Abstract: The role of glycerol as a green bio-based solvent, reactant, and/or a catalyst in the synthesis of novel heterocycles, under pressure, is studied. Synthesis of novel quinolines in good yields using a new modified Skraup synthesis, utilizing glycerol and pressure Q-tubes, is demonstrated. Novel aniline trimers are prepared using glycerol, and substituted anilines under pressure, in acidic medium and water. Glycerol was employed as a catalyst and a green solvent in the synthesis of novel pyridazines 13a–c. The mechanisms of the reactions and the catalytic effect of glycerol in protic and aprotic media are fully discussed. The structures of the synthesized compounds were determined via X-ray crystallography and spectroscopic methods.

Keywords: glycerol; green chemistry; modified Skraup’s quinoline synthesis; reactions under pressure; Q-tubes; polyaniline

1. Introduction

Glycerol was first isolated by the Swedish chemist: Carl W. Scheele, in 1779, upon treatment of olive oil with lead oxide [1,2]. Glycerol or propane-1,2,3-triol 1 is now produced in large quantities as a byproduct in many industries [3–5]. The large-scale production of biodiesel from fats, where glycerol is a waste product, has made glycerol a highly economic solvent and reactant [6–12]. This has attracted many researchers in the last two decades to find routes for converting this surplus into value added products [13–24]. Some of glycerol’s utilities in chemical industries are summarized in Scheme 1.

Since glycerol is highly hygroscopic and stable at high temperatures (B.P. = 290 °C), in addition to being environmentally friendly, nontoxic, nonvolatile, inflammable, non-corrosive, cheap, biodegradable, and recyclable, it could be considered a green medium and solvent in organic synthesis [25–27]. According to Arrhenius, the reaction rate doubles for every 10 °C rise in temperature [28]. Thus, glycerol would simply decrease the time of many reactions that take place in other low boiling-point solvents. Recently, Hamid et al. discussed the catalytic effect of glycerol by H-bond formation, which facilitates addition and condensation processes [29]. Glycerol has not yet been fully explored in the field of organic synthesis and catalysis. However, some studies have suggested that glycerol is a medium in “catalyst-free” reactions [30–32]. We think that these studies have neglected the possibility that glycerol itself acts as a catalyst in such reactions.

One of the oldest utilities of glycerol in organic chemistry is the synthesis of quinolines in poor yields, known as the “Skraup synthesis of quinolines” [33,34]. Skraup’s synthesis of quinolines has many limitations other than the low yield, including the multi-step addition of the reactants, in which
glycerol must first react with H$_2$SO$_4$ to yield the hazardous acrolein (propenal), which is followed by
the addition of the aromatic amine to form hydroquinoline that is converted to the quinoline by
adding an oxidizing agent as the final step (cf. Scheme 2).
formation of a thick tar, from which quinoline is difficult to extract are also among the problems of the Skraup synthesis. These limitations have urged researchers to attempt to modify the synthetic route, to increase the yield of the quinoline synthesis reactions, and to make it “greener.” The new modified synthesis of quinolines or “green recipes” [36] involve using green solvents or even solvent-less reactions, one-pot synthesis, new green catalysts alongside with new technologies such as microwave energy, ultrasonication, and grinding [37–49].

There is now a boom in the use of high pressure in science [50], and reactions under high pressure and/or temperature proved to behave in a different manner than those under normal thermal conditions [51,52]. The newly invented borosilicate tubes known as Q-tubes have allowed the performance of difficult or otherwise impossible chemical reactions in chemical laboratories [53–56]. Shifts in transition state along a reaction coordinate, a switch of the rate-determining step, and the possible transformation of a transition state into a stable minimum, are among the possible phenomena that can occur for reactions under pressure, especially in fluids [57]. A supercritical solvent is a solvent that is subjected to a temperature and pressure higher than those of its critical point. However, when both the temperature and/or the pressure are lower than those of the critical point, and the temperature is higher than that of the boiling point, with a pressure higher than 1 bar, a subcritical solvent is obtained. A subcritical solvent can be defined as a hot compressed solvent and, according to Galy et al., glycerol produces different products in subcritical and supercritical solvents [58]. In this study, we combined glycerol and water as green, efficient solvents, in addition to the pressure in Q-tubes, to modify the synthesis of quinolines and prepare new aniline trimers and pyridazines.

2. Results and Discussion

We initially started our work with the synthesis of quinolines. Quinolines are extremely important in the pharmaceutical industry, especially in the treatment of malaria and cancer [59–61]. Fluoroquinolones are used in many pharmaceutical compounds, especially in fluoroquinolone antibiotics, such as ciprofloxacin (Cipro), gemifloxacin (Factive), levofloxacin (Levaquin), moxifloxacin (Avelox), norfloxacin (Noroxin), and ofloxacin (Floxin) [62,63].

Selivanova et al. found that reacting polyfluoro-2-naphthylamines with glycerol in H2SO4 or CF3SO3H at 150–160 °C gives, surprisingly, the respective polyfluorobenzo[fl]quinolones, rather than the expected cyclization at the unsubstituted ortho-position [39]. We thought of investigating this phenomenon as well as modifying the Skraup quinoline synthesis using pressure Q-tubes, and studying the effect of glycerol in subcritical and supercritical solvents. Unlike the results reported by Selivanova et al., the reaction of 1 and 3a–b in the presence of conc. H2SO4, under pressure in a Q-tube at 200 °C proceeded to yield quinolines 6a and 6b, in 58% and 60% yield, respectively. To our knowledge, quinoline 6b has not been previously isolated (cf. Scheme 3).

Recently, Saggadi and co-workers synthesized 5-substituted, 6-substituted, 7-substituted, and 8-substituted quinolines using microwave conditions, aniline derivatives, and glycerol in the presence of sulfuric acid and water. The desired quinolines were obtained in 10%–66% yields [64]. Surprisingly, in our hands, the reaction of aromatic amines, glycerol, sulfuric acid, and water in pressurized conditions afforded a compound with an m/z value of 359.23, which was, after other spectroscopic investigations, assigned to 4,4′,4″-(propane-1,2,3-triyl)tris(2-methylaniline) 7. The 1H NMR spectrum of compound 7 shows a singlet at δ = 2.00 ppm for 9H that is assigned to 3-CH3 protons, a multiplet at δ = 3.34 ppm for 5H of 2 methylene and 1 methine protons, and another singlet at δ = 5.01 ppm for 6H assigned for the 3 NH2 protons as well as a multiplet at δ = 7.13 for aromatic 6 protons. The 13C-NMR spectrum of compound 7 shows a signal at δ = 146.53 assigned for 3C-NH2 at δ = 16.24 for 2CH2 and at δ = 16.95 for 3CH3. Conversely, when the unsubstituted aniline 3a was reacted under the same conditions, with glycerol and water under pressure (subcritical water), the aniline trimer 8 was the only product obtained. The structure of compound 8 was also confirmed via spectroscopic analysis. The mass spectrum of the reaction product 8 showed a molecular ion peak: m/z = 365.173 (100%). The 1H NMR spectrum revealed a singlet at δ = 2.4 ppm, integrated for 6H, which was assigned to the
3NH₂ protons. Two doublets at δ = 3.27 ppm and 3.29 ppm for two aliphatic CH₂ groups and multiplet at δ = 3.35 ppm were assigned for the methine CH proton and another multiplet at 6.94 ppm were assigned for the aromatic protons. The ¹³C-NMR spectral results were in agreement with the proposed structure, which showed a signal at δ = 63.09 ppm, assigned to the 2-O-CH₂ carbons, as well as another signal at δ = 72.49 ppm, assigned to the O-CH carbon. It is worth mentioning that trials to use 3f as the starting aniline produced a compound with an m/z value of 410.5, for which we could not assign any reasonable, suggested structure. Table 1 summarizes our results and reaction conditions of the reactions of glycerol with aromatic amines under pressure.

Scheme 3. Reaction of aromatic amines, glycerol, and sulfuric acid in the presence/absence of water, under a high pressure, and high temperatures in the Q-tubes.

Table 1. Variation of the nature of aniline products depending on the reaction conditions in the presence and absence of H₂O, starting from glycerol 1 under a high pressure, and high temperatures in the Q-tubes.

| Entry | R₁ | R₂ | R₃ | Reaction Conditions | Product | Yield% | MP (°C) | m/z |
|-------|----|----|----|---------------------|--------|-------|--------|-----|
| 3a    | H  | H  | H  | H₂SO₄/H₂O, Q-tube, 160°C | glycerol | 60    | 200 | BP = 238 |
| 3a    | H  | H  | H  | glycerol + H₂O, Q-tube, 200°C | 6a      | 15    | 160 | 58  | 359.23 |
| 3b    | F  | F  | H  | H₂SO₄/H₂O, Q-tube, 160°C | glycerol | 60    | 200 | 60  | 365.17 |
| 3c    | CH₃| I  | H  | H₂SO₄/H₂O, Q-tube, 200°C | glycerol | 15    | 160 | 7   | 359.23 |
| 3d    | CH₃| Br | H  | H₂SO₄/H₂O, Q-tube, 200°C | glycerol | 20    | 160 | 7   | 359.23 |
| 3e    | CH₃| Cl | H  | H₂SO₄/H₂O, Q-tube, 200°C | glycerol | 20    | 160 | 7   | 359.23 |
| 3f    | H  | H  | Cl | glycerol + H₂O, Q-tube, 200°C | not      | 30    | 160 | concluded  | 410 |

While acrolein is a minor product of the dehydration of glycerol under neutral hydrothermal conditions, it becomes the main product when an acid catalyst is added, but at temperatures above...
340 °C using conventional heating [58]. Under pressure, we could achieve the same results but at much lower temperatures. Thus, using Q-tubes and heating at only 200 °C for 1 h, we could prepare quinolines in high yields. Recently, the catalytic role of glycerol via H-bond was published by Hamid and coworkers [29]. We think that, in our work, the reaction proceeds via a typical Skraup reaction mechanism, but with glycerol having a dual role where one mol of glycerol acts as a starting material reacting with H₂SO₄ to produce acrolein 2, and another mol of glycerol acts as a catalyst and binds via H-bond with acrolein to generate complex 9. This then undergoes a Michael addition with the aromatic amines (3a, b). This is followed by the release of glycerol once more to produce the intermediate 4a, b that then cyclizes to 6a and 6b, respectively. Scheme 4 shows a suggested reaction mechanism for the formation of quinoline 6a, b. In our reaction conditions, there were no need to add any oxidizing agents since we believe that concentrated H₂SO₄ acts as a condensation agent and an oxidant.

A member of our group investigated the x-ray structure of compound 6b, which confirmed the suggested structure, and no loss of fluorine atoms occurred under our reaction conditions [65] (Cf. Figure 1). The preliminary inspection of the X-ray crystallographic data of 6(b) indicated that the molecules exist in aggregates, via intermolecular H-bonding between Fluorine at C-8 and the hydrogen at C-8, as well as between N-1 and H at C-4 (Cf. Figure 2). A detailed discussion of the x-ray structure of these quinolines will be reported separately after exploring this phenomenon with other compounds.
Subsequently, we shifted to utilizing glycerol in the synthesis of pyridazines. The pyridazine ring is an important structural feature in a number of pharmaceutical compounds, such as hydralazine (brand name Apresoline, vasodilator, US, FDA), cefozopran (anti-bacterial agent, Japan), and pipofezine (brand name Azafen or Azaphen, antidepressant, STADA, Nizhny Novgorod, Russia). Pyridazine derivatives have been reported to possess various pharmacological activities and intermediates for drugs synthesis, including antimicrobial, analgesic, anticancer, antitubercular, antidiabetic, antifungal, antihypertensive, anticonvulsant, anti-HIV, antiasthma, anti-inflammatory, phosphodiesterase (PDE) inhibitors, cyclooxygenase (COX) inhibitors, antipyretic, insecticidal, and neurological [66–73]. The reaction of arylazo 10d and ethylacetoacetate 11b in either acetic acid or ethanolic KOH, followed by reflux to afford pyridazinones 15d, has been reported. This reaction was limited to the formation of 12d, and was not consistently successful and Trials to form 12a failed, since malononitrile dimerized under these conditions [74,75]. In this case, we could efficiently prepare pyridazinones 13a–c in good yields, by the reaction of malononitrile 11a, phenylhydrazono esters 10a–c, and glycerol, either
under conventional heating at 250 °C for 5 h, or under pressure in the Q-tubes at 150 °C for 30 min (cf. Scheme 5).

\[
\begin{align*}
\text{13a–c} & \\
\text{Scheme 5. Synthesis of 4-oxo-1-phenyl-1,4,5,6-tetrahydropyridazine-3-carboxylate 13a–c.}
\end{align*}
\]

It was found that the yield of formation of 13a–c increased significantly under reactions caused by pressure, Table 2 summarizes our findings and compares these reaction yields.

**Table 2.** Reaction yield for 13a–c and 12d under pressure and conventional heating.

| Product | x     | y     | z     | Yield Percentage |
|---------|-------|-------|-------|------------------|
| 13a     | CN    | COOCH₂Ph | H    | 52               |
| 13b     | CN    | COOEt  | CN   | 64               |
| 13c     | COOEt | COOEt  | H    | 70               |
| 12d     | CN    | H      | CH₃  | 86.16            |

We assume that glycerol acts as a catalyst and a bio-based solvent. The catalytic activity of glycerol in this reaction might be via H-bond formation with the N-atom in compound 11, to form the intermediate 14. The H-bond formation facilitates the Michael-type addition of the active methylene of the arylazo 10 on the even more electron-poor CN carbon forming the protonated imine 15. It is suggested that another mole of glycerol coordinates with protonated imines 15, followed by an intramolecular cyclization and glycerol is released again to the medium, which affords the 4-oxo-1-phenyl-1,4,5,6-tetrahydropyridazine-3-carboxylate 13a–c. Scheme 6 shows our suggested mechanism for the formation of 13a–c.
The structures of compounds 13a–c were confirmed by spectroscopic analysis. Compound 13a had an m/z value of 362.53. The $^1$H NMR spectrum of 13a revealed two multiplets for the prochiral CH$_2$-CN at $\delta = 1.28$ and 1.31 ppm. A two multiplets for the prochiral ring methylene protons COCH$_2$ appears at $\delta = 2.39$ and 2.49 ppm. A singlet at $\delta = 4.30$ ppm is assigned for two methylene protons, a multiplet at $\delta = 7.10$ ppm for the aromatic 10H, and two singlets for the four NH$_2$ protons at $\delta = 11.56$ ppm and 14.22 ppm, respectively. The $^{13}$C-NMR spectrum of compound 13a showed a signal at $\delta = 196.8$ ppm significant for a true carbonyl, assigned to the pyridazine ring carbonyl, and showed another signal at $\delta = 163.4$ ppm for the ester carbonyl. The CH$_2$CN methylene carbon appears at $\delta = 25.9$ ppm. Figure 3 indicates the most important $^{13}$C-NMR signals for 13a.
3. Materials and Methods

3.1. General

Q-tube assisted reactions were performed in a Q-tube safe pressure reactor from Q Labtech (East Lyme, CT 06333, New London County, CT, USA, equipped with a cap/sleeve, pressure adapter (120 psi), needle adapter/needle, borosilicate glass tube, Teflon septum, and catch bottle. All reactions were monitored by using TLC with 1:1 ethyl acetate-petroleum ether as eluent and were carried out until starting materials were completely consumed. Melting points are reported uncorrected and were determined with a Sanyo (Gallenkamp, Osaka, Japan). 1H NMR and 13C-NMR spectra were done at the Analab Kuwait University and determined by using a Bruker DPX instrument at 600 MHz for 1H-NMR and 150 MHz for 13C-NMR and either CDCl3 or DMSO-d6 solutions with TMS as internal standards. Chemical shifts are reported in δ (ppm). Mass spectra and accurate mass measurements were made using a GCMS DFS spectrometer (Thermo, Bremen, Germany) with the EI (70 EV) mode. X-ray crystallographic structure determinations were performed by using Rapid II (Rigaku, Tokyo, Japan) and X8 Prospector (Bruker, Karlsruhe, Germany) single crystal X-ray diffractometers.

3.2. General Procedures for Q-Tube-Assisted Synthesis of Quinolines 6a,b

Glycerol 1 (5 mL), concentrated sulfuric acid (1 mL), and 0.01 mol of the corresponding aniline (0.93 g 3a or 1.29 g of 3b) were sequentially added in a 35 mL Q-tube pressure tube, furnished by Q Labtech. A Teflon septum was placed on top of the tube, and an appropriate cap was used. The mixture was heated in an oil bath at 200 °C for about 60 min. The mixture was cooled and poured into ice-water. The solid was collected by filtration and purified by column chromatography and crystallized from ethanol.

3.3. 6,8-Difloroquinoline 6b

Yellow crystals, yield 60%, mp > 250 °C, 1H-NMR (DMSO-d6, 600 MHz): δ = 7.62–7.70 (3H, m, H-3, H-5, H-7), 8.38 (1H, m, H-4), 8.90 (1H, t, H-2). 13C-NMR (150 MHz, DMSO-d6): δ = 105.12, 107.13, 123.37, 129.23, 135.04, 150.16, 156.90, 157.75, 158.61, 159.38. El-HRMS: m/z for C9H5F2N, calcd. 165.0390, found: 165.0384.

3.4. General Procedure to Aniline Trimers 7 and 8

A 35 mL Q-tube pressure tube, furnished by Q Labtech was charged with aniline derivative 3c-e (10 mmol) (2.23 g of 3c, 1.86 g of 3d, 1.41 g of 3e), 5 mL glycerol, 3 mL H2SO4, and 10 mL of water. A Teflon septum was placed on top of the tube, and an appropriate cap was used. The mixture was heated in an oil bath at 160 °C for 15 min. After cooling at room temperature, pH was adjusted at 8–9 by adding NaOH and the reaction mixture was extracted with ethyl acetate (2×20 mL). The combined
organic layers were dried over MgSO₄ and were then filtered and evaporated under reduced pressure. The crude residue was purified by column chromatograph (cyclohexane–EtOAc) on silica gel yielding the corresponding quinoline.

3.4.1. 4,4′,4″-(propane-1,2,3-triyl)tris(2-methylaniline) 7

Yellow crystals yield 75%. mp 178–180 °C. ¹H-NMR (DMSO-d₆, 600 MHz) : δ = 2.00 (9H, s, 3-CH₃), 3.34 (5H, m, 2CH₂ and CH aliphatic), 5.01 (6H, s, 3NH₂), 6.42 (3H, d, Ar-H), 7.13–7.20 (6H, m, Ar-H), 13C-NMR (150 MHz, DMSO-d₆): δ = 16.95 (3CH₃), 74.0 (CH-aliphatic), 76.24 (2CH₂-aliphatic), 116.27 (3 ortho-C), 124.21 (3C-CH₂), 134.63 (6 meta-C), 137.55 (3 para-C), 146.53 (3C-NH₂). EI-HRMS: m/z for C₂₄H₂₀N₃, calcd. 359.2361, found: 359.2362.

3.4.2. 4-(2-(4-aminophenoxy)-3-(4-aminophenoxy))aniline 8

Brown crystals, yield 72%. mp 240 °C. ¹H-NMR (DMSO-d₆, 600 MHz): δ = 2.49 (6H, s, 3NH₂), 3.27 (2H, d, J = 6 Hz, CH₂), 3.39 (2H, d, J = 6 Hz, CH₂). 3.5 (1H, m, CH), 6.94–7.26 (14H, m, Ar-H). 13C-NMR (150 MHz, DMSO-d₆): δ = 63.09 (2C, CH₂), 72.49 (CH), 118.57 (3C, C-NH₂), 122.01 (2C-O), 129.32 (12C, Ar-C), 140.07 (C-O), EI-HRMS: m/z for C₂₁H₂₃N₃O₃; calcd. 365.1739; found: 365.1736.

3.5. General Procedure for Syntheses of 13a–c

3.5.1. Method A: Conventional Heating

A mixture of 0.01 mol of the appropriate azo compound 10a–c (10a, 2.96 g, 10b, 2.59 g, 10c, 2.34 g) is added to 11a (0.66 g, 0.01 mol) in glycerol (5 mL). The reaction mixture was refluxed for 3–5 h (followed until completion by TLC using 1:1 ethyl acetate–petroleum ether as an eluent). The mixture was cooled and then was poured onto ice-water. The solid, so formed, was collected by filtration and recrystallized from EtOH.

3.5.2. Method B: Q-Tube Assisted Reactions

A 35 mL Q-tube pressure tube, furnished by Q Labtech was charged with 0.01 mol of the appropriate azo compound 10a–c (–), 2.96 g, 10b, 2.59 g, 10c, 2.34 g) – 0.66 g of 11a and 5mL glycerol. A Teflon septum was placed on top of the tube, and an appropriate cap was used. The mixture was heated at 150 °C for 30 min followed until completion by TLC using 1:1 ethyl acetate–petroleum ether as an eluent. The mixture was cooled and then was poured onto ice-water. The solid, so formed, was collected by filtration and recrystallized from EtOH.

3.6. Benzyl 6-amino-6-(cyanomethyl)-4-oxo-1-phenyl-1,4,5,6-tetrahydropyridazine-3-carboxylate 13a

Yellow crystals, yield 52% (method A), 76% (method B); mp >340 °C. ¹H-NMR (DMSO-d₆, 600 MHz): δ = 1.28,1.31 (2H, m, CH₂), 2.39,2.49 (2H, CH₂, m), 4.30 (2H, s, CH₂), 7.10–7.53 (10H, m, 2-Ph), 11.56, 14.22 (2H, 2s, NH₂). 13C-NMR (150 MHz, DMSO-d₆): δ = 196.8 (C=O), 164.5 (C=O), 163.0 (N-C-Ar), 142.8 (N=C), 132.0 (2C-Ar), 131.2 (3C-Ar), 129.8 (2C-Ar), 125.8 (2C-Ar), 116.6 (CN), 115.6 (2C-Ar), 72.9 (C-NH₂), 60.8 (CH₂-O), 30.8 (CH₂), 25.9 (CH₂). HRMS: m/z (EI) for C₂₀H₁₈N₄O₃, calcd. 362.1379, found: MS: m/z (%) = 362.53 (M⁺).

3.7. Ethyl-6-amino-5-cyano-6-(cyanomethyl)-4-oxo-1-phenyl-1,4,5,6-tetrahydropyridazine-3-carboxylate 13b

Red crystals, yield 64% (method A), 88% (method B); mp 256–258 °C, IR (KBr): 3425 (NH), 2202 (CN), 1620 (CO) cm⁻¹. ¹H-NMR (DMSO-d₆, 600 MHz): δ = 1.04 (3H,t, CH₃), 1.05 (2H,m, CH₂), 2.03 (1H,s, CH), 3.33 (2H,s, CH₂), 4.32 (2H,m, CH₂), 7.27–7.64 (5H, m, H=Ph). 13C-NMR (150 MHz, DMSO-d₆): δ = 13.90 (CH₃), 24.0 (C-CN), 26.69 (CH₂), 61.23 (C-O), 66.0 (C-NH₂), 115.90 (2C; 2CN), 119.21 (2C-Ar), 123.87 (C-Ar), 128.88 (2C-Ar), 129.51 (C=N), 138.34 (3Ar), 160.97 (2C=O). MS (EI): m/z = 326.0 (M⁺). HRMS: m/z (EI) for C₁₆H₁₅N₅O₃, calcd. 325.1175, found: MS: m/z (%) = 326.0 (M⁺).
3.8. Ethyl-6-amino-6-(2-ethoxy-2-oxoethyl)-4-oxo-1-phenyl-1,4,5,6-tetrahydropyridazine-3-carboxylate 13c

Brown crystals, yield 70% (method A), 92% (method B), m.p. 266–268 °C, IR (KBr): 3439 (NH), 2222 (CN), 1670 (CO) cm\(^{-1}\), 1H-NMR (DMSO-\(d_6\), 600 MHz): \(\delta = 1.20\) (3H,t, CH\(_3\)), 1.40 (3H,t, CH\(_3\)), 2.50 (2H,s, CH\(_2\)), 3.36 (2H,s, CH\(_2\)), 4.10 (2H,m, CH\(_2\)), 4.35 (2H,m, CH\(_2\)), 7.07-7.55 (5H, m, H-Ph), 10.29 (1H, s, NH). 13C-NMR (150 MHz, DMSO-\(d_6\)): \(\delta = 8.37\) (2C- CH\(_3\)), 62.59 (CH\(_2\)), 63.06 (CH\(_2\)), 66.24 (CH\(_2\)-O), 68.81 (CH\(_2\)-O), 72.48 (C-NH\(_2\)), 114.96 (C-Ar), 116.15 (CN), 116.30 (C-Ar), 123.62 (C-Ar), 129.05 (C-Ar), 129.62 (C-Ar), 130.16 (C=N), 142.42 (C=O), 161.72 (C=O), 196.22 (C=O). HRMS: m/z (EI) for C\(_{17}\)H\(_{21}\)N\(_3\)O\(_5\): 347.1481, found: MS: m/z (%) = 347.1 (M\(^+\)).

4. Conclusions

In this study, we combined glycerol and water as green, efficient solvents, in addition to pressure in Q-tubes, to modify the synthesis of quinolines and prepare new aniline trimers and pyridazines. Glycerol was efficiently employed either as a catalyst or a reactant and green bio-based solvent in the synthesis of novel quinolines, aniline trimers, and pyridazines. The dual use of glycerol along with reactions under pressure proved its efficiency as a green method for synthesis of quinolines as reactions products were obtained in higher yields, shorter time, and without any oxidizing agents. Reactions of anilines, sulphuric acid, water, and glycerol under pressure allowed for the synthesis of unexpected novel aniline trimers. Lastly, glycerol also proved to be an efficient medium/catalyst for synthesis of novel pyridazines in very good yields under pressure. Future perspectives for this work are various since our techniques should open the appetite of researchers to extend this work for the synthesis of azoles, azines, and other polyanilines.

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**Sample Availability:** Samples of the compounds 22a–c are available from the authors.