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# Parallel Synthesis of Structurally Diverse Heterocycle Compounds using Microwave Assisted Three Component Reaction †

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**Abstract:** Among biologically active compounds, heterocyclic macromolecules are of considerable importance. They offer a new approach to drug discovery by enabling the development of simple and efficient methods for the synthesis of compounds containing a variety of those structures. In addition, they play an important role in the design of pharmaceutical products. Those containing nitrogen, sulphur and oxygen have attracted the interest of medicinal chemists due to their innumerable biological applications. In previous work, our group studied the synthesis of heterocycle macromolecules substituted with a carbohydrate moiety via microwave assisted three-component reaction (MCR). Taking into account these results, we present here a proposal for the "one pot" generation of heterocycle compounds using ethanol, water or benzene in order to study how they would modify the products and yields of the MCR. This study not only extends previous work on the scope of substrates, but also provides further insight into the chemistry of such drug scaffolds. All compounds were characterized by GC-MS, NMR techniques, and X-Ray diffraction studies.

**Keywords:** 1,4-thioazepan-3-ones; 4-thiazolidinones; 1,3-oxathiolan-5-ones

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## 1. Introduction

Small heterocyclic systems, both natural and synthetic, have provided a wide variety of biological activities that proved to be relevant for medicinal chemistry [1]. In addition, they behave as synthetic cores of great relevance since they allow the insertion of functionalities in their chemical structures.

1,3-oxathiolan-5-one and its derivatives are attractive compounds, not only because of their broad biological activities, but also because of their implications as intermediates in the synthesis of highly useful pharmaceuticals [2].

On the other hand, the 1,4-thiazepine ring is an important residue that contains nitrogen and sulfur and exhibits various pharmacological properties such as antitumor [3], antimicrobial [4], insecticidal [5], and anti-inflammatory [6].

In view of the importance of these compounds and our continuing efforts to synthesize carbohydrate-bound heterocyclic macromolecules with potential bioactivities, we present here the parallel synthesis via microwave assisted three-component reaction of some different heterocyclic structures.

## 2. Results and Discussion

As mentioned above, our research group have previously explored the synthesis of 1,3-thiazolidin-4-ones [7]. In order to generate a new battery of 4-thiazolidinones, we proposed to use different nitrogenous heteroaromatic amines and substituted anilines.

Thus, the MCR under microwave conditions was studied using 3-amino-5-methylpyrazole (3a) and 3 amino-1,2,4-triazole (3b) and water, benzene or ethanol as different solvents, in order to determine the influence of them in the products and/or the efficiency of the reaction. Unexpected new heteroaromatic rings of great synthetic and biological interest were obtained under the same reaction conditions (Figure 1). Interestingly, some of these heterocycles (5 and 7) were not observed in our previously work and considering their biological activities their synthesis became another objective of this work. The results obtained are summarized in Table 1.

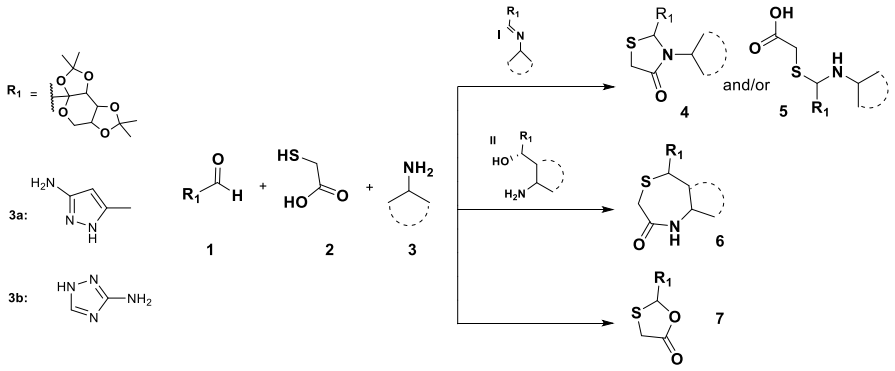



**Figure 1.** Three component assisted microwave reaction using amines **3a** and **3b** under different solvent conditions (Microwave conditions: 300 W/120 °C/30 min).

**Table 1.** Solvent effect on the synthesis of macroheterocycle compounds using amines **3a** and **3b**.

| Entry | Amine | Solvent | Product Yield (%) [a] | | | |
|---|---|---|---|---|---|---|
| | | | **4** | **5** | **6** | **7** |
| **1** | **3a** | Benzene | 87 | - | 0 | 12 |
| **2** | | Ethanol | 0 | - | 98 | 2 |
| **3** | | Water | 0 | - | 17 | 56 |
| **4** | **3b** | Bezene | 63 | - | - | 32 |
| **5** | | Ethanol | - | 52 | - | 8 |
| **6** | | Water | - | 92 | - | 8 |

[a] Determined by GC-MS analysis of crude reaction through a standard curve generated from isolated product.

As can be seen in entries **1** and **4**, using benzene as the reaction solvent the expected 4-thiazolidinones (**4a** and **4b**) are generated in good yields, leaving traces of imine (**I**) unreacted. In addition, 1,3-oxathiolan-5-one (**7**) is formed as a reaction by-product in low yields in all cases.

When the reaction is carried out in ethanol, using amine 3-amino-5-methylpyrazole (**3a)** the formation of 1,4-thioazepan-3-one (**6a**, entry 2) is observed and traces of product **7** are detected. In contrast, under the same reaction conditions but using 3 amino-1,2,4-triazole (**3b**, entry 5), product **5b** is generated in a 52% yield as the majority reaction product and only 8% of 1,3-oxathiolan-5-one (**7**) is observed together with intermediate imine (**I**) that remained unreacted (40%).

Finally, using water as reaction solvent, in the presence of amine **3a** (entry 3), 1,4-thioazepan-3-ones (**6a**) are obtained in low yields (17%) and 1,3-oxathiolan-5-one (**7**) was the main product (56%), also 27% of the unreacted type **II** intermediate was detected.

When the reaction is carried out with amine **3b** (entry 6), the main product is **5b** (92%). In addition, 8% of 1,3-oxathiolan-5-one (**7**) is observed without evidence of reaction intermediates.

Based on the results obtained and taking into account the new synthesized heterocyclic compounds (Figure 2), some interesting observations can be made.

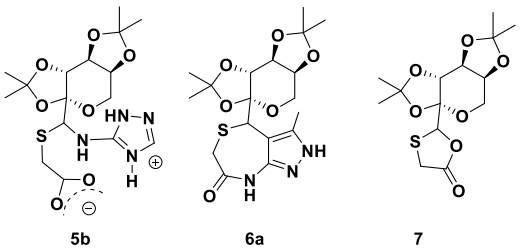



**Figure 2.** New heterocyclic compounds synthetized in this work.

The presence of the same reaction intermediate (I: *entries 1, 4* and *5*) suggests that the generation of type 4 and 5 products occurs through the same mechanism. The nature of the amine and the type of reaction solvent are responsible for the generation of one of the products with respect to the other.

Considering entries 1 and 4, where benzene is used and taking into account the proposal made by Bolognese and co-workers [8] (p 2811), the thiazolidinone formation mechanism could be hypothesized as a concerted soft–soft reaction [9]. Since the opening of the thiazolidine ring and the formation of type 5 products are reversible processes, thiazolidinones 4a and 4b are formed in an irreversible dehydration step that is the driving force for this reaction (Figure 3).

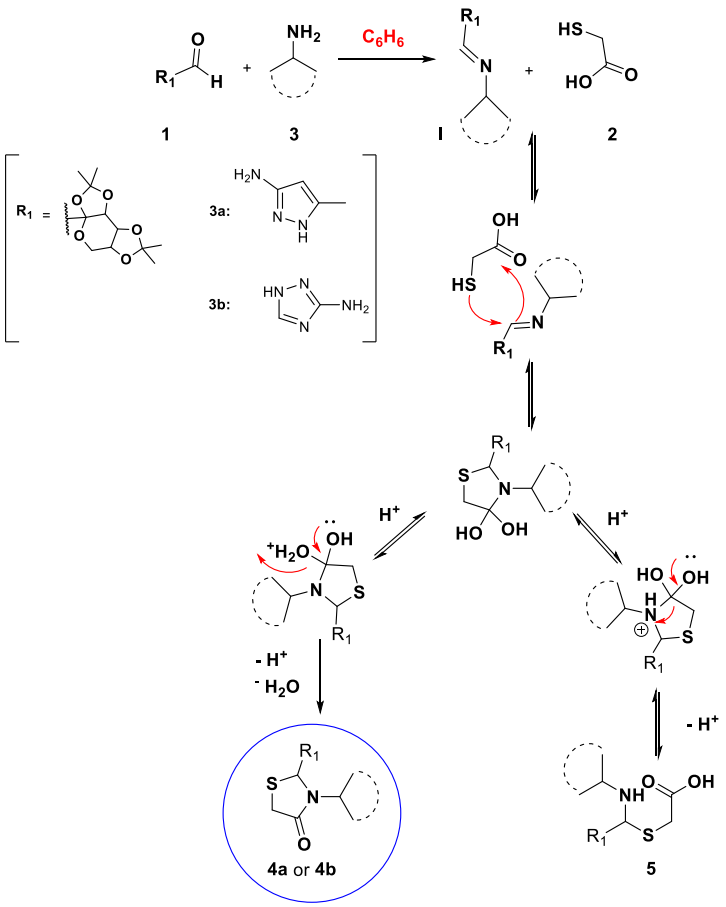


**Figure 3.** Hypothesized formation mechanism of the 4-thiazolidinones 4a and 4b and product 5 in benzene.

Since benzene is an aprotic solvent, the proton activity is free. The reaction proceeds through the generation of the type **I** intermediate to form the corresponding 4-thiazolidinones **4a** and **4b** as the major product.

On the other hand, there is evidence of a clear tendency for protic solvents to generate type **5** or **6** products in parallel to the 1,3-oxathiolan-5-one (**7**), depending on the nature of the amine. When amine **3a** is used, products of type **6** and **7** are obtained in proportions that vary according to the protic solvent used. With amine **3b**, the reaction produces type **5** products in high yields and 8% of the 1,3-oxathiolan-5-one (**7**) in both water and ethanol.

Since **5b** is the first product to form in the reaction of amine **3b** in EtOH and $H_2O$, one possible explanation could be that the thiol group attacks the imine bond and the proton moves from sulfur to the negatively charged nitrogen (Figure 4). Looking at the structure of **5b**, it could be said that the presence of a hydrogen bond between the NH hydrogen of the triazole ring and the carbonyl oxygen of the carboxylic group helps to stabilize the structure.

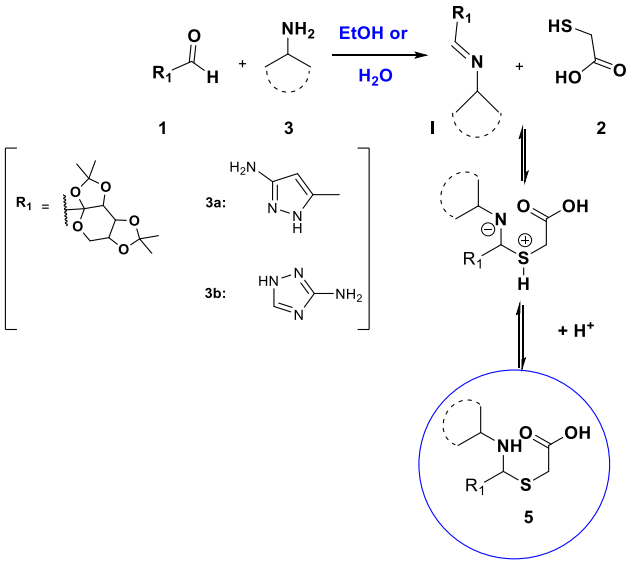
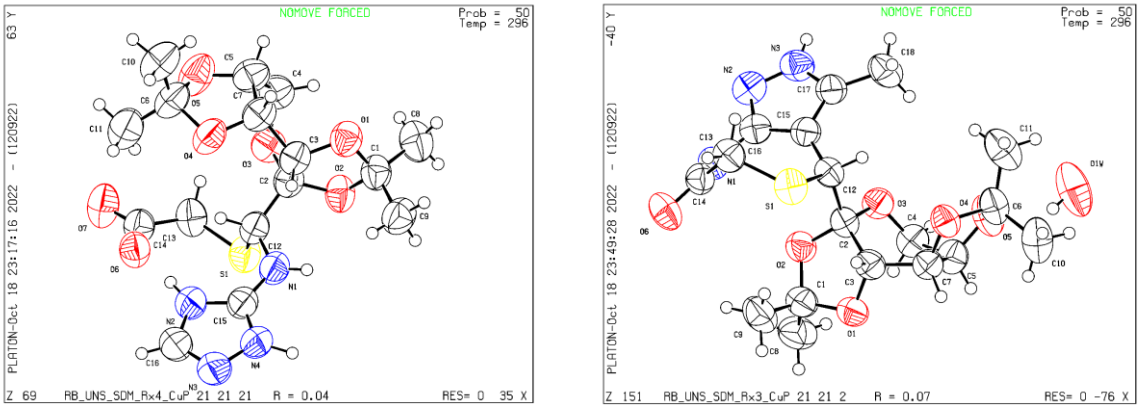



**Figure 4.** Hypothesized formation mechanism of the 5b product in ethanol and water.

All products were characterized by $^{1}H$ NMR, $^{13}C$ NMR spectra and GC-MS data. The structure of **5b** and **6a** was also established by X-ray crystallographic analysis (Figure 5) Compounds **4a** and **4b** were reported in previous studies by our research group [10].




(**5b**) (**6a**)

**Figure 5.** ORTEP diagram of (**5b**) and (**6a**).

It should be noted that there is a delicate electronic effect on the chemoselectivity in these reactions. In search of the extent of the reaction with respect to glycosidic aldehyde 2,3:4,5-di-*O*-isopropylidene-*β*-*D*-arabino-hexos-2-ulo-2,6-pyranose (**1**), various aromatic amines with electron donor groups such as *p*-methoxy (**3f**) or *p*-methyl (**3e**) and electron withdrawing groups such as *p*-chloro (**3d**) or *p*-nitro (**3c**), were reacted under microwave conditions. The results indicate that the substituted anilines only gave the corresponding 4-thiazolidinones (**4c–4f**) and the 1,3-oxathiolan-5-one (**7**¸ Table 2).

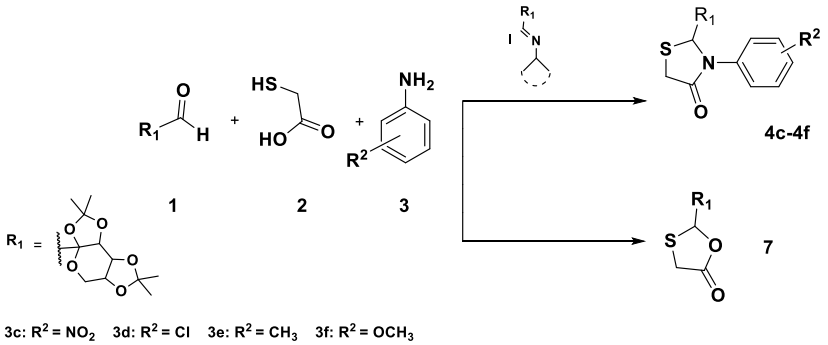



**Figure 6.** Proposed intermediate **I** using substituted anilines **3c–3f** of the tricomponent assisted microwave reaction (Microwave conditions: 100 W/110 °C/10 min).

**Table 2.** Solvent effect on the synthesis of macroheterocycle compounds using substituted anilines **3c–3f**.

| Entry | Amine | Solvent | Intermediate Yield (%) [a] | Product yield (%) [a] | |
|---|---|---|---|---|---|
| | | | **I** | **4** | **7** |
| **1** | **3c** | Benzene | 43 | 37 | 20 |
| **2** | | Ethanol | 66 | 4 | 23 |
| **3** | **3d** | Benzene | 20 | 75 | 5 |
| **4** | | Ethanol | 27 | 53 | 16 |
| **5** | **3e** | Benzene | 17 | 79 | 3 |
| **6** | | Ethanol | 5 | 70 | 25 |
| **7** | **3f** | Benzene | 3 | 92 | 5 |
| **8** | | Ethanol | 10 | 70 | 20 |

[a] Determined by CG-MS analysis of crude reaction through a standard curve generated from isolated product.

In all cases, the use of benzene as reaction solvent favors the formation of type **4** rings (entries 1, 3, 5 and 7). The yields increases together with nucleophilic nature of the substituted anilines (**3f** > **3e** > **3d** > **3c**). Besides, the proportion of intermediate **I** that remains unreacted decreases. Product **7** appears in low yields in all cases. In particular, with amine **3c** (entry 2) using the same irradiation conditions with ethanol as solvent, a large amount of unreacted reaction intermediate is observed and the main product is the 1,3-oxathiolan-5-one (**7**). With the rest of the anilines (entries 4, 6 and 8) the trend is similar to that observed in benzene with a slight increase in the yield of product **7** to the detriment of **4**. The presence of 1,3-oxathiolane-5-one (**7**) in the reaction mixture could suggest that imine **I** is unstable under the reaction conditions and that the formation of this product is a highly favored reaction but lowering the yield of the thiazolidinones (**4**). Also, as the nucleophilic character of the aniline decreases, the reaction between thioglycolic acid with the aldehyde is favored.

## 3. Conclusions

We have developed a strategy for the parallel synthesis of interesting bioactive macroheterocycle compounds, specially the 5-((((2,2-di(l1-oxidanyl)ethyl)thio)((3aS,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis ([1,3]dioxolo) [4,5-b:4′,5′-d]pyran-3a-yl)methyl)amino)-1H-1,2,4-triazol-4-ium (**5b**); the 3-methyl-4-((3aS,5aS,8aS,8bR) -2,2,7,7- tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4′,5′-d]pyran-3a-yl)-2,8-dihydro-4H-pyrazolo [3,4-e][1,4]thiazepin-7(6H)- one (**6a**) and the 2-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-phenylthiazolidin-4-one (**7**) under different solvents. Thus, this methodology provided a convenient route for the assembly of various useful five- and seven- membered heterocyclic units and also for the construction of C-S and C-N bond-forming reactions.

With both heteroaromatic amines (**3a** and **3b**) and substituted anilines (**3c**–**3f**), benzene appears to be the solvent of choice for the generation of 4-thiazolidinones (**4**). Regarding the use of protic solvents in this type of reactions, it seems that the electronic effect of amines on chemoselectivity is quite sophisticated and a broader and deeper study is required to achieve a complete understanding of it.

Given the few bibliographical references found for the generation of 1,4-thioazepan-3-ones; open ring 4-thiazolidinones and 1,3-oxathiolan-5-ones, it is extremely important to continue the studies to broaden the knowledge in their synthesis.

## 4. Materials and Methods

### *4.1. General Information*

Microwave reactions were performed with a microwave oven (CEM Discover®) with a continuous focused microwave power delivery system in a pressure glass vessel (10 mL) sealed with a septum under magnetic stirring. The reaction mixture temperature was monitored using a calibrated infrared temperature control under the reaction vessel, and control of the pressure was performed with a pressure sensor connected to the septum of the vessel. Thin layer chromatography was performed on Merck precoated silica gel 60 F254 plates and visualization was accomplished with UV light and/or 5% ethanol solution of phosphomolibdic acid. Mass spectra were obtained with a GC/MS instrument (HP5-MS capillary column, 30 m/0.25 mm/0.25 mm) equipped with 5972 mass selective detector operating at 70 eV (EI). NMR spectra were recorded in $CDCl_3$ or DMSO-$_{d6}$ on a Bruker ARX 300 Multinuclear instrument (300.1 MHz for 1H and 75.5 MHz for 13C) at 23 °C.

*4.2. Microwave Reactions*

**Method A**: A mixture of 2,3:4,5-di-*O*-isopropylidene-β-D-arabino-hexos-2-ulo-2,6-pyranose (**1**, 0.26 g, 1mmol), mercaptoacetic acid (2, 0.07 mL, 1mmol), 1 mL of different solvents (EtOH, $H_2O$ or $C_6H_6$) and different heteroaromatic amines (3a-b, 1mmol) were heated in the microwave apparatus at 300 W and 120 °C during 30 min. The reaction was monitored by TLC and analyzed by GC-MS and $^1$H-NMR. The crude reaction product is rotavaporated, taken up in ethyl acetate and washed twice with water. It was then dried with a drying agent, and the organic phase was vacuum filtered. The corresponding products were purified by recrystallization from EtOH (for 5b) or Acetone (for 6a). The structure of the pure compounds was determined by $^1$H, $^{13}$C and DEPT NMR spectroscopy and X-ray crystallography.

**Method B**: A mixture of 2,3:4,5-di-O-isopropylidene-β-D-arabino-hexos-2-ulo-2,6-pyranose (1, 0.26 g, 1mmol), mercaptoacetic acid (2, 0.07 mL, 1mmol), 1.5 mL of different solvents (EtOH or $C_6H_6$) and different different substituted anilines (3c–f, 1mmol) were heated in the microwave apparatus at 100 W and 110°C. The reaction was monitored by TLC every 10 min and was left 10 min as total reaction time. The crude reaction product is rotavaporated, taken up in ethyl acetate and washed twice with water. It was then dried with a drying agent, and the organic phase was vacuum filtered. Purification of the corresponding products by column chromatography using hexane-EtOAc (8:2) as eluant is still in progress.

**5-((((2,2-di(l1-oxidanyl)ethyl)thio)((3aS,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4′,5′-d]pyran-3a-yl)methyl)amino)-1H-1,2,4-triazol-4-ium (5b)**: white solid, Pf: 155–157 °C. $^1$H-NMR (300 MHz, DMSO-$d_6$): δ 7.62 (s, 1H), 4.94 (s, 1H), 4.27 (t, J3(H,H) = 7.0 Hz, 1H), 4.10 (d, J3(H,H) = 6.9 Hz, 1H), 4.04–3.92 (m, 2H), 3.90–3.82 (m, 2H), 3.61 (dd, J3(H,H) = 124, 7.0 Hz, 1H), 1.47 (s, 3H), 1.44 (s, 3H), 1.39 (s, 3H), 1.35 (s, 3H). $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 171.9, 159.8, 146.1, 109.0, 108.8, 104.1, 71.4, 70.3, 70.1, 63.8, 61.6, 33.4, 27.0, 26.2, 26.0, 24.4.

**3-methyl-4-((3aS,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4′,5′-d]pyran-3a-yl)-2, 8-dihydro-4H-pyrazolo[3,4-e][1,4]thiazepin-7(6H)-one (6a)**: white solid, Pf: 169–170 °C $^1$H-NMR (300 MHz DMSO-$d_6$): δ 12.36 (s, 1H), 9.42 (s, 1H), 4.65 (d5, J = 8 Hz, J = 2.6 Hz 1H), 4.46 (d, J= 2.6 Hz, 1H), 4.27 (s, 1H), 3.75 (dd, J= 13 Hz, J = 1.8 1H), 3.59 (d, J= 13 Hz 2H), 2.65 (dd, J= 13 Hz, J= 1.8 1H), 2.22, (s, 3H),1.55 (s, 6H), 1.41 (s, 3H), 1.34 (s, 3H). $^{13}$C-NMR (75 MHz, DMSO-$d_6$): δ 172.4, 141, 139.5, 110.6, 110.4, 107.6, 107.1, 74.4, 72.3, 71.9, 63.7, 44.8, 34.18, 29.3, 28.5, 28.26, 26.06, 12.5.

**2-((3aS,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4′,5′-d]pyran-3a-yl)-1,3-oxathiolan-5-one (7)**: light yellow solid, Pf: 159–162 °C. $^1$H-NMR (300 MHz, DMSO-$d_6$) δ 7.55–7.05 (m, 5H), 5.28 (d, J = 7.1 Hz, 1H), 4.75 (c, J = 7.0 Hz, 1H), 3.76 (dd, J = 11.5, 7.1 Hz, 2H), 3.63 (dd, J =11.5, 7.1 Hz 2H), 1.18 (s, 3H), 1.13 (s, 3H). $^{13}$C-NMR (75 MHz, DMSO-$d_6$) δ 172.2, 136.4, 129.3, 126.4, 125.4, 109.7, 74.1, 68.6, 66.3, 32.6, 25.7.

**Author Contributions:** Conceptualization, R.A.O. and S.D.M.; methodology, R.A.O. and S.D.M.; formal analysis, R.A.O. and S.D.M.; investigation, R.A.O.; S.T., F.J.L, S.D.M and R.B. resources, R.A.O, F.J.L. and S.T.; data curation, R.A.O.; writing—original draft preparation, R.A.O.; S.T., F.J.L. and S.D.M.; writing—review and editing, R.A.O.; visualization, R.A.O.; supervision, S.D.M.; project administration, R.A.O. and S.D.M.; funding acquisition, S.D.M. All authors have read and agreed to the published version of the manuscript.

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## References


1. (a) Jampilek, J. Heterocycles in medicinal chemistry. *Molecules*, **2019**, *24*, 3839. https://doi.org/10.3390/molecules24213839. (b) Younus, H.A.; Al-Rashida, M.; Hameed, A.; Uroos, M.; Salar, U.; Rana, S.; Khan, K.M. Multicomponent reactions (MCR) in medicinal chemistry: A patent review (2010–2020*). Expert Opin. Ther. Pat.* **2021**, *31*, 267–289. https://doi.org/10.1080/13543776.2021.1858797. (c) Ebenezer, O.; Jordaan, M.A.; Carena, G.; Bono, T.; Shapi, M.; Tuszynski, J.A. An Overview of the Biological Evaluation of Selected Nitrogen-Containing Heterocycle Medicinal Chemistry Compounds. *Int. J. Mol. Sci.* **2022**, *23*, 8117. https://doi.org/10.3390/ijms23158117.
2. (a) Popp, A.; Gilch, A.; Mersier, A.L.; Petersen, H.; Mechlem, J.R. Stohrer, Peculiar Reaction Chemical Reactivity Behavior of 1,3-Oxathiolane-5-one Towards Various Reagents: Assisted by Molecular Modeling Studies and in Vitro Antioxidant and Cytotoxicity Evaluation *J. Adv. Synth. Catal*. **2004**, *346*, 682. https://doi.org/10.1002/adsc.200303184. (b) Yang, L.C.; Deng, H.; Renata, H. Recent Progress and Developments in Chemoenzymatic and Biocatalytic Dynamic Kinetic Resolution. *Org. Process Res. Dev.* **2022**, *26*, 1925–1943. https://doi.org/10.1021/acs.oprd.1c00463. (c) Dewan, M.; Kumar, A.; Saxena, A.; De, A.; Mozumdar, S. Molecular iodine in [bmim][BF4]: A highly efficient green catalytic system for one-pot synthesis of 1, 3-oxathiolan-5-one. *Tetrahedron Lett.* **2010**, *51*, 6108–6110. https://doi.org/10.1016/j.tetlet.2010.09.052.
3. (a) Wang, B.; Wang, L.R.; Liu, L.L.; Wang, W.; Man, R.J.; Zheng, D.J.; Zhu, H.L. A novel series of benzothiazepine derivatives as tubulin polymerization inhibitors with anti-tumor potency. *Bioorganic Chem.* **2021**, *108*, 104585. https://doi.org/10.1016/j.bioorg.2020.104585. (b) Syrota, N.A.; Kemskiy, S.V.; Bol'but, A.V.; Chernobaev, I.I.; Liavinets, O.S.; Vovk, M.V. 4-(N-Boc-amino)-1H-1, 2, 3-triazolecarbothioamides in the synthesis of a new heterocyclic [1, 2, 3] triazolo [4, 5-e][1, 4] thiazepine system. *Chemistry of Heterocycl. Compd.* **2021**, *57*, 841–847. https://doi.org/10.24959/ophcj.22.258512. (c) Kumar, N.; Goel, N. Heterocyclic Compounds: Importance in Anticancer Drug Discovery. Anti-Cancer Agents in Medicinal Chemistry. *Former. Curr. Med. Chem. Anti Cancer Agents* **2022**, *22*, 3196–3207. https://doi.org/10.2174/1871520622666220404082648. (d) Bhabal, S.R.; Shaikh, S.F.; Yellapurkar, I.P.; Pavale, G.S.; Ramana, M. Synthesis of novel fluorinated 1, 5-benzothiazepine derivatives and their biological evaluation as anticancer and antibacterial agent. *J. Serb. Chem. Soc.* **2022**, 41. https://doi.org/10.2298/JSC210428041B.
4. (a) Mohamed Ahmed, M.S.; Farghaly, T.A. Antimicrobial activity of [1, 2, 4] triazolo [4, 3-a] pyrimidine and new pyrido [3, 2-f][1, 4] thiazepine derivatives. *Lett. Org. Chem.* **2018**, *15*, 183–190. https://doi.org/10.2174/1570178614666171010161751. (b) Saini, R.; Malladi, S.R.; Dharavath, N. Diversity-oriented One-pot Synthesis of Novel Imidazo [4′, 5′: 4, 5] benzo [e][1, 4] thiazepinones and Benzo [d] imidazolyl Thiazolidinones through pTSA Promoted Cyclization and Evaluation of Antimicrobial and Anti-inflammatory Activities. *J. Heterocycl. Chem.* **2018**, *55*, 1579–1588. https://doi.org/10.1002/jhet.3191. (c) Kadnor, V.A.; Shelke, S.N. Synthesis, antimicrobial and antimalarial activityof1, 4-benzothiazepine and pyrazolinederivatives incorporating carbazolemoiety. *Bulg. Chem. Commun.* **2019**, 234–241. https://doi.org/10.34049/bcc.51.2.4921.
5. (a) Brahmachari, G. Synthesis of biologically relevant heterocycles in aqueous media. *Asian J. Org. Chem.* **2018**, *7*, 1982–2004. https://doi.org/10.1002/ajoc.201800396. (b) Bandyopadhyay, D.; Banik, B.K. Microwave-assisted synthesis of medicinally privileged heterocycles. *Green Synth. Approaches Biol. Relev. Heterocycles* **2021**, *49*, 110. https://doi.org/10.1016/B978-0-12-820586-0.00009-1.
6. (a) Abozeid, M.A.; El-Sawi, A.A.; Abdelmoteleb, M.; Awad, H.; Abdel-Aziz, M.M.; Abdel-Rahman, A.R.H.; El-Desoky, E.S.I. Synthesis of novel naphthalene-heterocycle hybrids with potent antitumor, anti-inflammatory and antituberculosis activities. *RSC Adv.* **2020,** *10*, 42998–43009. https://doi.org/10.1039/D0RA08526J. (b) Barce Ferro, C.T.; Dos Santos, B.F.; da Silva, C.D.; Brand, G.; da Silva, B.A.L.; de Campos Domingues, N.L. Review of the syntheses and activities of some sulfur-containing drugs. *Curr. Org. Synth.* **2020**, *17*, 192–210. https://doi.org/10.2174/1570179417666200212113412.
7. (a) Ocampo, R.; Quiroga, A.; Costilla, I.; Lorenzo, F.; Calmels, J.; Villafain, D.; D'Accorso, N. Study of the effect of solvent and different Lewis acids in one pot multicomponent microwave assisted reaction for the chemoselective generation of 1.4-thiazepan-3-ones and 4-tiazolidinones. *Presented XXI ECSOC 2017*, *1*, 30. (b) Lorenzo, F.J.; Ocampo, R.A.; Mandolesi, S.D. Microwave Assisted Three Component Reaction Conditions to Obtain New Thiazolidinones with Different Heterocyclic Skeletons. *Multidiscip. Digit. Publ. Inst. Proc.* **2019**, *41*, 38. https://doi.org/10.3390/ecsoc-23-06474.
8. Bolognese, A.; Correale, G.; Manfra, M.; Lavecchia, A.; Novellino, E.; Barone, V. Thiazolidin-4-one formation. Mechanistic and synthetic aspects of the reaction of imines and mercaptoacetic acid under microwave and conventional heating. *Org. Biomol. Chem.* **2004**, *2*, 2809–2813. https://doi.org/10.1039/B405400H.
9. Fleming. *Frontier Orbitals and Organic Chemical Reactions;* John Wiley and Sons: Chichester, UK, 1976.
10. Ocampo, R.A.; Koll, L.C.; Fascio, M.; Mandolesi, S.D.; D'Accorso, N.B. Highly efficient and chemoselective synthetic route to de thiazolidinones via a microwave assisted, three component reaction. *Presented XVIII ECSOC* **2014**.