [86]          | Sulfonic acid on silica-coated cobalt ferrite nanoparticles (0.05 g/1 mmol)                                         | Yes (10)           | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl (7)                                         | Solvent-free | 80     | 10–20 min | 84–96  |
| [87]          | Bis(benzoyl acetone ethylene diimine) complex of nickel(II) supported on magnetite silica nanoparticles (1.5 mol%)  | Yes (5)            | R <sup>1</sup> = Aryl, Hexyl<br>R <sup>2</sup> = Methyl, Phenyl, NH <sub>2</sub> (11)        | Solvent-free | 100    | 3.5–4 h   | 86–95  |
| [88]          | SBA-amino-amido-carboxylic acid (0.05 g/1 mmol)                                                                     | Yes (5)            | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl (12)                                        | Ethanol      | reflux | 10 min    | 85–91  |
| [89]          | KCC-1/ECH-Meg/CdCl <sub>2</sub> (0.025 g/1 mmol)                                                                    | Yes (5)            | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl, Phenyl (12)                                | Solvent-free | 100    | 3–10 min  | 85–98  |
| [90]          | CuFe <sub>2</sub> O <sub>4</sub> /KCC-1/PMA (0.03 g/1 mmol)                                                         | Yes (5)            | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl, Phenyl (12)                                | Solvent-free | 80     | 2–13 min  | 82–95  |
| [91]          | Phenyltetraazolethiol-based nickel complex (0.01 g/1 mmol)                                                          | Yes (7)            | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl, Phenyl (10)                                | Solvent-free | 75     | 1–25 min  | 74–93  |
| [92]          | Pine-cone-derived carbon-based acid nanocatalyst (0.05 g/1 mmol)                                                    | Yes (4)            | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl, Chloromethyl, Phenyl, NH <sub>2</sub> (10) | Solvent-free | 80     | 20–30 min | 90–96  |
| <b>Others</b> |                                                                                                                     |                    |                                                                                              |              |        |           |        |
| [93]          | Sulfonated chitosan (0.02 g/1 mmol)                                                                                 | Yes (5)            | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl (11)                                        | Solvent-free | 80     | 8–25 min  | 85–94  |
| [94]          | Hydroxyapatite loaded with zinc chloride (0.05 g/1 mmol)                                                            | Yes (5)            | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl, Phenyl, NH <sub>2</sub> (22)               | Solvent-free | 80     | 25–40 min | 86–96  |
| [95]          | NaHSO <sub>4</sub> .SiO <sub>2</sub> (0.002 g/1 mmol)                                                               | Yes (not reported) | R <sup>1</sup> = Pyrazolyl<br>R <sup>2</sup> = Methyl (10)                                   | Acetic acid  | 80     | 4–6 h     | 70–92  |
| [96]          | Zirconium silicate (0.05 g/1 mmol)                                                                                  | Yes (5)            | R <sup>1</sup> = Aryl<br>R <sup>2</sup> = Methyl, Phenyl (12)                                | Solvent-free | 110    | 30–40 min | 92–95  |

It can be seen (Table 1) that when a Bronsted acid is applied as a catalyst the reaction times are relatively long. In most cases, between 1 and 7 h are needed for the reaction to finish. The exception is ascorbic acid, with the use of which the products were obtained quite quickly (within 10 min) [61]. Furthermore, only one of the catalysts (dipicolinic acid) was recycled and reused [62]. Despite these drawbacks, the products' yields were good to excellent. The advantages of ionic liquids/deep eutectic solvents (Table 2) as catalysts are short reaction times, the possibility of recycling and reusing some of them, and obtaining the target compounds in good to excellent yields. The only drawback that

could be noted about these catalysts is they are not commercially available and must be prepared beforehand.

Almost all of the heterogeneous catalysts (Table 3) were easy to remove from the reaction mixture (separated by an external magnetic field or simple filtration) and could be involved in other reaction cycles which demonstrated their reusability. This advantage, as well as the short reaction times (typically below 1 h and in many cases within a few minutes) and the high yields of the products, make nanomaterials a preferable choice as catalysts for the synthesis of amidoalkyl naphthols. Like ionic liquids/deep eutectic solvents, this type of catalysts are not commercially available and they must be prepared in-house.

## 5. Conclusions

Undoubtedly, 1-amidoalkyl-2-naphthols are endowed with great biological potential. Therefore, it comes no surprise that a lot of effort has been dedicated to their synthesis using the Mannich reaction. Notwithstanding the numerous attempts to achieve this transformation under homogeneous conditions, the use of heterogeneous catalysts proved superior in terms of green chemistry metrics. In several instances under solvent-free conditions, very high yields in a time scale of minutes have been achieved in the presence of nanocatalysts. Notable, this class of catalysts exhibits excellent recyclability for up to 10 cycles. As a note, future research should be more interdisciplinary and focused on biological evaluation of the synthesized amidoalkyl naphthols because of their promising bioactivities and structural similarities to some natural products and marketed drugs.

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