Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

Hantzsch synthesis of bis(1,4-dihydropyridines) and bis(tetrahydrodipyrazolo[3,4-*b*:4',3'-*e*]pyridines) linked to pyrazole units as novel hybrid molecules

Sherif M. H. Sanad, Mahmoud A. E. Hawass, Ahmed H. M. Elwahy & Ismail A. Abdelhamid

To cite this article: Sherif M. H. Sanad, Mahmoud A. E. Hawass, Ahmed H. M. Elwahy & Ismail A. Abdelhamid (2020): Hantzsch synthesis of bis(1,4-dihydropyridines) and bis(tetrahydrodipyrazolo[3,4-*b*:4′,3′-*e*]pyridines) linked to pyrazole units as novel hybrid molecules, Synthetic Communications, DOI: 10.1080/00397911.2020.1761395

To link to this article: https://doi.org/10.1080/00397911.2020.1761395

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2020.1761395

Taylor & Francis
Taylor & Francis Group

Hantzsch synthesis of bis(1,4-dihydropyridines) and bis(tetrahydrodipyrazolo[3,4-*b*:4′,3′-*e*]pyridines) linked to pyrazole units as novel hybrid molecules

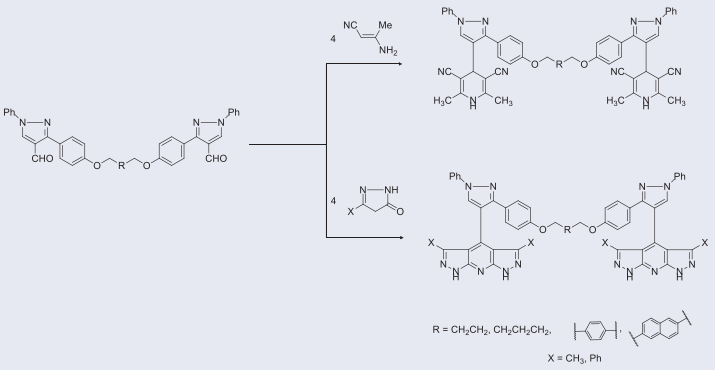
Sherif M. H. Sanad, Mahmoud A. E. Hawass, Ahmed H. M. Elwahy, and Ismail A. Abdelhamid

Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt

ABSTRACT

A novel series of bis(1,4-dihydropyridine-3,5-dicarbonitrile) and bis(tetrahydrodipyrazolo[3,4-*b*:4′,3′-*e*]pyridine) derivatives which are linked to pyrazole units were prepared *via* Hantzsch like reaction of the bis-aldehydes with the respective 3-aminocrotonitrile and pyrazolone derivatives.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 19 February 2020

KEYWORDS
Bis(1,4-dihydropyridine-3,5-dicarbonitrile); bis(tetrahydrodipyrazolo[3,4-*b*:4′,3′-*e*]pyridine); Hantzsch; pyrazole linker

Introduction

Hantzsch reaction is a well-known, multi-component route for the straightforward synthesis of 1,4-dihydropyridines (1,4-DHPs) *via* the cyclocondensation of aldehydes with *β*-dicarbonyl compounds, and ammonium acetate.[1–3] 1,4-DHPs are important heterocyclic compounds owing to their wide spectra of bioactivities that include anti-inflammatory,[4] anti-oxidant,[5] anti-microbial,[4] antiulcer[5] and anticancer activities.[6–8] In addition, 1,4-DHPs drug molecules, such as nicardipine, nifedipine and others[9–18] are effective as calcium Ca^{2+} channel blockers for the treatment of heart diseases and hypertension.[12] Recently, great interest has been increasingly paid to the synthesis of bis(heterocycles). These compounds were found to exhibit various bioactivities that

CONTACT Ahmed H. M. Elwahy aelwahy@hotmail.com; Ismail A. Abdelhamid ismail_shafy@yahoo.com
Chemistry Department, Faculty of Science, Cairo University, Giza 12613, Egypt.

Supplemental data for this article can be accessed on the publisher's website.

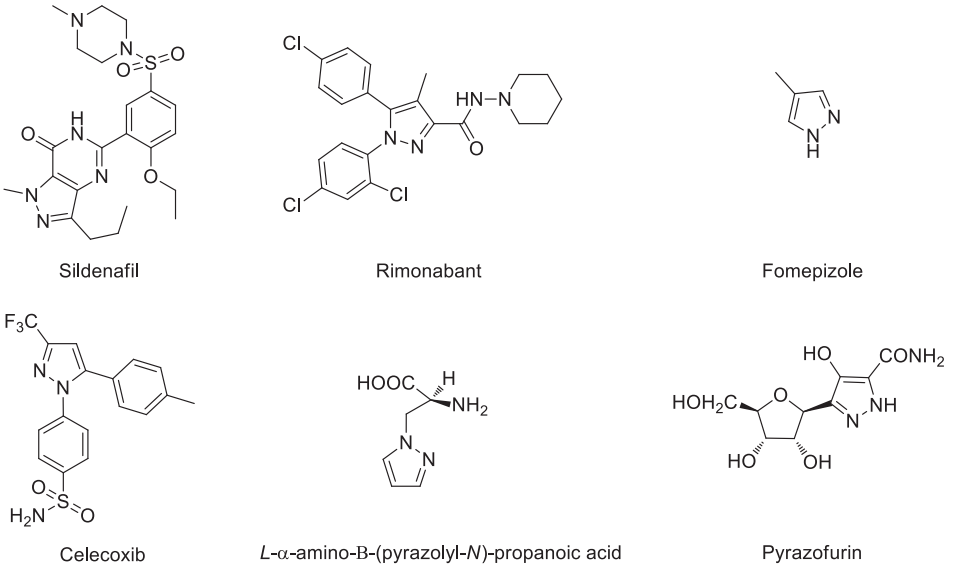


Figure 1. Drug molecules and natural products containing pyrazole scaffolds.

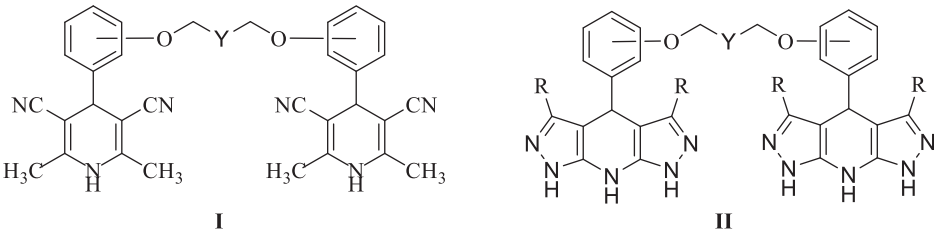
include antibacterial, tuberculostatic, and fungicidal properties.[19] Also, they have numerous applications as chelating agents, electrical materials, and metal ligands.[20] Moreover, pyrazole derivatives were reported to possess a wide spectrum of biological activities.[21–26] The pyrazole moiety is found in many pharmaceutical drugs such as celecoxib (anti-inflammatory drug), rimonabant (functions as a cannabinoid receptor and is utilized to treat obesity), fomepizole (inhibits alcohol dehydrogenase), and sildenafil (inhibits phosphodiesterase) (Figure 1).[27] The pyrazole motif is also present in a number of natural products including *L*-α-amino-*β*(pyrazolyl-*N*)-propanoic acid (antidiabetic, isolated from *Citrullus vulgaris*) and pyrazofurin (antiviral isolated from *Streptomyces candidus*) (Figure 1).[27]

As a part of an ongoing research program on *C*–*C* bond formation reactions that includes Michael addition[28–36] and Hantzsch reactions and in addition to our interest in the synthesis of bis(heterocycles), we report herein the results of our investigations aiming at the synthesis of novel bis(1,4-dihydropyridine-3,5-dicarbonitrile) and bis(tetrahydrodipyrazolo[3,4-*b*:4′,3′-*e*]pyridin) linked to aliphatic or aromatic spacer *via* pyrazole units.

Results and discussion

We recently described the synthesis of some *bis*-dihydropyridines **I** and their corresponding fused derivatives **II** and studied their anti-cytotoxic activities (Figure 2).[37]

The aim of the present work is to modify the structure of **I** and **II** by introducing additional pyrazole ring aiming at achieving the concept of molecular hybridization. This tool involves the combination of two pharmacophoric moieties of different bioactivities in one molecule to improve their biological efficacy and overcoming drug resistance.[38–41] There are two possible synthetic approaches can be considered for the synthesis of the target bis(1,4-dihydropyridine-3,5-dicarbonitriles) **5**. In the first



I II

Figure 2. Structures of some *bis*-dihydropyridines **I** and their corresponding fused derivatives **II**.

approach, 4-(3-(4-hydroxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile **3** was prepared *via* the cyclocondensation of 3-(4-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde **1** with 3-aminocrotononitrile **2** in acetic acid at reflux. Repeated attempts to get the target products **5** by the direct *bis*-alkylation of **3** with the appropriate dibromoalkanes **4** under different basic conditions were unsuccessful. The reaction gave instead an inseparable mixture of products that have not been fully characterized (Scheme 1).

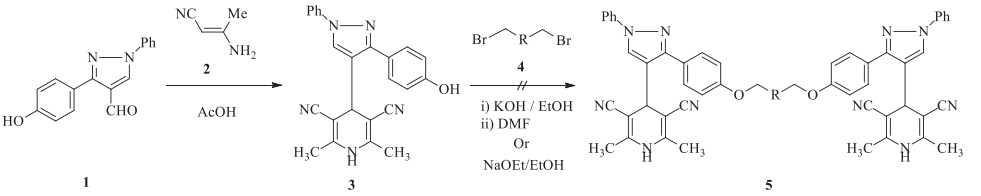
In the second approach, the bis(1-phenyl-1*H*-pyrazole-4-carbaldehydes) **6** were chosen as precursors to our target molecules. Thus, in the first step, the appropriate bis-aldehydes **6a–f** have been prepared through the reaction of 3-(4-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde **1** with the dibromo compounds **4a–f** in boiling DMF in the presence of potassium hydroxide (Scheme 2).

Subsequent acid-catalyzed condensation reaction of one mole of bis(1-phenyl-1*H*-pyrazole-4-carbaldehydes) **6a–c** with four moles of 3-aminocrotononitrile **2** afforded the respective bis(1,4-dihydropyridine-3,5-dicarbonitrile) **5a–c** in good yields (Scheme 3).

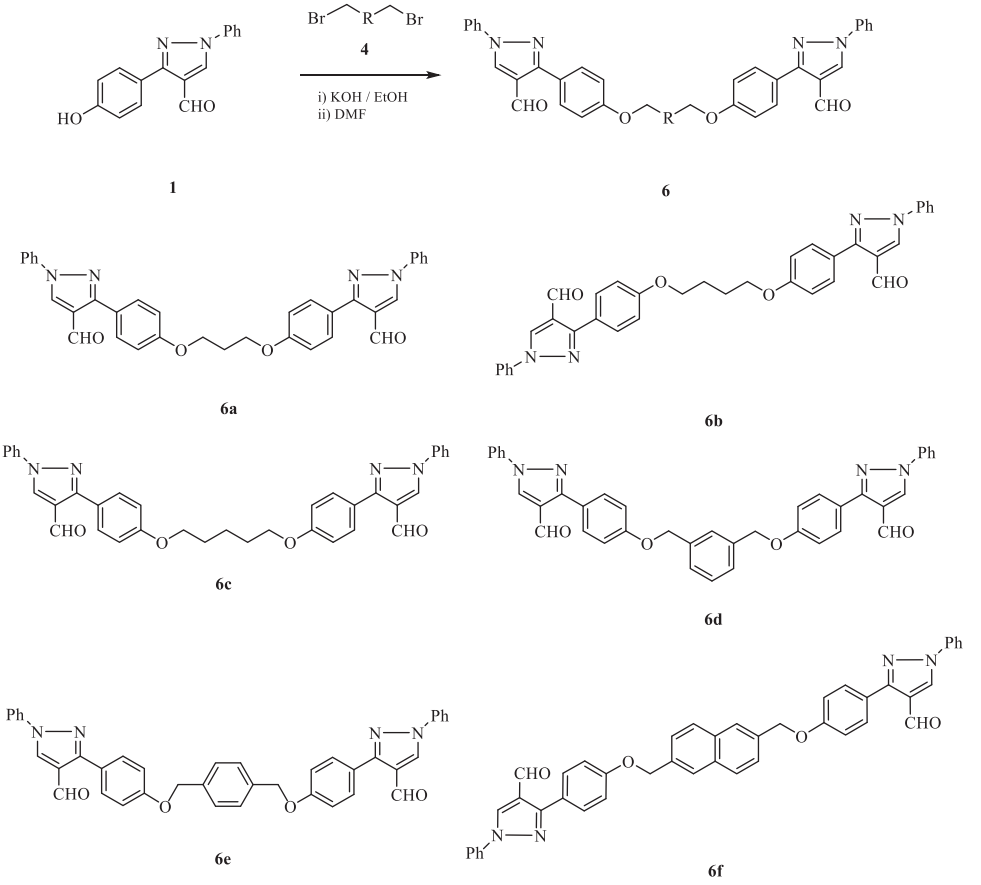
The structures of the bis(1,4-dihydropyridine-3,5-dicarbonitrile) derivatives **5a–c** were confirmed by their spectral data. The IR spectrum of **5a** revealed strong absorption bands at υ 3357 and 2207 cm^{-1} attributable to NH and CN groups, respectively. The ^{1}H-NMR spectrum of **5a**, as a representative example, revealed a singlet signal integrated by 12H at 1.93 ppm referring to the four methyl groups. The multiplet at 2.23 ppm and the triplet signal at 4.23 ppm are assigned to the linker CH_2 and OCH_2 groups, respectively. Moreover, ^{1}H-NMR spectrum of **5a** also featured singlet signal at 4.60 ppm owing to the pyridine-H4. The aromatic protons appear as multiplets at 7.06–7.90 ppm. It also showed a singlet signal at 8.55 ppm in addition to a broad signal at 9.37 ppm characteristic for the pyrazole-H5 and the dihydropyridine NH, respectively.

Our study was extended to include the reaction of 3-aminocrotononitrile **2** with bis(1-phenyl-1*H*-pyrazole-4-carbaldehydes) **6d** and **6e**, in which the two pyrazole units are linked to phenyl core *via* phenoxymethyl linkage. The reactions afforded inseparable mixtures of the bis(1,4-dihydropyridine-3,5-dicarbonitriles) **5** and its aromatized derivative bis(pyridine-3,5-dicarbonitriles) **7** with considerable difference in the product ratios (as indicated in ^{1}H-NMR spectra). Thus, when **6d** was used, the two mixture products **5d**/**7d** were obtained in a ratio of 1.5:1, while the two mixture products **5e**/**7e** were formed in ratio of 1.23:1, when **6e** was used (Scheme 4).

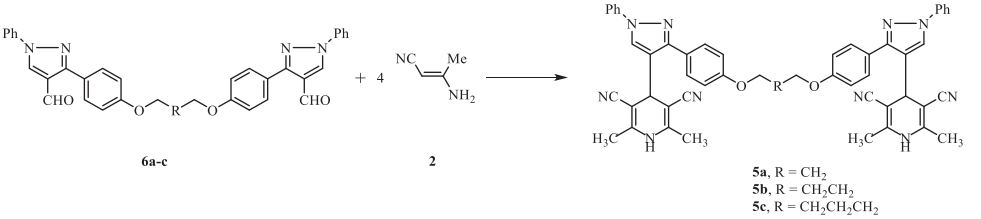
On the other hand, the reaction of the bis(1-phenyl-1*H*-pyrazole-4-carbaldehyde) with naphthalene core **6f** with four equivalents of 3-aminocrotononitrile **2** resulted in



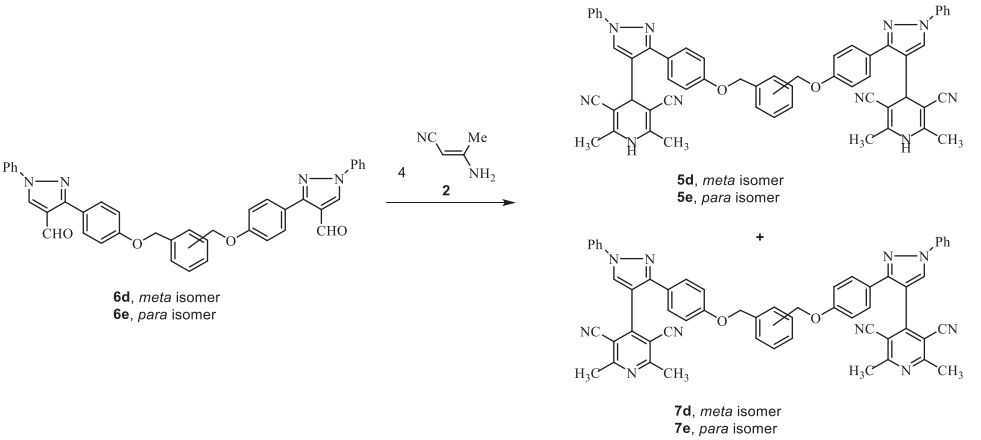
Scheme 1. Attempted synthesis of **5** through the direct bis-alkylation of **3** with the appropriate dibromoalkanes **4**.



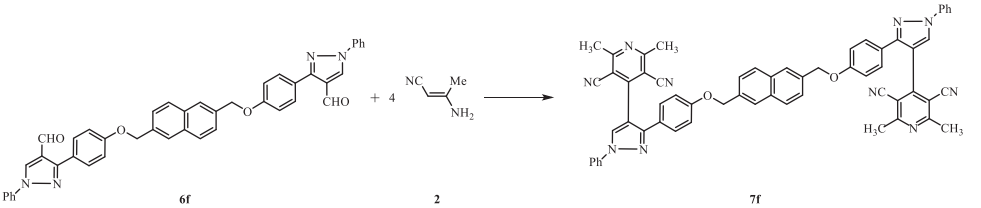
Scheme 2. Synthesis of bis-aldehydes **6a–f**.



Scheme 3. Synthesis of bis(1,4-dihydropyridine-3,5-dicarbonitrile) **5a–c**.



Scheme 4. Reaction of 3-aminocrotononitrile **2** with bis(aldehydes) **6d** and **6e**.

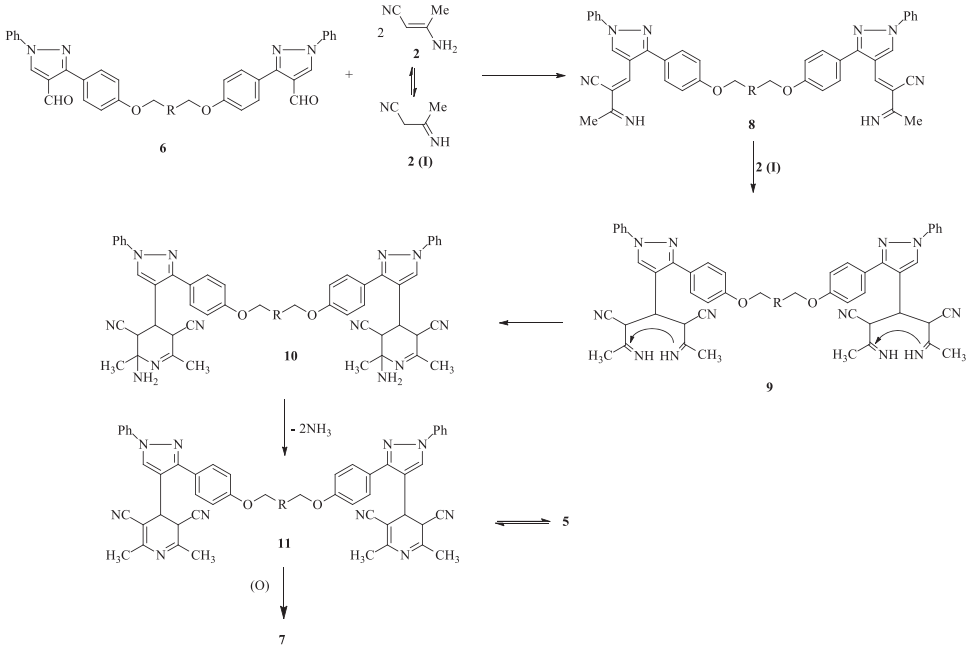


Scheme 5. Synthesis of the aromatized bis(pyridine-3,5-dicarbonitrile) **7f**.

the direct formation of the aromatized product **7f**, while no traces of the non-oxidized form was detected (Scheme 5).

Apparently, the reaction mechanism involves the initial condensation of the bis(1-phenyl-1*H*-pyrazole-4-carbaldehydes) **6** with two equivalents of the 3-aminocrotonitrile **2** to yield the bis(arylidene) intermediates **8** which then interact with another two moles of 3-aminocrotonitrile **2** affording the bis(iminoalkanenitrile) intermediate **9**. Intramolecular cyclization involving imino group leads to the formation of **10**. The intermediates **10** lose two molecules of NH_3 yielding compounds **11** that rearrange into the final isolable products **5**. Some derivatives underwent auto-oxidation to give the oxidized form **7** (Scheme 6). Spontaneous oxidation of dihydropyridines and other related systems has been previously investigated.[42–48]

The reactivity of the bis(aldehydes) **6** toward 1*H*-pyrazol-5(4*H*)-one in the presence of ammonium acetate was also investigated (Scheme 7). Thus, the cyclocondensation reaction of one equivalent of bis(aldehydes) **6b**, **6c**, **6e** or **6f** with four equivalents of 1*H*-pyrazol-5(4*H*)-ones **12a** and **12b** and five equivalents of ammonium acetate in acetic acid at reflux, resulted in the formation of the bis(4-(4-(1,7-dihydrodipyrazolo[3,4-*b*:4′,3′-*e*]pyridin-4-yl)-1-phenyl-1*H*-pyrazol-3-yl)phenoxy)alkanes **14a–e** *via* initial formation of non-oxidized form **13** (not isolated) and subsequent oxidation under the reaction conditions. The reaction was followed by TLC and was found to be completed after 6 h to give **14** as sole products. It is worthy to mention that the TLC of the reaction mixture before 6 h showed always two spots and its NMR spectrum indicated the



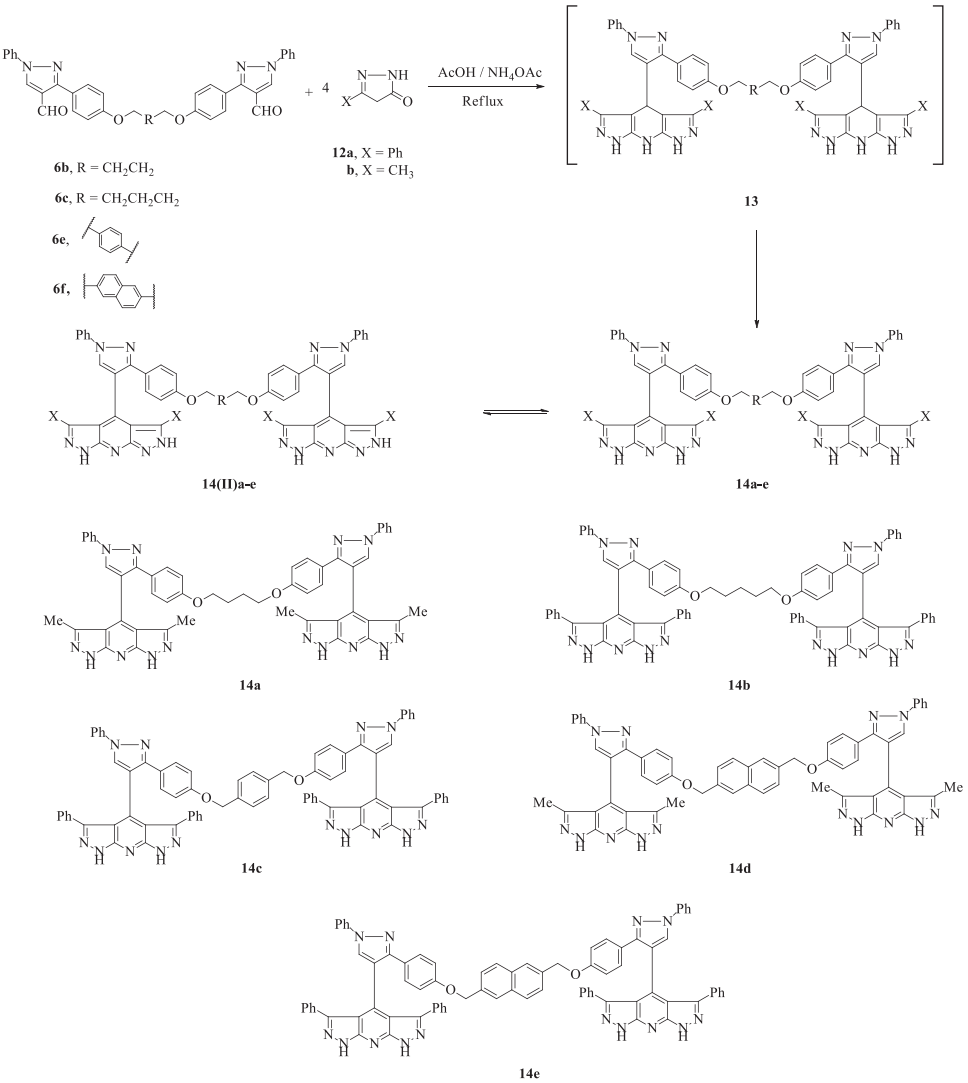
Scheme 6. Plausible mechanism for the formation of **5** and **7**.

presence of a non-separable mixture of the oxidized and non-oxidized forms, whereas the latter form disappeared completely at the end of the reaction.

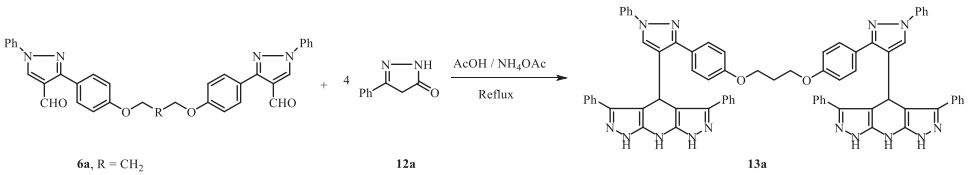
The structures of the formed products were confirmed based on their spectral data. Thus, the ^{1}H-NMR spectrum of **14b** indicated the absence of pyridine-H4 which is characteristic for **13**. In addition, the two broad signals at 10.20 and 11.78 ppm were assigned for two pyrazole-NH groups, produced as a result of the tautomerism that may exist between **14** and **14(II)**. The ^{1}H-NMR spectrum of **14b** showed also three broad bands at 1.63, 1.82, and 4.08 ppm characteristic for the three different CH_2 linker groups. Moreover, it exhibited the aromatic protons and pyrazole-H5 as multiplets at 6.95–8.16 ppm.

Exceptionally, under the same reaction conditions, the reaction of bis(aldehyde) **6a** with four equivalents of 1*H*-pyrazol-5(4*H*)-ones **12a** and five equivalents of ammonium acetate in acetic acid at reflux, afforded the respective non-oxidized bis(4-(4-(1,4,7,8-tetrahydrodipyrazolo[3,4-*b*:4′,3′-*e*]pyridin-4-yl)-1-phenyl-1*H*-pyrazol-3-yl)phenoxy)alkanes **13a** (Scheme 8). The structure of the formed product **13a** was confirmed on the basis of the elemental analyses and spectral analysis. The IR spectrum of compound **13a** revealed a broad band at 3348 cm^{-1} assigned to the NH group. Its ^{1}H-NMR spectrum indicated the presence of pyridine-H4 at 5.18 ppm, in addition to two broad singlets at 6.48 and 12.21 ppm characteristic for the two sets of NH groups. The other signals appeared at their expected positions (as shown in Experimental section).

The reaction pathway, includes the initial formation of the bis(1-phenyl-1*H*-pyrazole-3,4-diyl))bis(methaneylylidene))bis(5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one) **15** *via* the Knoevenagel condensation reaction of bis(aldehydes) **6** with two moles of pyrazolone **12**.

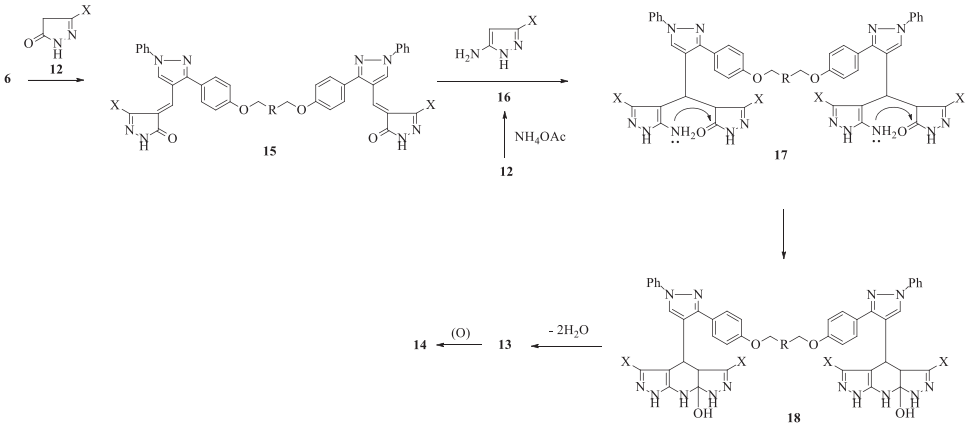


Scheme 7. Synthesis of bis(dihydrodipyrazolo[3,4-*b*:4′,3′-*e*]pyridines) **14a–e**.



Scheme 8. Synthesis of bis(tetrahydrodipyrazolo[3,4-*b*:4′,3′-*e*]pyridines) **13a**.

Michael addition reaction of **15** with the pyrazole-5-amine **16** (formed by the action of ammonium acetate on pyrazolone **12**) leads to the formation of the Michael adduct **17**. Intramolecular cyclization involving NH and CO groups affords **18**. Subsequent, water elimination gives the non-oxidized **13** that in most cases undergoes auto-oxidation to give **14** (Scheme 9).



Scheme 9. Plausible mechanism for the formation of bis(dihydrodipyrazolo[3,4-*b*:4′,3′-*e*]pyridines) **14a–e**.

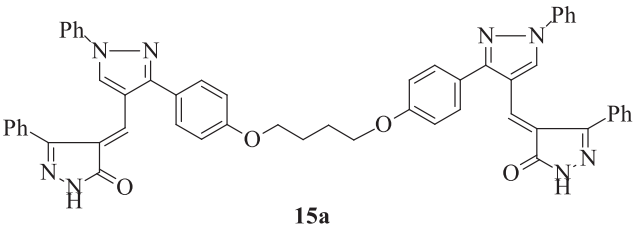


Figure 3. Structure of bis(1*H*-pyrazol-4-yl)methylene)-1*H*-pyrazol-5(4*H*)-one **15a**.

In support to this mechanism, we managed to separate the bis(1-phenyl-1*H*-pyrazole-3,4-diyl))bis(methaneylylidene))bis(5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one) derivatives **15a** by the reaction of **6b** with **12** in acetic acid at reflux (Figure 3).

Conclusions

An efficient synthetic strategy for the bis(1,4-dihydropyridine-3,5-dicarbonitrile) and bis(tetrahydrodipyrazolo[3,4-*b*:4′,3′-*e*]pyridine) derivatives was developed. The two heterocyclic units were linked to an aliphatic or aromatic spacer *via* pyrazole units. Full characterization of the new compounds is reported. We think that the presence of two pharmacophoric units in the new synthesized compounds should promote their biological activities.

Experimental

All melting points are uncorrected. IR spectra (KBr discs) were recorded on Shimadzu FT-IR-8201PC spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on Varian Mercury at 300 and 75 MHz spectrophotometer, respectively, using TMS as an internal standard and DMSO-d_6 as solvent and chemical shifts were expressed as δ ppm units. Elemental analyses were carried out on a EuroVector instrument C, H, N analyzer EA3000 Series.

General procedure for the synthesis of compounds 3, 5, and 7

A warm solution of aldehyde **1**, or bis(aldehydes) **6a–f** (1 mmol) in glacial acetic acid (5 mL), 3-aminobut-2-enenitrile **2** (2 mmol for **1**, 4 mmol for **6a–f**). The resulting solution was heated at reflux for 5 h, then allowed to cool to room temperature. The formed precipitate was filtered, dried, and purified by recrystallization from the proper solvent to afford crystals of **3**, **5** and/or **7**, respectively.

4-(3-(4-Hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (3)

Colorless crystals (ethyl acetate, 89%), m.p. 274–276 °C, IR (KBr): υ_{max} 3356 (OH), 3340 (NH), 2202 (CN) cm^{-1}, ^{1}H-NMR (DMSO-d_6): δ 1.93 (s, 6H, 2 CH_3), 4.57 (s, 1H, pyridine-H4), 6.84 (d, 2H, ArH), 7.30–7.38 (m, 3H, ArH), 7.49 (t, 2H, ArH), 7.88 (d, 2H, ArH), 8.52 (s, 1H, pyrazole-H5), 9.36 (s, 1H, pyridine-NH), 9.57 (s, 1H, OH), ^{13}C-NMR (DMSO-d_6): δ 17.6, 31.0, 82.5, 115.0, 117.8, 119.3, 123.5, 125.0, 126.0, 128.4, 129.4, 129.6, 139.2, 146.1, 151.2, 157.3 ppm. Anal. Calcd. for $C_{24}H_{19}N_5O$ (393.4): C, 73.27; H, 4.87; N, 17.80; found: C, 73.11; H, 4.72; N, 17.89%.

4,4′-(((Propane-1,3-diylbis(oxy))bis(4,1-phenylene))bis(1-phenyl-1H-pyrazole-3,4-diyl))bis(2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile) (5a)

Yellow crystals (glacial acetic acid, 63%), m.p. 162–264 °C, IR (KBr): υ_{max} 3357 (NH), 2207 (CN) cm^{-1}, ^{1}H-NMR (DMSO-d_6): δ 1.93 (s, 12H, 4 CH_3), 2.23 (m, 2H, $OCH_2\mathit{CH_2}CH_2O$), 4.23 (t, 4H, $O\mathit{CH_2}CH_2\mathit{CH_2}O$), 4.60 (s, 2H, 2 pyridine-H4), 7.06 (d, 4H, ArH), 7.32 (t, 2H, ArH), 7.48–7.53 (m, 8H, ArH), 7.90 (d, 4H, ArH), 8.55 (s, 2H, 2 pyrazole-H5), 9.37 (s, 2H, 2 pyridine-NH), ^{13}C-NMR (DMSO-d_6): δ 17.6, 28.6, 31.1, 64.3, 82.5, 114.3, 117.9, 119.3, 125.1, 125.2, 126.1, 128.6, 129.4, 129.6, 139.2, 146.1, 150.9, 158.3, Anal. Calcd. for $C_{51}H_{42}N_{10}O_2$ (826.9): C, 74.07; H, 5.12; N, 16.94; found: C, 74.22; H, 5.08; N, 16.87%.

1,5-Bis(4-(4-(3,5-diphenyl-1,7-dihydrodipyrazolo[3,4-b:4′,3′-e]pyridin-4-yl)-1-phenyl-1H-pyrazol-3-yl)phenoxy)pentane (14b)

Orange crystals (DMF, 90%); m.p. 328–330 °C, IR (KBr): υ_{max} 3341 (NH) cm^{-1}, ^{1}H-NMR (DMSO-d_6): δ 1.63 (br s, 2H, $OCH_2CH_2\mathit{CH_2}CH_2CH_2O$), 1.82 (br s, 4H, O $CH_2\mathit{CH_2}CH_2\mathit{CH_2}$ CH_2O), 4.07 (br s, 4H, $O\mathit{CH_2}CH_2CH_2CH_2\mathit{CH_2}O$), 6.95–8.16 (m, 40H, 38 ArH and 2 pyrazole-H5), 10.20 (s, 2H, 2 NH), 11.78 (s, 2H, 2 NH), Anal. Calcd. for $C_{73}H_{54}N_{14}O_2$ (1159.3): C, 75.63; H, 4.70; N, 16.91; found: C, 75.81; H, 4.90; N, 17.11%.

Full experimental details, ^{1}H and ^{13}C NMR spectra, catalyst characterization are available.

ORCID

Sherif M. H. Sanad http://orcid.org/0000-0002-0186-6418
Ahmed H. M. Elwahy http://orcid.org/0000-0002-3992-9488
Ismail A. Abdelhamid http://orcid.org/0000-0003-1220-8370

References

[1] Hantzsch, A. R. *Justus Liebigs. Ann. Chem.* **1882**, *215*, 1–82. DOI: 10.1002/jlac.18822150102.

[2] Kumar, S.; Sharma, P.; Kapoor, K. K.; Hundal, M. S. *Tetrahedron* **2008**, *64*, 536–542. DOI: 10.1016/j.tet.2007.11.008.

[3] Isambert, N.; Duque, M.; del, M. S.; Plaquevent, J.-C.; Génisson, Y.; Rodriguez, J.; Constantieux, T. *Chem. Soc. Rev.* **2011**, *40*, 1347–1357. DOI: 10.1039/C0CS00013B.

[4] Kumar, S.; Idhayadhulla, A.; Nasser, A.; Selvin, J. *J. Serb. Chem. Soc.* **2011**, *76*, 1–11. DOI: 10.2298/JSC091127003K.

[5] Swarnalatha, G.; Prasanthi, G. *Int. J. ChemTech Res.* **2011**, *3*, 75. DOI: 10.1254/jphs.12248FP.

[6] Mohamed, M. F.; Abdelmoniem, A. M.; Elwahy, A. H. M.; Abdelhamid, I. A. *CCDT.* **2018**, *18*, 372–381. DOI: 10.2174/1568009617666170630143311.

[7] Mohamed, M. F.; Darweesh, A. F.; Elwahy, A. H. M.; Abdelhamid, I. A. *RSC Adv.* **2016**, *6*, 40900–40910. DOI: 10.1039/C6RA04974E.

[8] Mohamed, M. F.; Ibrahim, N. S.; Elwahy, A. H. M.; Abdelhamid, I. A. *ACAMC.* **2019**, *18*, 2156–2168. DOI: 10.2174/1871520618666181019095007.

[9] Reid, J. L.; Meredith, P. A.; Pasanisi, F. *J. Cardiovasc. Pharmacol.* **1985**, *7*, S18. DOI: 10.1097/00005344-198507004-00004.

[10] Véniant, M.; Clozel, J. P.; Hess, P.; Wolfgang, R. *J. Cardiovasc. Pharmacol.* **1991**, *18*, S55–S58. DOI: 10.1097/00005344-199106191-00010.

[11] Iijima, T.; Yanagisawa, T.; Taira, N. J. *Mol. Cell. Cardiol.* **1984**, *16*, 1173–1177. DOI: 10.1016/S0022-2828(84)80043-7.

[12] Wallin, J. D.; Cook, M. E.; Blanski, L.; Bienvenu, G. S.; Clifton, G. G.; Langford, H.; Turlapaty, P.; Laddu, A. *Am. J. Med.* **1988**, *85*, 331–338. DOI: 10.1016/0002-9343(88)90582-7.

[13] Miri, R.; Javidnia, K.; Hemmateenejad, B.; Azarpira, A.; Amirghofran, Z. *Bioorg. Med. Chem.* **2004**, *12*, 2529–2536. DOI: 10.1016/j.bmc.2004.03.032.

[14] Subramani, S.; Vijayanand, C.; Tharion, E. *Br. J. Pharmacol.* **2002**, *137*, 756–760. DOI: 10.1038/sj.bjp.0704921.

[15] Bossert, F.; Meyer, H.; Wehinger, E. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 762–769. DOI: 10.1002/anie.198107621.

[16] Bohlooli, S.; Mahmoudian, M.; Skellern, G. G.; Grant, M. H.; Tettey, J. N. A. *J. Pharm. Pharmacol.* **2004**, *56*, 1469–1474. DOI: 10.1211/0022357044760.

[17] Miri, R.; Javidnia, K.; Hemmateenejad, B.; Tabarzad, M.; Jafarpour, M. *Chem. Biol. Drug Des.* **2009**, *73*, 225–235. DOI: 10.1111/j.1747-0285.2008.00770.x.

[18] Navidpour, L.; Shafaroodi, H.; Miri, R.; Dehpour, A. R.; Shafiee, A. *Farmaco* **2004**, *59*, 261–269. DOI: 10.1016/j.farmac.2003.11.013.

[19] Iqbal, P. F.; Parveen, H.; Bhat, A. R.; Hayat, F.; Azam, A. *Eur. J. Med. Chem.* **2009**, *44*, 4747–4751. DOI: 10.1016/j.ejmech.2009.06.016.

[20] Wang, C.; Jung, G.-Y.; Batsanov, A. S.; Bryce, M. R.; Petty, M. C. *J. Mater. Chem.* **2002**, *12*, 173–180. DOI: 10.1039/b106907c.

[21] El-Feky, S. A. H.; Abd El-Samii, Z. K.; Osman, N. A.; Lashine, J.; Kamel, M. A.; Thabet, H. K. *Bioorg. Chem.* **2015**, *58*, 104–116. DOI: 10.1016/j.bioorg.2014.12.003.

[22] El-Sabbagh, O. I.; Baraka, M. M.; Ibrahim, S. M.; Pannecouque, C.; Andrei, G.; Snoeck, R.; Balzarini, J.; Rashad, A. A. *Eur. J. Med. Chem.* **2009**, *44*, 3746–3753. DOI: 10.1016/j.ejmech.2009.03.038.

[23] Insuasty, B.; Tigreros, A.; Orozco, F.; Quiroga, J.; Abonía, R.; Nogueras, M.; Sanchez, A.; Cobo, J. *Bioorg. Med. Chem.* **2010**, *18*, 4965–4974. DOI: 10.1016/j.bmc.2010.06.013.

[24] Michon, V.; Du Penhoat, C. H.; Tombret, F.; Gillardin, J. M.; Lepage, F.; Berthon, L. *Eur. J. Med. Chem.* **1995**, *30*, 147–155. DOI: 10.1016/0223-5234(96)88220-1.

[25] Rangaswamy, J.; Vijay Kumar, H.; Harini, S. T.; Naik, N. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4773–4777. DOI: 10.1016/j.bmcl.2012.05.061.

[26] Horrocks, P.; Pickard, M. R.; Parekh, H. H.; Patel, S. P.; Pathak, R. B. *Org. Biomol. Chem.* **2013**, *11*, 4891. DOI: 10.1039/c3ob27290g.
[27] Ansari, A.; Ali, A.; Asif, M.; Shamsuzzaman, S. *New J. Chem.* **2017**, *41*, 16–41. DOI: 10.1039/C6NJ03181A.
[28] Ghozlan, S. A. S.; Abdelmoniem, A. M.; Butenschön, H.; Abdelhamid, I. A. *Tetrahedron* **2015**, *71*, 1413–1418. DOI: 10.1016/j.tet.2015.01.026.
[29] Ghozlan, S. A. S.; Mohamed, M. H.; Abdelmoniem, A. M.; Abdelhamid, I. A. *Arkivoc* **2009**, *2009*, 302. DOI: 10.3998/ark.5550190.0010.a27.
[30] Abdelhamid, I. A.; Darwish, E. S.; Nasra, M. A.; Abdel-Gallil, F. M.; Fleita, D. H. *Synthesis* **2010**, *2010*, 1107–1112. DOI: 10.1055/s-0029-1219235.
[31] Ghozlan, S. A. S.; Mohamed, M. F.; Ahmed, A. G.; Shouman, S. A.; Attia, Y. M.; Abdelhamid, I. A. *Arch. Pharm. Chem. Life. Sci.* **2015**, *348*, 113–124. DOI: 10.1002/ardp.201400304.
[32] Abdelhamid, I. A. *Synlett.* **2009**, *2009*, 625–627. DOI: 10.1055/s-0028-1087558.
[33] Abdelhamid, I. A.; Mohamed, M. H.; Abdelmoniem, A. M.; Ghozlan, S. A. S. *Tetrahedron* **2009**, *65*, 10069–10073. DOI: 10.1016/j.tet.2009.09.081.
[34] Ghozlan, S. A. S.; Abdelhamid, I. A.; Hassaneen, H. M.; Elnagdi, M. H. *J. Heterocycl. Chem.* **2007**, *44*, 105–108. DOI: 10.1002/jhet.5570440118.
[35] Ghozlan, S. A. S.; Abdelhamid, I. A.; Elnagdi, M. H. *Arkivoc* **2006**, *xiii*, 147. DOI: 10.3998/ark.5550190.0007.d15.
[36] Ghozlan, S. A. S.; Ahmed, A. G.; Abdelhamid, I. A. *J. Heterocyclic Chem.* **2016**, *53*, 817–823. DOI: 10.1002/jhet.2341.
[37] Abdella, A. M.; Abdelmoniem, A. M.; Ibrahim, N. S.; El-Hallouty, S. M.; Abdelhamid, I. A.; Elwahy, A. H. M. *Mini Rev. Med. Chem.* **2020**, *20*, 801–816. DOI: 10.2174/1389557519666190919160019.
[38] Mir, F.; Shafi, S.; Zaman, M. S.; Kalia, N. P.; Rajput, V. S.; Mulakayala, C.; Mulakayala, N.; Khan, I. A.; Alam, M. S. *Eur. J. Med. Chem.* **2014**, *76*, 274–283. DOI: 10.1016/j.ejmech.2014.02.017.
[39] Siddiqui, N.; Rana, A.; Khan, S. A.; Haque, S. E.; Alam, M. S.; Ahsan, W.; Ahmed, S. *J. Enzyme Inhib. Med. Chem.* **2009**, *24*, 1344–1350. DOI: 10.3109/14756360902888176.
[40] Prakash, O.; Aneja, D. K.; Hussain, K.; Lohan, P.; Ranjan, P.; Arora, S.; Sharma, C.; Aneja, K. R. *Eur. J. Med. Chem.* **2011**, *46*, 5065–5073. DOI: 10.1016/j.ejmech.2011.08.019.
[41] Sumangala, V.; Poojary, B.; Chidananda, N.; Arulmoli, T.; Shenoy, S. *Eur. J. Med. Chem.* **2012**, *54*, 59–64. DOI: 10.1016/j.ejmech.2012.04.024.
[42] Sanad, S. M. H.; Kassab, R. M.; Abdelhamid, I. A.; Elwahy, A. H. M. *Heterocycles* **2016**, *92*, 910. DOI: 10.3987/COM-16-13441.
[43] Krauze, A.; Sile, L.; Duburs, G. *Heterocycl. Commun.* **2001**, *7*, 375. DOI: 10.1515/HC.2001.7.4.375.
[44] Tanji, S.; Shibata, T.; Sato, I.; Soai, K. J. *J. Chem. Soc. Perkin Trans. 1* **2001**, *2001*, 217–218. DOI: 10.1039/b009474i.
[45] Quiroga, J.; Portilla, J.; Insuasty, B.; Abonía, R.; Nogueras, M.; Sortino, M.; Zacchino, S. *J. Heterocycl. Chem.* **2005**, *42*, 61–66. DOI: 10.1002/jhet.5570420108.
[46] Oqba, A.-S.; Hameed, N.; Fawzy, A.; Res, A. *J. Chem. Environ.* **2019**, *23*, 32.
[47] Pelit, E. J. *Soc. Sect. A Chem.* **2017**, *4*, 631. DOI: 10.18596/jotcsa.295465.
[48] Bhuyan, P.; Boruah, R. C.; Sandhu, J. S. *J. Org. Chem.* **1990**, *55*, 568–571. DOI: 10.1021/jo00289a033.