MANSOURA JOURNAL OF CHEMISTRY
Official Journal of Faculty of Science, Mansoura University, Egypt
E-mail: scimag@mans.edu.eg ISSN: 2974-4938

CONVENIENT SYNTHESIS OF SOME NEW THIAZOLIDIN-4-ONE, CHROMEN-2-IMINE AND PYRROL-2-ONE DERIVATIVES CONTAINING FURAN MOIETY

Tajdida-imhimmed Musbah, Noha S. Mohammed, and Ahmed El-Mekabaty*

Chemistry Department, Faculty of Science, Mansoura University, El-Gomhoria Street, ET-35516 Mansoura, Egypt.

**** Correspondence to:** elmekabaty@mans.edu.eg, 01003677361*

Received: 3/6/2024
Accepted: 12/06/2024

Abstract: The attending work used Gewald's approach to produce ethyl 2-amino-4,5-diphenylfuran-3-carboxylate (2) by condensing benzoin (1) with ethyl cyanoacetate while stirring in dimethylformamide containing a catalytic amount of diethylamine. Through its interactions with practical chemical reagents, this 2-aminofuran derivative worked as a crucial synthon for the synthesis of novel thiazolidin-4-one, chromen-2-imine, and pyrrol-2-one derivatives. It was also addressed how the novel furan derivatives were achieved mechanistically.

keywords: Furan; thiazolidinone; chromene; pyrrolone; Gewald's methodology.

1.Introduction

One type of heterocycle having aromatic and lipophilic properties is furan, which is regarded as a cyclic ether [1]. Furan ring is a one of the most privileged cores in numerous biologically active molecules together with numerous marketing drugs [2], for example, cholinesterase inhibitor "Galantamine" act as anti- Alzheimer agent [3], ANAVEX 2-73 has neuroprotective properties [4], (-)-BPAP is effective for serotonergic activity in neurons [5] (**Fig. 1**). The fused heterocycles incorporated furan scaffold and the related substituted analogues demonstrated potent and diverse biological properties such as antitumor, antimicrobial, antiviral, antihistaminic, and antidepressant activities [6], in addition, analogues of 5-phenyl-furan-2-carboxylic acid demonstrated remarkable antitubercular activities [7]. In the industrial sector, furan was widely used and often considered a promising synthetic resource for the synthesis of tetrahydrofuran and other useful compounds [8], including lacquers, resins, insecticides, and medications such furanochromones and furanones [9, 10]. Furthermore, because of its high-energy radiation and thermal progressions, it is regarded as a by-product of food production [11]. Furan heterocycles can be synthesized by reacting furan derivatives with a variety of other reagents [12]. Due to the great biological and industrial importance of furan derivatives, this study aims to synthesize novel thiazolidin-4-one, chromen-2-imine, and pyrrol-2-one derivatives having furan nucleus produced from 2-aminofuran **2**.

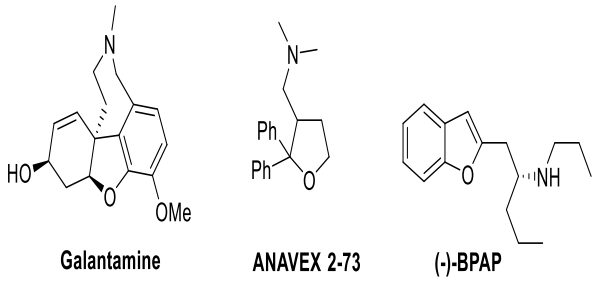


Fig. 1. Biologically active compounds with furan nucleus.

2. Materials and methods

On the Gallenkamp electric melting point apparatus, melting points (uncorrected) were measured in degrees Celsius. The Mattson 5000 FTIR Spectrometer (USA) was used to obtain the IR (υ cm^{-1}) (KBr). The Bruker Avance III spectrophotometer was used to record the 1H-NMR spectra (DMSO-d_6/400 MHz). With an ionising potential of 70 eV, the mass spectra were captured using the Kratos MS (Kratos Analytical Instrument, Ramsey, NJ) apparatus in the EI mode. The elemental analyses of carbon, hydrogen, and nitrogen were performed on Perkin-Elmer 2400 Instruments, Shelton, CT.

Reaction of 2-aminofuran 2 with aromatic aldehydes (General procedure):

2-Aminofuran **2** (1.536 g, 0.005 mol), benzaldehyde and/or 4-methylbenzaldehyde (0.005 mol) and melted NaOAc (0.41 g, 0.005 mol) were fused at 120-125°C for 5 h. The crude was allowed to cool after the reaction was completed using TLC, and the ethyl alcohol was then used as a solvent to recrystallized the product.

Ethyl-2-(benzylideneamino)-4,5-diphenyl furan-3-carboxylate (3a)

Brown crystals; mp 190-192ºC; yield 52%. IR (KBr, cm^{-1}): 1675 (CO, ester), 1610 (C=N), 1600 (C=C). ^{1}H-NMR δ (ppm): 8.99 (s, 1H, CH=N), 8.04-6.65 (m, 15H, Ar-H), 4.75 (q, *J* = 8.0 *Hz*, 2H, ester, $\underline{CH_2}CH_3$), 1.15 (t, *J* = 8.0 *Hz*, 3H, ester, CH_2-$\underline{CH_3}$). MS: (*m/z*, %): 395.78 (M^+, 6.63). Elemental analyses for $C_{26}H_{21}NO_3$ (395.46), calcd: C, 78.97; H, 5.35; N, 3.54%; Found: C, 79.05; H, 5.40; N, 3.59%.

Ethyl-2-((4-methylbenzylidene)amino)-4,5-diphenylfuran-3-carboxylate (3b)

Brown crystals; yield 55%; mp 160-162ºC. IR (KBr, cm^{-1}): 1677 (CO, ester), 1620 (C=N), 1605 (C=C). ^{1}H-NMR δ (ppm): 8.98 (s, 1H, CH=N), 8.21-7.04 (m, 14H, Ar-H), 4.52 (q, *J* = 8.0 *Hz*, 2H, CH_2-ester), 2.46 (s, 3H, CH_3), 1.12 (t, *J* = 8.0 *Hz*, 3H, CH_3-ester). MS: (*m/z*, %): 409.21 (M^+, 12.08). Elemental analyses for $C_{27}H_{23}NO_3$ (409.49), calcd: C, 79.20; H, 5.66; N, 3.42%; Found: C, 79.31; H, 5.72; N, 3.51%.

Synthesis of thiazolidin-4-ones 4a and 4b (General procedure):

For eight hours, a solution containing equimolar ratios of Schiff bases **3a,b** (0.003 mol) and 2-mercaptoacetic acid (0.276 g, 0.003 mol) in pyridine (20 mL) was refluxed. Once the mixture had cooled, pour it into ice-cold water. The resulting thiazolidin-4-ones were then filtered off and crystallized again from ethyl alcohol.

Ethyl 2-(4-oxo-2-phenylthiazolidin-3-yl)-4,5-diphenylfuran-3-carboxylate (4a)

Yellow crystals; yield 49%; mp 185-187ºC. IR (KBr, cm^{-1}): 1688 (CO, ester), 1644 (CO, amidic), 1608 (C=C). ^{1}H-NMR δ (ppm): 8.06-7.17 (m, 15H, Ar-H), 6.15 (s, 1H, CH), 4.81 (q, *J* = 8.0 *Hz*, 2H, ester, $\underline{CH_2}$-CH_3), 2.75 (s, 2H, H5), 1.04 (t, *J* = 8.0 *Hz*, 3H, ester, $CH_2\underline{CH_3}$). MS: (*m/z*, %): 469.72 (M^+, 13.51). Elemental analyses for $C_{28}H_{23}NO_4S$ (469.56), calcd: C, 71.62; H, 4.94; N, 2.98%; Found: C, 71.70; H, 4.82; N, 3.08%.

Ethyl 2-(4-oxo-2-(p-tolyl)thiazolidin-3-yl)-4,5-diphenylfuran-3-carboxylate (4b)

Yellow crystals; yield 55%; mp 212-214ºC. IR (KBr, cm^{-1}): 1680 (CO, ester), 1660 (CO, amidic), 1622 (C=C). ^{1}H-NMR δ (ppm): 8.26-7.33 (m, 14H, Ar-H), 5.80 (s, 1H, CH), 4.31 (q, 2H, ester, $\underline{CH_2}$-CH_3), 3.57 (s, 2H, H5), 2.11 (s, 3H, methyl), 1.24 (t, 3H, ester, CH_2-$\underline{CH_3}$). MS: (*m/z*, %): 483.77 (M^+, 21.24). Elemental analyses for $C_{29}H_{25}NO_4S$ (483.58), calcd: C, 72.03; H, 5.21; N, 2.90%; Found: C, 72.11; H, 5.30; N, 3.06%.

Ethyl 2-(2-chloroacetamido)-4,5-diphenylfuran-3-carboxylate (5)

A stirred cold mixture of 2-aminofuran **2** (0.615 g, 0.002 mol) and 1 mL of triethylamine in 20 mL dioxane was stirreded with 0.23 g of 2-chloroacetyl chloride (0.002 mol). Stirring was then continued for a further 2 hours at 25 °C. The resulting 2-chloroacetamide derivative was collected by filtration and subsequently purified by boiling in DMF. Yellow needles; yield 68%; mp 218-220°C. IR (KBr, cm^{-1}): 3373 (NH), 2955 (C-H, aliphatic), 1702 (C=O, ester), 1650 (C=O, amidic), 1608 (C=C). ^{1}H-NMR δ (ppm): 8.90 (s, 1H, NH), 7.97-7.04 (m, 10H, Ar-H), 4.34 (s, 2H, CH_2Cl), 4.08 (q, *J* = 8.0 *Hz*, 2H, CH_2-ester), 1.09 (t, *J* = 8.0 *Hz*, 3H, CH_3-ester). MS: (*m/z*, %): 385.22 (M^++2, 18.12), 383.31 (M^+, 7.40). Elemental analyses for $C_{21}H_{18}ClNO_4$ (383.83), calcd: C, 65.71; H, 4.73; N, 3.65%. Found: C, 65.79; H, 4.80; N, 3.72%.

Ethyl 2-(2-cyanoacetamido)-4,5-diphenylfuran-3-carboxylate (6)

For three hours, a solution containing 1.92 g (0.005 mol) of 2-chloroacetamide 5 and 0.325 g (0.005 mol) of KCN in 30 mL of EtOH was heated to 70 °C. Pour onto cold water while swirling constantly. After filtering off the precipitated cyanoacetamide, it was heated in DMF to recrystallize. Pale yellow crystals; yield 93%; mp 222-224°C. IR (KBr, cm^{-1}): 3355 (NH), 2221 (CN), 1690 (C=O, ester), 1664 (C=O, amidic), 1600 (C=C). ^{1}H-NMR δ (ppm): 10.56 (s, 1H, NH), 8.08-7.20 (m, 10H, Ar-H), 4.31 (q, *J* = 8.0 *Hz*, 2H, ester, $\underline{CH_2}$-

CH_3), 3.11 (s, 2H, CH_2-CN), 1.30 (t, *J* = 8.0 *Hz*, 3H, ester, CH_2-$\underline{CH_3}$). MS: (*m/z*, %): 374.21 (M^+, 21.48). Elemental analyses for $C_{22}H_{18}N_2O_4$ (374.40), calcd: C, 70.58; H, 4.85; N, 7.48%; Found: C, 70.66; H, 4.96; N, 7.54%.

Ethyl 2-(2H-chromene-2-imino--3-carboxamido)-4,5-diphenylfuran-3-carboxylate (7)

Five drops of piperidine were added to equimolar amounts of 2-cyanoacetamide 6 (1.12 g, 0.003 mol) and 2-hydroxybenzaldehyde (0.36 g, 0.003 mol) in 25 mL ethanol, and the mixture was heated for 12 hours. Poured upon cold water and allowed to stand at 25°C for the entire night. After filtering, the resultant chromene was boiled in methanol to recrystallize. Pale yellow crystals; yield 68%; mp 232-234°C. IR (KBr, cm^{-1}): 3346 (NH, amidic), 3267 (NH), 1702 (CO, ester), 1659 (CO, amidic), 1633 (C=N), 1595 (C=C). ^{1}H-NMR δ (ppm): 10.65 (s, 1H, NH), 9.54 (s, 1H, NH), 8.23 (s, 1H, CH=C), 8.03-7.10 (m, 14H, Ar-H), 4.31 (q, *J* = 8.0 *Hz*, 2H, ester, $\underline{CH_2}$-CH_3), 1.30 (t, *J* = 8.0 *Hz*, 3H, ester, CH_2-$\underline{CH_3}$). MS: (*m/z*, %): 478.88 (M^+, 12.19). Elemental analyses for $C_{29}H_{22}N_2O_5$ (478.50), calcd: C, 72.79; H, 4.63; N, 5.85%; Found: C, 72.90; H, 4.72; N, 5.92%.

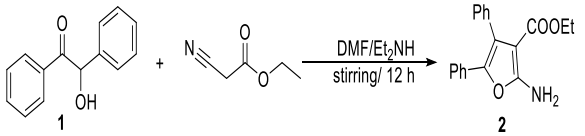
Ethyl 2-(4-cyano-2-oxo-2,3-dihydro-5-amino-1H-pyrrol-1-yl)-4,5-diphenylfuran-3-carboxylate (8)

After adding K_2CO_3 (0.69 g, 0.005 mol) and heating the mixture of 2-chloroacetamide **5** (1.151 g, 0.003 mol) and malononitrile (0.198 g, 0.003 mol) in 20 mL DMF for 20 hours, the mixture was allowed to cool. After being poured onto cold water, the resulting pyrollone was filtered off and heated in methyl alcohol to recrystallize. Yellow crystals; yield 39%; mp 191-192°C. IR (KBr, cm^{-1}): 3288-3200 (NH_2), 2216 (CN), 1693 (CO, ester), 1664 (CO, amidic), 1620 (C=C). ^{1}H-NMR δ (ppm): 7.96-7.17 (m, 10H, Ar-H), 6.57 (s, 2H, NH_2), 4.87 (q, *J* = 8.0 *Hz*, 2H, ester, $\underline{CH_2}$-CH_3), 2.76 (s, 2H, H3), 1.05 (t, *J* = 8.0 *Hz*, 3H, ester, CH_2-$\underline{CH_3}$). MS: (*m/z*, %): 413.70 (M^+, 61.65). Elemental analyses for $C_{24}H_{19}N_3O_4$ (413.43), calcd: C, 69.72; H, 4.63; N, 10.16%; Found: C, 69.80; H, 4.69; N, 10.27%.

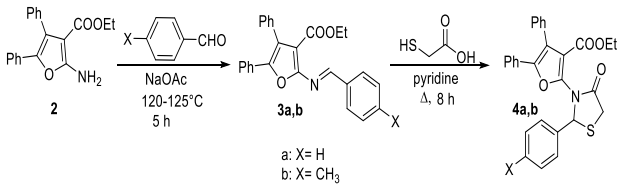
Results and Discussion

The key compound, 2-aminofuran **2** [13, 14] was synthesized from readily attainable reagents through Gewald condensation of benzoin (**1**) with ethyl cyanoacetate in dimethylformamide containing diethylamine (few drops) in a good yield as outlined in **Scheme 1**. The mass spectrum of 2-aminofuran derivative **2** verified the molecular ion peak at *m/z* = 307.01 (M^+, 16.09%), which was also accompanied by the structure's precise molecular formula ($C_{19}H_{17}NO_3$).

Schiff bases are compounds incorporating a parent azomethine group and having various synthetic applications such as catalysts, dyeing processes, synthetic intermediates, polymer stabilizers and metal corrosion inhibitors. In addition, these compounds have shown diverse, potent and remarkable biological performance when applied in the medical field [15]. Therefore, condensation of 2-aminofuran **2** with aromatic aldehydes at 120-125°C in the presence of freshly melted NaOAc provide a facile route to yield the corresponding Schiff bases **3a,b**. Subsequent cyclocondensation reactions of mercaptoacetic acid with each of Schiff bases **3a,b** afforded the desired thiazolidin-4-ones **4a,b**, respectively (**Scheme 2**).



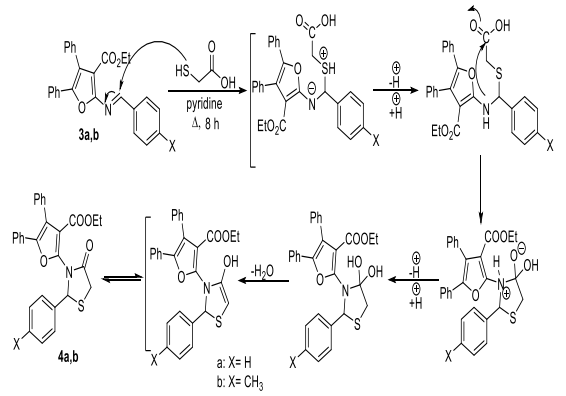
Scheme 1. Synthesis of 2-aminofuran derivative **2**.



Scheme 2. Synthesis of thiazolidin-4-ones **4a,b**.

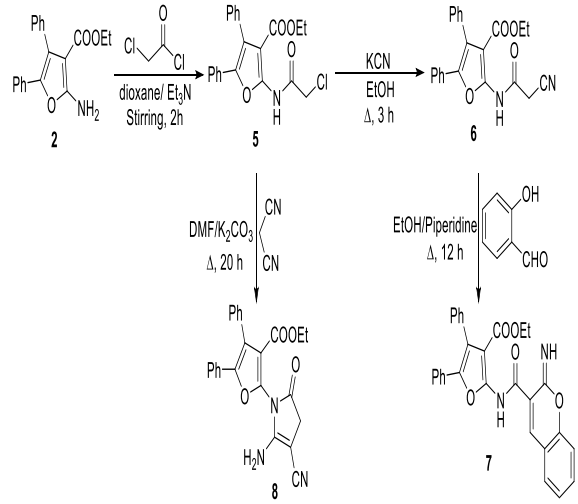
The reactions of Schiff bases **3a,b** with mercaptoacetic acid were progressed initially through the nucleophilic attack of sulfur atom of mercaptoacetic acid to the C=N group of Schiff bases followed by intramolecular

cyclization with the loss of H_2O molecule (**Scheme 3**).



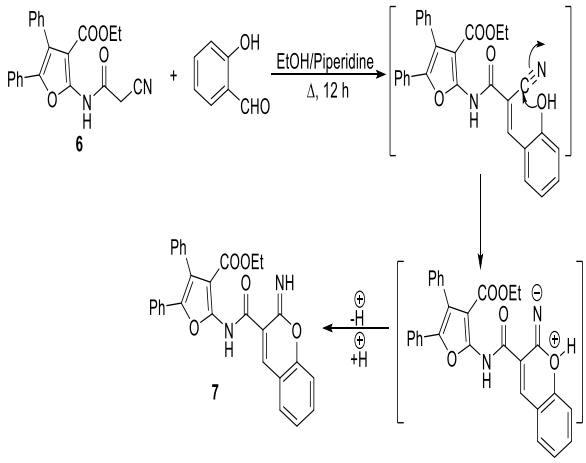
Scheme 3. The suggested mechanism for the synthesis of thiazolidin-4-ones **4a,b**.

Cyanoacetamides were applied as versatile synthetic intermediates for the synthesis of diverse dyes, biologically active components, and agrochemical analogues [16, 17]. On the other side, the researcher's interest in the synthesis of chromene heterocycles has been increased in the last decades due to their remarkable biological impacts [18, 19]. Thus, treatment of 2-aminofuran **2** with chloroacetyl chloride in dioxane catalyzed by Et_3N afforded the desired chloroacetamide **5**. Heating of **5** with potassium cyanide in ethanol yielded the corresponding cyanoacetamide **6** through nucleophilic substitution step. Cyanoacetamide **6** reacted with salicylaldehyde in refluxing ethanol containing piperidine to give the chromen-2-imine **7** (**Scheme 4**).



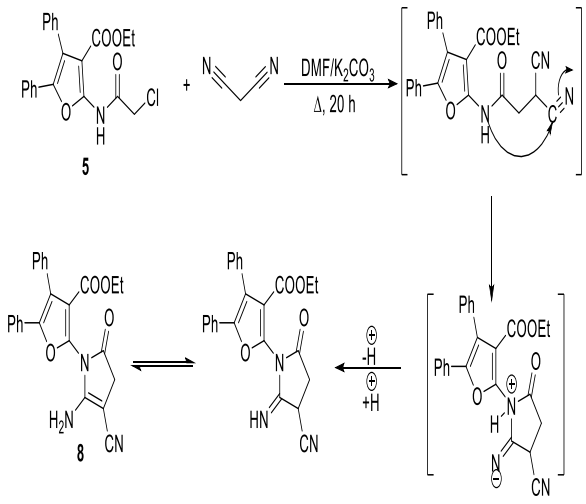
Scheme 4. Synthesis of chromen-2-imine **7** and pyrrol-2-one **8**.

The mechanism for the formation of chromene **7** was projected as outlined in **Scheme 5**.



Scheme 5. The projected mechanistic route for the synthesis of chromen-2-imine **7**.

α-Haloketones have been applied in a wide range in synthetic organic researches considering their high reactivity as intermediates in the preparation of various classes of heterocyclic systems [20, 21]. Chloroacetamide **5** reacted with malononitrile in refluxing DMF and potassium carbonate as a basic medium to give the respective pyrrol-2-one derivative **8** (**Scheme 4**). The mechanism for the formation of pyrrol-2-one derivative **8** was projected as outlined in **Schemes 6**.



Scheme 6. The estimated mechanistic route for the synthesis of pyrrol-2-one **8**.

Conclusion

In conclusion, the current consideration's results note that 2-aminofuran 2 is a suitable synthon for creating new derivatives of thiazolidin-4-one, chromen-2-imine, and pyrrol-2-one through its reactions with some convenient chemical reagents.

4. References

1 Abbas, S. E.; Gawad, N. M. A.; George, R. F.; Akar, Y. A. (2013) *Eur. J. Med. Chem.*, *65*, 195.

2 Martorana, A.; Giacalone, V.; Bonsignore, R.; Pace, A.; Gentile, C.; Pibiri, I.; Buscemi, S.; Lauria, A.; Piccionello, A. P (2016). Curr. Pharm. Design *22*, 3971.

3 Raskind, M. A.; Peskind, E. R.; Wessel, T.; Yuan, W. (2000) Neurology, **54**(12), 2261.

4 Lahmy, V.; Meunier, J.; Malmström, S. (2013) Neuropsycho-pharmacology, 38(9): 1706.

5 Gaszner, P.; Miklya, I. *Prog* (2006) Neuropsychopharmacol Biol Psychiatry, **30(1)**, 5.

6 Rumpa, B.; Kumar, H. K. S.; Mrityunjay, B (2012) *Int. J. Life Sci. 2*, 7.

7 Chiarelli, L. R.; Mori, M.; Beretta, G.; Gelain, A.; Pini, E.; Sammartino, J. C.; Stelitano, G.; Barlocco, D.; Costantino, L.; Lapillo, M.; Poli, G.; Caligiuri, I.; Rizzolio, F.; Bellinzoni, M.; Tuccinardi, T.; Villa, S.; Meneghetti, F (2019.) *J. Enzyme Inhib. Med. Chem.*; **34(1)**: 823.

8 Foroumadi, A.; Mansouri, S.; Kiani, Z.; Rahmani, A (2003),. *Eur. J. Med. Chem.* 38, 851.

9 Bozorov, K.; Nie, L. F.; Zhao, J.; Aisa, H. A (2017) *Eur. J. Med. Chem.*, *140*, 465.

10 Ram, V. J.; Goel, A.; Shukla, P. K.; Kapil, A**1997**. Bioorg. Med. Chem. Lett., 7, 3101.

11 Ozcan, B.; Esen, M.; Caliskan, M.; Mothana, R. A.; Cihan, A. C.; Yolcu, H. (2011) Eur. Rev. Med. Pharmacol. Sci., 15, 900.

12 Abdou, M. M. Am (2013.) *J. Chem*., *3*, 126.

13 Khan, M. W.; Uddin, M. K.; Ali, M.; Rahman, M. S.; Rashid, M. A.; Chowdhury, R.(2014) *J. Heterocycl. Chem*. **51**, E216.

14 Kidway, M.; Mishra, A. D.; Saxena, S. (2005), *Indian J. Chem. 44B*, 581.

15 Kajal, A.; Bala, S.; Kamboj, S.; Sharma, N.; Saini, V (2013),. *J. Catal.* **2013**, 1.

16 Fadda, A. A.; Bondock, S.; Rabie, R.; Etman, H. A. (2008) ,*Turk. J. Chem*. *32*, 259.

17 Kabir, M. U.; Mehnaz H. M.; Mokseda A.; Shofiur R.; Mahmoud A. A. G.; Nahed A.; Hamad A.; Abdullah A.; Raymond A. P.; Md. Mosharef H. B.(2024) MethodsX, 12, 102691.

18 Ghate, M.; Kusanur, R. A.; Kulkarni, M. V. (2005), *Eur. J. Med. Chem. 40*, 882.

19 Andrea, C.; Serena, V.; Christian, D.; Laura, I. (2024) Front. Chem. 12, 1362992.

20 Erian, A. W.; Sherif, S. M.; Gaber, H. M. (2003), Molecules 8, 793.

21 Marre, P.; Gianmarco, P.; Fady, N.; Catherine, S. J. C (2022), Molecules 27, 3583.