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Hantzsch synthesis of *bis*(pyrido[2,3-*d*:6,5-*d*']dipyrimidines), *bis*(pyrimido[4,5-*b*]quinolines), and *bis*(benzo[4,5]imidazo[2,1-*b*]quinazolines) linked to pyrazole units as novel hybrid molecules

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

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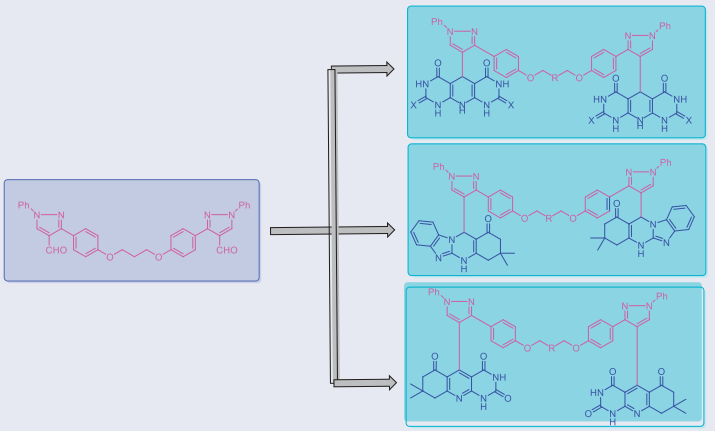
ABSTRACT

Bis(1-phenylpyrazole-4-carboxaldehydes) were utilized as versatile precursors to novel series of *bis*(pyrido[2,3-*d*:6,5-*d*']dipyrimidines), *bis*(pyrimido[4,5-*b*]quinolines), and *bis*(benzo[4,5]imidazo[2,1-*b*]quinazolines) derivatives which are linked to pyrazole units.

GRAPHICAL ABSTRACT



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Bis(benzo[4,5]imidazo[2,1-b]quinazolines); bis(pyrido[2,3-d:6,5-d']dipyrimidines); bis(pyrimido[4,5-b]quinolines); Hantzsch like reaction; 6-aminouracil

Introduction

Uracil is a naturally occurring pyrimidine moiety and represents one of the four nucleobases in the biopolymer RNA.[1–5] The uracil and its derivatives display a wide range of bioactivities that include, treatment of viral and cancer diseases.[6–8] Also, they have a variety of applications as antihypertensive agents,[9] antiallergics,[10,11] bronchodilators,[10,11] and adenosine receptor antagonists.[12,13] Besides, uracil derivatives were used as versatile reagents for the synthesis of a wide range of heterocyclic compounds including, pyrido[2,3-*d*]pyrimidines,[14,15] pyrimido[4,5-*d*]pyrimidines,[15] and

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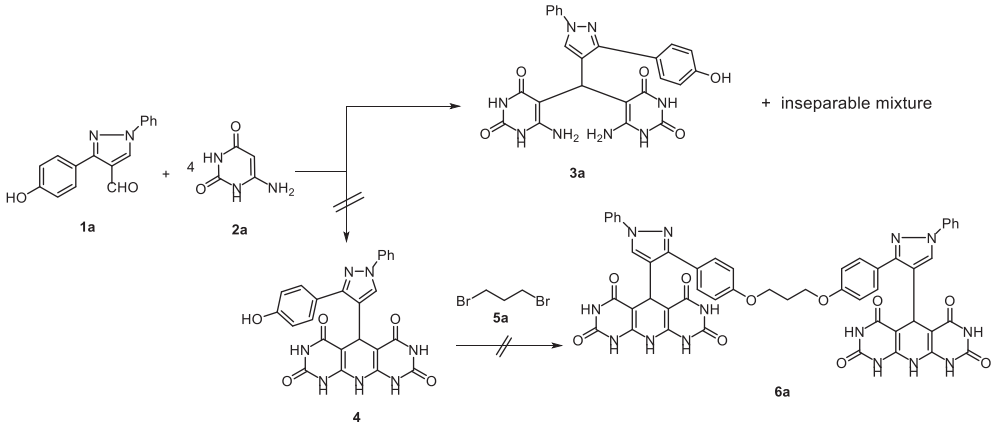
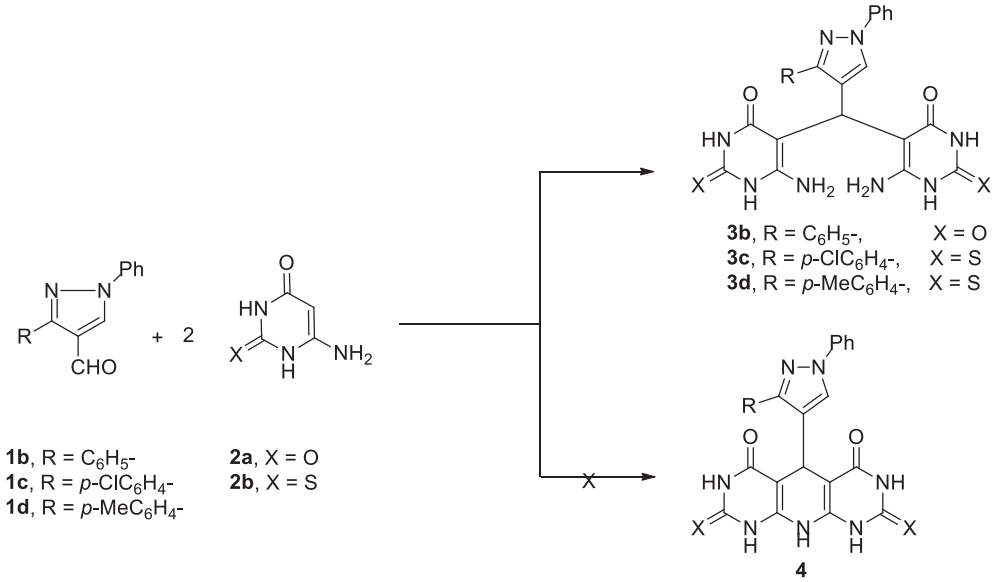


Scheme 1. Attempted synthesis of *bis*(5,10-dihydropyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8-tetraone) **6a**.

pyrimido[4,5-*b*]quinolines.[14,16–22] In addition, the pyrazole derivatives are found in many pharmaceutical drugs[21–26] that exhibit anti-inflammatory properties and inhibit alcohol dehydrogenase in addition to sildenafil phosphodiesterase.[27] Furthermore, in the last decades, the synthesis of hybrid molecules and their evaluation as broad types of pharmacological agents have been extensively studied.[28–36] These compounds are characterized by linking two differently active compounds in novel scaffolds with improved biological and medicinal applications. Multi-component reactions (MCRs) are economically and environmentally friendly as compared to the normal multistep reactions[37–41] which produce considerable amounts of waste mainly due to toxic and hazardous solvents. On the other hand, MCRs provide rapid access to organic compounds with higher simplicity, selectivity, atom-economy and an overall efficiency.[37–41] With reference to the significance of the uracil and pyrazole moieties and in conjunction to our work on Michael addition,[42–46] Hantzsch reactions[47–50] multicomponent reactions,[48,51,52] as well as on the synthesis of *bis*-heterocycles[47–49,51–54] our study aims at the synthesis of novel *bis*(5,10-dihydropyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8-tetraones), *bis*(5,8,9,10-tetrahydropyrimido[4,5-*b*]quinoline-2,4,6-triones) and *bis*(3,4,5,12-tetrahydro-benzo[4,5]imidazo[2,1-*b*]quinazolin-1-ones) each linked to pyrazole moiety.

Results and discussion

Two strategies were assumed for the synthesis of *bis*(1-phenylpyrazole-3,4-diyl))*bis*(5,10-dihydropyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8-tetraone) **6a**. In the first strategy (Pathway A), we studied the synthesis of 5-(3-(4-hydroxyphenyl)-1-phenylpyrazol-4-yl)-5,10-dihydropyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8-tetraone **4** which should then undergo *bis*-alkylation reaction with 1,3-dibromopropane **5a**, under basic reaction conditions to give *bis*(1-phenylpyrazole-3,4-diyl))*bis*(5,10-dihydropyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8-tetraone) **6a** (Scheme 1). Unfortunately, pseudo-multicomponent reaction of 3-(4-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde **1a** with two equivalents of 6-aminouracil **2a** in acetic acid at reflux did not lead to the formation of

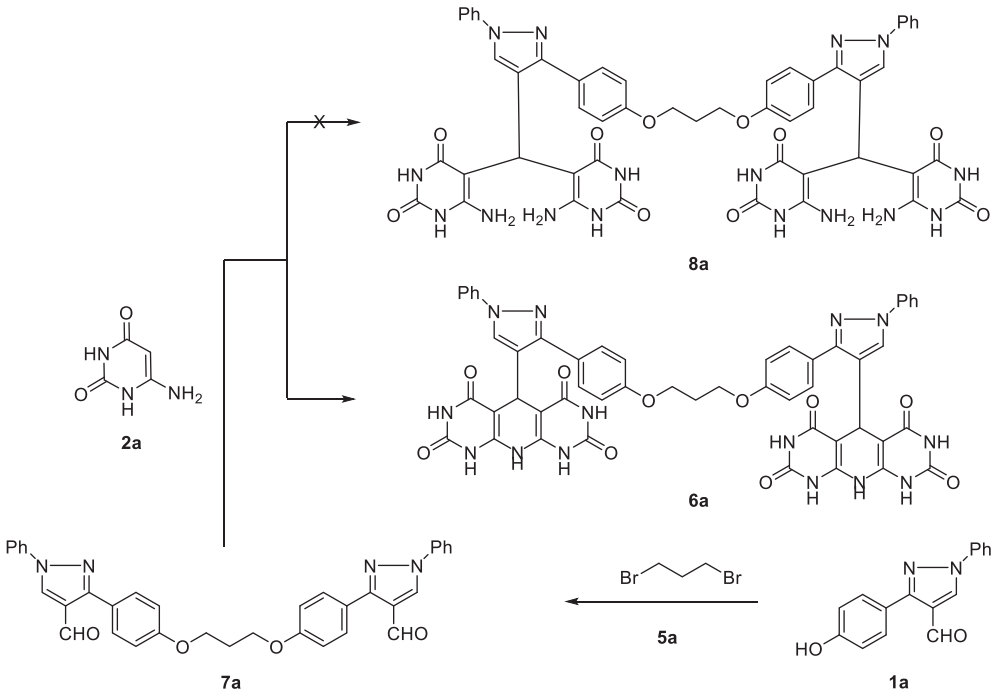


Scheme 2. Synthesis of 5,5′-((3-aryl-1-phenylpyrazol-4-yl)methylene)*bis*(6-aminopyrimidine-2,4-dione) **3b–d**.

4a even after prolonged heating. Instead, the reaction afforded an inseparable mixture of the 5,5′-((3-aryl-1-phenylpyrazol-4-yl)methylene)bis(6-aminopyrimidine-2,4-dione) **3a** together with other undefined products.

It is worthy to mention that we also investigated the reactivity of other 1-arylpyrazole-4-carboxaldehydes **1b–d** with two equivalents of either 6-aminouracil **2a** or thiouracil **2b** in acetic acid at reflux. Likewise, in all cases, the reactions did not afford the corresponding 5,10-dihydropyrido[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8-tetraone **4**, and instead the 5,5′-((3-aryl-1-phenylpyrazol-4-yl)methylene)*bis*(6-aminopyrimidine-2,4-dione) **3b–d** were obtained as sole products in good to excellent yields (Scheme 2). The structures of the formed products were confirmed based on the ^{1}H NMR spectrum of **3b** that indicated the presence of two amino groups at 6.63 ppm. Besides, it revealed the presence of a characteristic singlet signal at δ 5.45 for the methine protons. Besides, the two broad singlets at δ 10.07 and δ 10.46 are assigned to the two NH groups. The pyrazole-H and aromatic protons appear at their expected position. The IR spectrum of compound **3b** revealed bands at ν 3357, 3168, and 1630 cm^{-1} characteristic for NH_2, NH and CO groups. Moreover, the mass spectrum of compound **3b** features the correct molecular ion peak at *m/z* 484.

The unsuccessful synthesis of **6** using the above strategy prompted us to study another approach (Pathway B). This strategy includes two steps; in the first one, the *bis*-aldehyde **7a** was prepared as previously described[55] v*ia* the *bis*-alkylation reaction of 3-(4-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde **1a** with the 1,3-dibromopropane **5a** in boiling DMF in the presence of potassium hydroxide (Scheme 3). Subsequent acid-catalyzed cyclocondensation reaction of one mole equivalent of **7a** with four mole equivalents of 6-aminouracil **2a** afforded the *bis*(9,10-dihydropyrido[2,3-*d*:6,5-



Scheme 3. Synthesis of *bis*(5,10-dihydropyrido[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8-tetraone) **6a**.

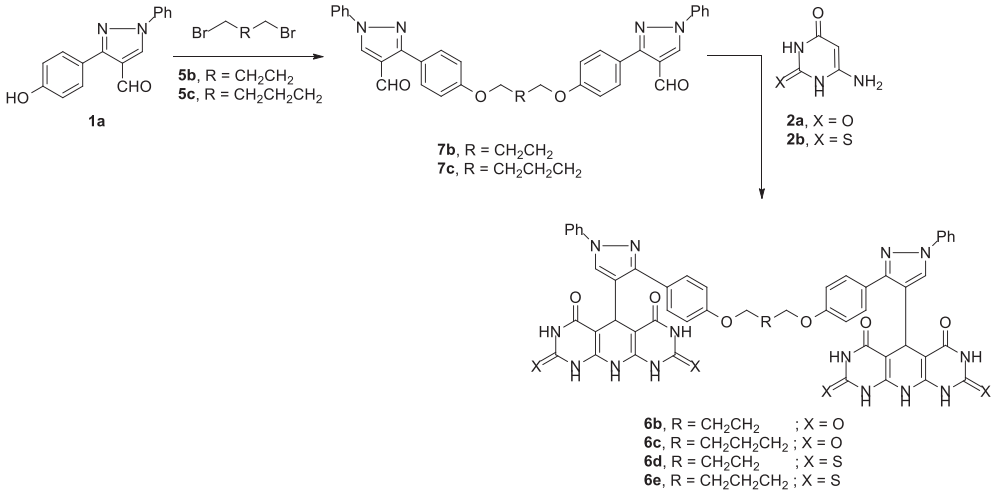
d']dipyrimidinetetraone) **6a** rather than the other possible tetrakis(aminouracil) derivative **8a** (Scheme 3).

The *tetrakis*(aminouracil) **8a** was readily excluded based on the absence of primary amino groups in their IR as well as ^{1}H NMR spectra. On the other hand, the ^{1}H-NMR spectrum of **6a** revealed a singlet signal at δ 5.42 for the pyridine-H5. It showed also three different broad signals at 6.53, 10.13, and 10.50 ppm corresponding to three different NH groups. The aromatic protons, as well as the pyrazole-H5, appear at their expected positions at 6.87–7.85 ppm and 8.05 ppm, respectively.

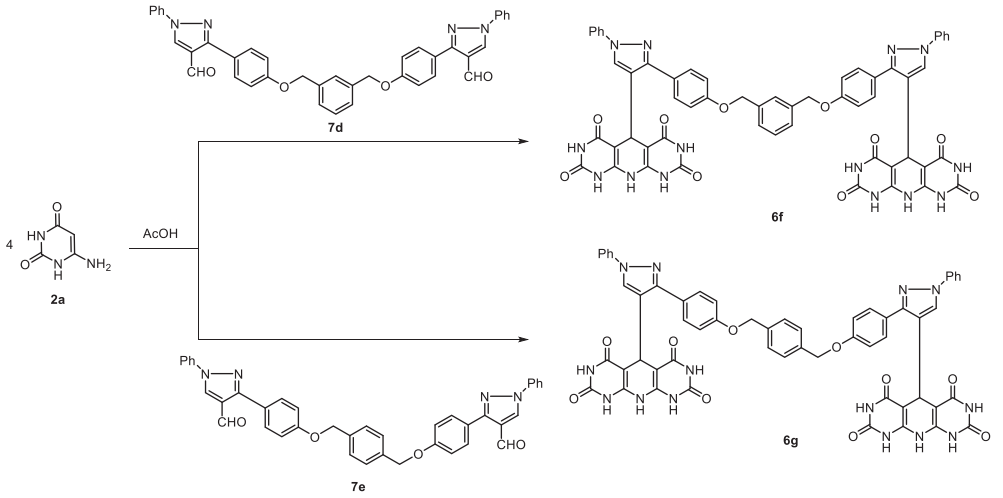
Encouraged by this success, and in a trial to expand the scope of this reaction, *bis*(9,10-dihydropyrido[2,3-*d*:6,5-*d*']dipyrimidinetetraone) derivatives **6b–e**, which are linked to alkyl spacer *via* phenoxy groups, were furnished through the reaction of compounds **7b,c** with four equivalents of either 6-aminouracil **2a** or 6-aminothiouracil **2b** in acetic acid at reflux (Scheme 4). It is worth mentioning that, the *bis*-aldehydes **7b,c** were prepared *via* the bis(alkylation) of **1d** with the appropriate dibromo compounds **5b,c**[55] (Scheme 4).

The synthetic scope of this reaction was also demonstrated by preparing the *bis*(9,10-dihydropyrido[2,3-*d*:6,5-*d*']dipyrimidinetetraone) **6f** and **6g** which are linked to benzene core *via* phenoxymethyl linkage by the reaction of the respective *bis*(1-phenylpyrazole-4-carboxaldehyde) **7d** and **7e**[55] with four equivalents of 6-aminouracil **2a** in acetic acid at reflux (Scheme 5).

Exceptionally, the reaction of *bis*(1-phenylpyrazole-4-carboxaldehyde) **7e** with 6-aminothiouracil **2b** yielded the cyclic aromatized product **9a**, whose constitution was



Scheme 4. Synthesis of *bis*(9,10-dihydropyrido[2,3-*d*:6,5-*d*′]dipyrimidinetetraone) derivatives **6b–e**.

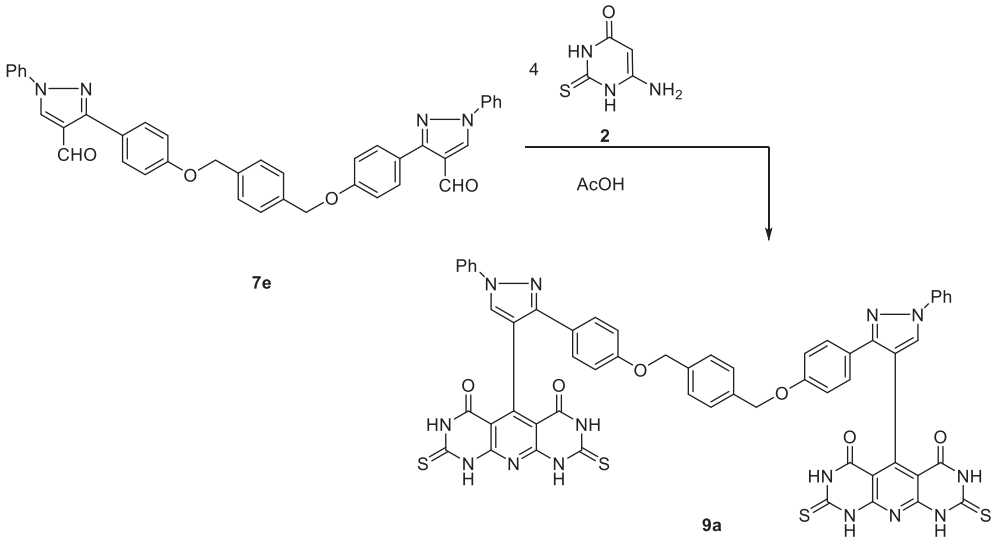


Scheme 5. Synthesis of *bis*(9,10-dihydropyrido[2,3-*d*:6,5-*d*′]dipyrimidinetetraone) **6f** and **6g**.

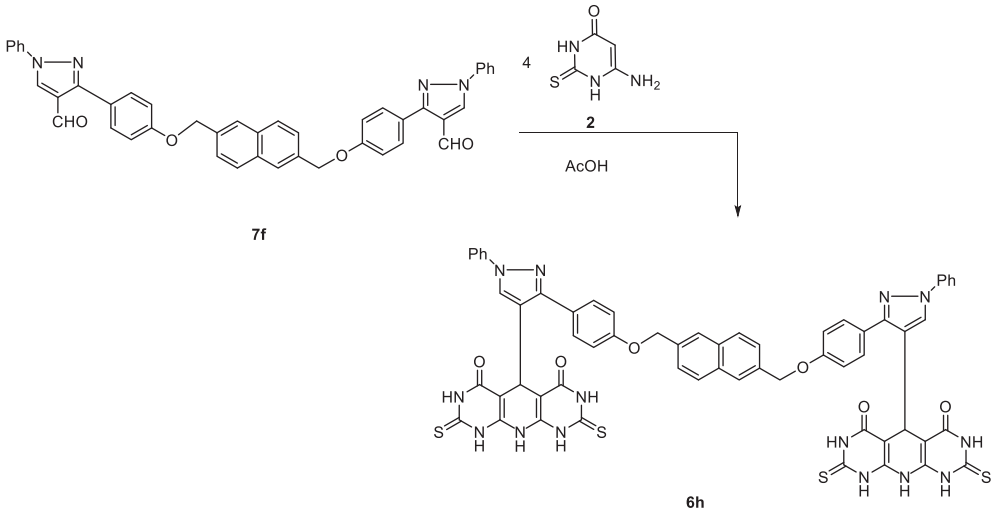
confirmed based on ^{1}H NMR that indicated the absence of a signal for pyridine-H5 in area 4–6 ppm. The ^{1}H NMR spectrum of **9a** indicated also only two types of NH groups each one integrated by 2 protons at 10.13 and 10.50 ppm, respectively (Scheme 6).

Interestingly, the *bis*(9,10-dihydropyrido[2,3-*d*:6,5-*d*′]dipyrimidinetetraone) **6h** which is linked to naphthalene core *via* phenoxymethyl linkage was also prepared when a warm glacial acetic solution of one equivalent of the 3,3′-(((naphthalene-2,6-diyl*bis*(methylene))*bis*(oxy))*bis*(4,1-phenylene))*bis*(1-phenylpyrazole-4-carboxaldehyde) **7f** (prepared as reported earlier),[55] was added to four equivalents of **2b** (Scheme 7).

Apparently, the reaction mechanism depends on the fact that each formyl group reacts with two-mole equivalents of 6-aminouracil. Thus, the reaction involves the initial condensation of the phenylpyrazole-4-carboxaldehydes **1** or its *bis*-analogues **7** with one



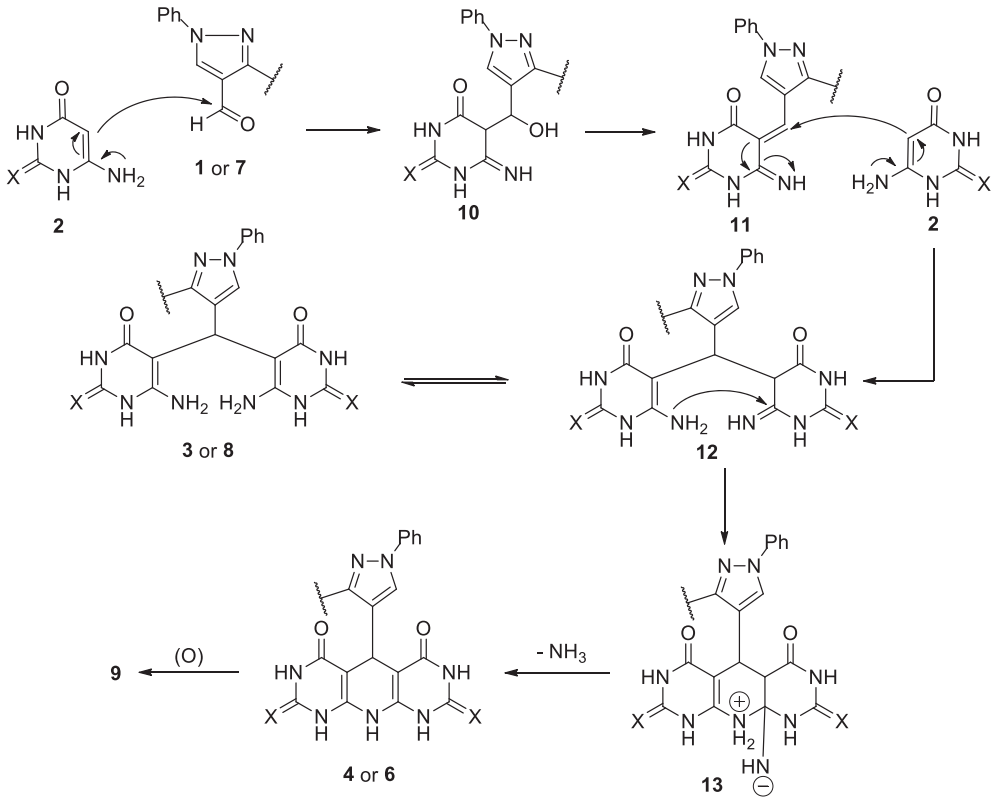
Scheme 6. Synthesis of *bis*(2,8-dithioxo-2,3,8,9-tetrahydropyrido[2,3-*d*:6,5-*d*′]dipyrimidine-4,6(1*H*,7*H*)-dione) **9a**.



Scheme 7. Synthesis of *bis*(9,10-dihydropyrido[2,3-*d*:6,5-*d*′]dipyrimidinetetraone) **6h**.

or two equivalents of the 6-aminouracil **2** producing, the unstable ylidene derivative **11** *via* the intermediacy of **10**. The intermediates **11** then, undergo Michael-type addition with another one or two equivalents of the 6-aminouracil **2** to afford **12**, which either tautomerize into the diamine (**3** or **8**) or cyclize into **13**. The intermediates **13** loss NH_3 yielding the final product (**4** or **6**). In one exceptional case, further oxidation of the latter compounds under the reaction conditions leads to the formation of the fully oxidized compound **9** (Scheme 8).

The synthetic utility of *bis*(1-phenylpyrazole-4-carboxaldehydes) was also extended to involve the synthesis of a new series of *bis*(pyrimido[4,5-*b*]quinolines) linked to prazole

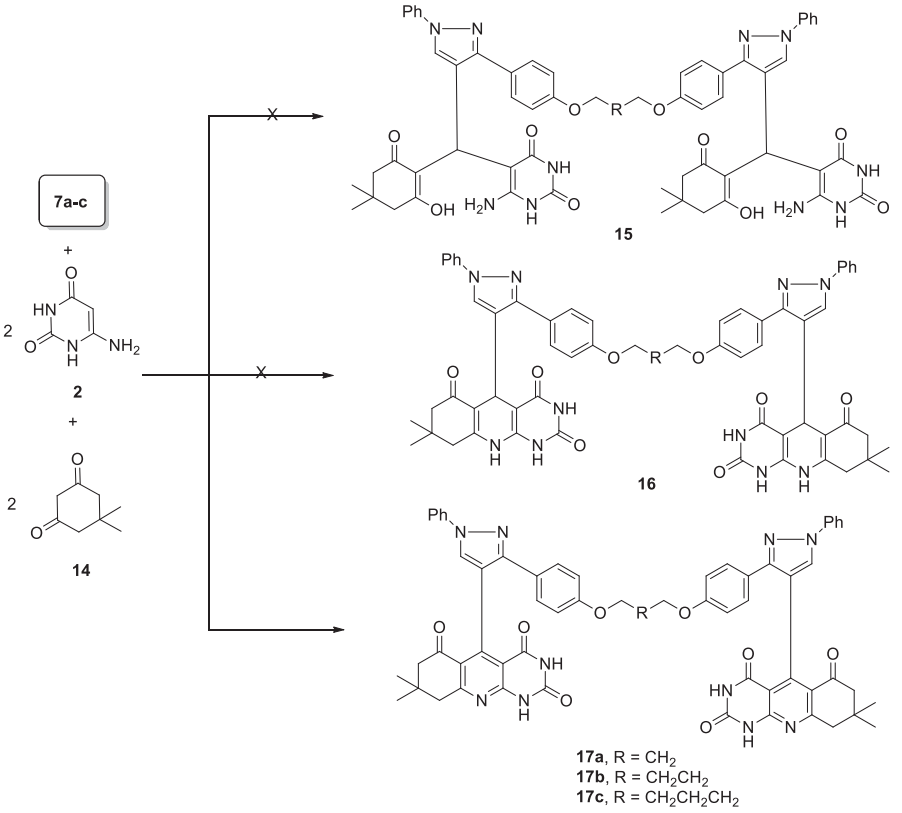


Scheme 8. A plausible mechanism for the synthesis of *bis*(pyrido[2,3-*d*:6,5-*d'*]dipyrimidines) **9**.

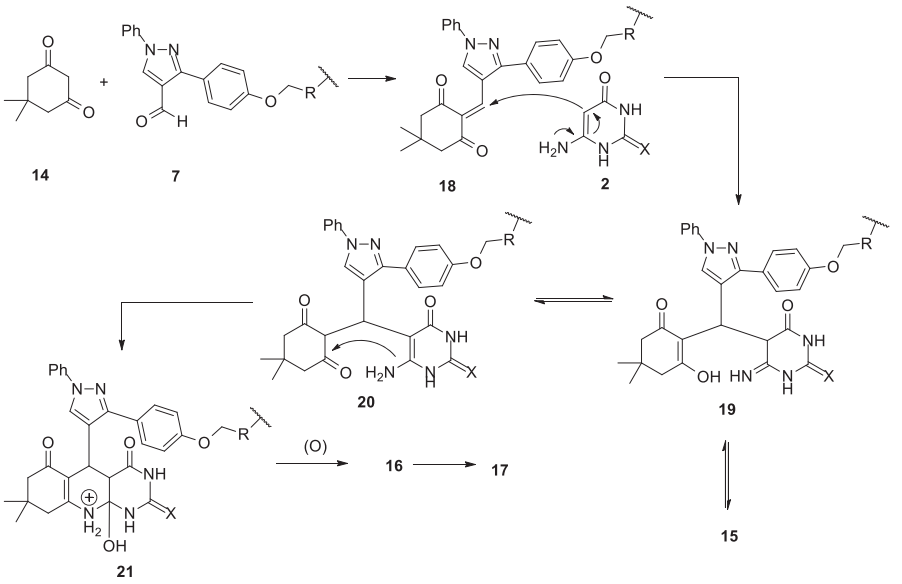
moiety. Thus, the three-component reaction of *bis*(1-phenylpyrazole-4-carboxaldehydes) **7a–c** with two equivalents of both 6-aminouracil **2** and dimedone **14** afforded the corresponding *bis*(4,1-phenylene))*bis*(1-phenylpyrazole-3,4-diyl))*bis*(8,8-dimethyl-8,9-dihydropyrimido[4,5-*b*]quinoline-2,4,6-trione) **17a–c** in good yields (Scheme 9). It is worth mentioning that the adduct **15** or the non-oxidized *bis*(5,8,9,10-tetrahydropyrimido[4,5-*b*]quinoline-2,4,6-trione) **16** were readily excluded based on ^{1}H NMR that indicated the absence of amino groups in case of **15** and the absence of H-5 and NH-10 in case of **16** at their expected positions.

Mechanistically, the reaction proceeds *via* the initial formation of the Knoevenagel condensation product **18,** upon treatment of **14** with **7**, followed by its reaction with 6-aminouracil **2** to give intermediate **19** that either tautomerizes into **15**, or **20**. Intermediate **20** undergoes cyclization involving the amino and the carbonyl group to give **21** that eliminate water to afford **16**. Subsequent oxidation under the reaction conditions leads to the formation of **17** (Scheme 10). The oxidation of dihydropyridine under reaction conditions were previously reported.[48,55]

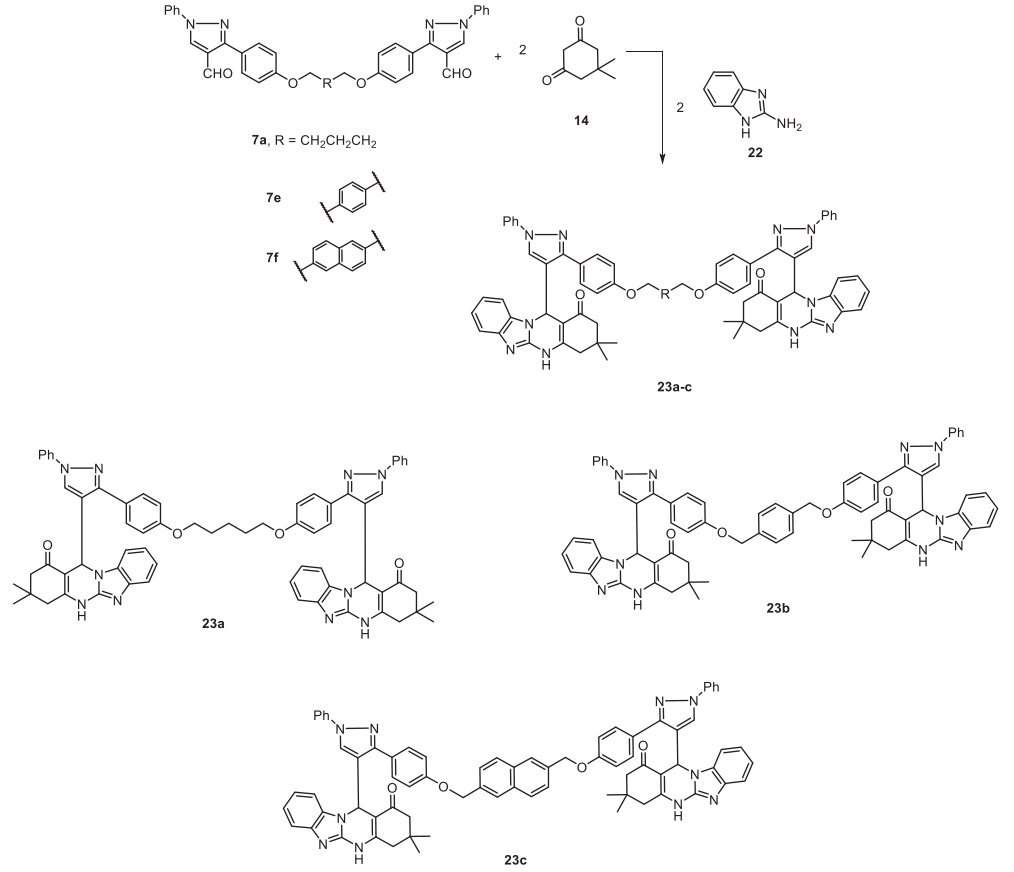
Our study was also extended utilizing the *bis*(1-phenylpyrazole-4-carboxaldehydes) **7** as versatile precursors for novel *bis*(1-phenylpyrazole-3,4-diyl))*bis*(3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-*b*]quinazolin-1-ones) **23a–c**. Thus, cyclocondensation reaction of



Scheme 9. Synthesis of *bis*(8,8-dimethyl-8,9-dihydropyrimido[4,5-*b*]quinolinetriones) **17a–c**.



Scheme 10. A plausible mechanism for the synthesis of *bis*(pyrimido[4,5-*b*]quinolinetriones) **17a–c**.

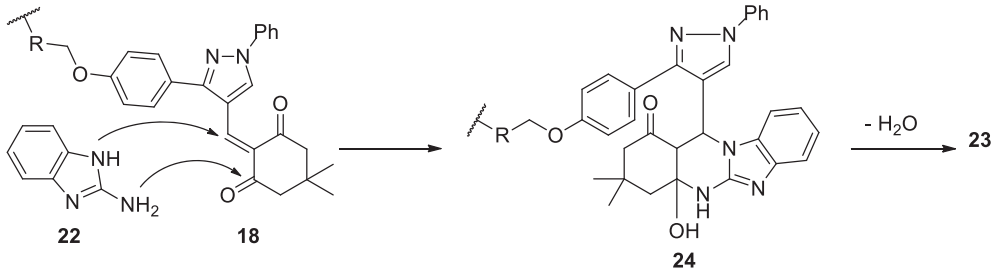


Scheme 11. A plausible mechanism for the synthesis of *bis*(benzo[4,5]imidazo[2,1-*b*]quinazolin-1-ones) **23a–c**.

bis(1-phenylpyrazole-4-carboxaldehydes) **7a**, **7e**, and **7f** with two equivalents of both of dimedone **14**, and 2-aminobenzimidazole **22** in DMF afforded **23a–c,** respectively, in good yields (Scheme 11). The fused tetrahydrobenzo[4,5]imidazo[2,1-*b*]quinazolinones have received considerable attention and are frequently investigated due to their wide range of bioactivities as compared to homonuclear scaffold.[56–61]

The structures of compounds **23** were confirmed based on elemental analyses as well as spectral data. Thus, the ^{1}H NMR spectrum of **23a** showed the presence of two singlets integrated by 12 protons at δ 1.02 and δ 1.05 assigned to four CH_3 groups. Besides, the singlet signal at 6.56 ppm is due to H12. It also revealed the NH group as a broad singlet signal at 11.48 ppm. All other signals appeared at their expected positions.

The reaction is assumed to proceed *via* the intermediacy of α,β-unsaturated ketone **18** that undergo addition and condensation reactions with 2-aminobenzimidazole **22** to afford the intermediate **24**. Subsequent removal of water leads to the formation of the target products **23** (Scheme 12).



Scheme 12. Synthesis of *bis*(3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-*b*]quinazolin-1-ones) **23a–c**.

Conclusions

We managed to develop an efficient synthetic approach for the synthesis of novel *bis*(-pyrido[2,3-*d*:6,5-*d*']dipyrimidines), *bis*(pyrimido[4,5-*b*]quinolines) as well as *bis*(benzo[4,5]imidazo[2,1-*b*]quinazolines linked to pyrazole moiety *via* one-pot multi-component cyclocondensation reaction of *bis*(1-phenylpyrazole-4-carboxaldehydes) with the respective (4 equiv. 6-aminouracil), (2 equiv. 6-aminouracil and 2 equiv. dimedone) or (2 equiv. dimedone and 2 equiv. 2-aminobenzimidazole).

Experimental

Introduction

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 a 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 3a–3d

A solution of each of 1-phenyl-1*H*-pyrazole-4-carboxaldehydes (**1a–1d**) (1 mmol) and 6-aminouracil **2a** or 6-aminothiouracil **2b** (2 mmol) in acetic acid (5 ml) was heated at reflux for 3 h. The solid obtained was collected and recrystallized from the proper solvent to give compounds **3a–d**.

5,5'-((1,3-Diphenyl-1H-pyrazol-4-yl)methylene)bis(6-aminopyrimidine-2,4(1H,3H)-dione) (3b)

Colrless solid (DMF, 73%); m.p. $>$ 300 °C, IR (KBr): υ_{max} 3346, 3163 (br, NH_2 and NH), 1630 (CO), ^{1}H-NMR (DMSO-d_6): δ 5.45 (s, 1H, CH), 6.63 (br s, 4H, 2 NH_2), 7.22–7.48 (m, 8H, ArH), 7.85 (d, 2H, ArH), 8.07 (s, 1H, pyrazole-H5), 10.07 (br s, 2H, 2 NH), 10.46 (br s, 2H, 2 NH), Anal. Calcd. for $C_{24}H_{20}N_8O_4$ (484.48): C, 59.50; H, 4.16; N, 23.13; found: C, 59.69; H, 3.98; N, 23.30%.

General procedure for the synthesis of 6a–6h and 9a

A solution of each of *bis*(1-phenylpyrazole-4-carboxaldehydes) (**7a–7f**) (1 mmol) and 6-aminouracil **2a** or 6-aminothiouracil **2b** (4 mmol) in acetic acid (5 ml) was heated at reflux for 3 h. The solid obtained was collected and crystallized from the proper solvent to give the respective compounds **6a–6h** and **9a**.

5,5′-(((Propane-1,3-diylbis(oxy))bis(4,1-phenylene))bis(1-phenyl-1H-pyrazole-3,4-diyl))-bis(5,10-dihydropyrido[2,3-d:6,5-d′]dipyrimidine-2,4,6,8(1H,3H,7H,9H)-tetraone) (6a)

Yellow solid (DMF, 75%); m.p. > 300 °C, IR (KBr): υ_{max} 3347 (br, NH), 1709, 1627 (2CO), ^{1}H-NMR (DMSO-d_6): δ 2.18 (br s, 2H, $OCH_2CH_2CH_2O$), 4.14 (br s, 4H, $OCH_2CH_2CH_2O$), 5.42 (s, 2H, 2 CH), 6.53 (br s, 4H, 4 NH), 6.88 (d, 4H, ArH), 7.24–7.47 (m, 10H, ArH), 7.84 (d, 4H, ArH), 8.05 (s, 2H, 2 pyrazole-H5), 10.13 (br s, 4H, 4 NH), 10.50 (br s, 2H, 2 NH), ^{13}C-NMR (DMSO-d_6): δ 25.9, 29.0, 64.9, 87.4, 113.8, 118.0, 119.6, 120.1, 125.7, 126.8, 129.1, 129.8, 140.2, 150.0, 151.1, 154.0, 158.1, Anal. Calcd. for $C_{51}H_{38}N_{14}O_{10}$ (1006.95): C, 60.83; H, 3.80; N, 19.47; found: C, 60.97; H, 3.64; N, 19.55%.

General procedure for the synthesis of 17a–c

A solution of each of bis(1-phenylpyrazole-4-carboxaldehydes) (**7a–c**) (1 mmol), dimedone **14** (2 mmol), and 6-aminouracil **2a** or 6-aminothiouracil **2b** (2 mmol) in acetic acid (5 ml) was heated at reflux for 3 h. The solid obtained was collected and crystallized from the proper solvent to give the respective compounds **17a–c**.

5,5′-(((Propane-1,3-diylbis(oxy))bis(4,1-phenylene))bis(1-phenyl-1H-pyrazole-3,4-diyl))-bis(8,8-dimethyl-8,9-dihydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione) (17a)

Orange solid (DMF, 82%); m.p. 185–186 °C, IR (KBr): υ_{max} 3142 (NH), 3052 (NH), 1606, 1511 (CO), ^{1}H-NMR (DMSO-d_6): δ 1.03 (s, 12H, $4CH_3$), 2.23 (m, 2H, $OCH_2CH_2CH_2O$), 2.50 (s, 4H, $2CH_2$), 2.96 (s, 4H, 2 CH_2), 4.21 (t, 4H, $OCH_2CH_2CH_2O$), 6.94–7.86 (m, 16H, ArH), 8.51 (s, 2H, ArH), 8.55 (s, 2H, 2 pyrazole-H5), 11.59 (s, 2H, 2NH), 11.99 (s, 2H, 2NH), ^{13}C-NMR (DMSO-d_6): δ 28.2, 29.1, 32.8, 46.0, 51.3, 64.7, 105.3, 109.5, 115.1, 118.5, 123.0, 125.8, 127.3, 129.9, 135.0, 140.1, 150.7, 152.2, 155.0, 158.9, 162.3, 168.6, 172.5, 196.0. Anal. Calcd. for $C_{59}H_{50}N_{10}O_8$ (1027.1): C, 68.99; H, 4.91; N, 13.64; found: C, 68.71; H, 4.78; N, 13.75%.

General procedure for the synthesis of 23a–c

A solution of each of bis(1-phenylpyrazole-4-carboxaldehydes) (**7a, 7e,** and **7f**) (1 mmol), dimedone (2 mmol), and 2-aminobenzimidazole **22** (2 mmol) in acetic acid (5 ml) was heated at reflux for 3 h. The solid obtained was collected and crystallized from the proper solvent to give the respective compounds **23a–c**.

12,12′-(((Pentane-1,5-diylbis(oxy))bis(4,1-phenylene))bis(1-phenyl-1H-pyrazole-3,4-diyl))bis(3,3-dimethyl-3,4,5,12-tetrahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1(2H)-one) (23a)

Yellow solid (Ethanol, 77%); mp. 201–202 °C, IR (KBr): υ_{max} 3395 (NH), 1618, 1569 (CO), ^{1}H-NMR (, DMSO-d_6): δ 1.02 (s, 6H, 2CH_3), 1.05 (s, 6H, 2CH_3), 1.65 (br s, 2H, $OCH_2CH_2CH_2CH_2CH_2O$), 1.87 (br s, 4H, $OCH_2CH_2CH_2CH_2CH_2O$), 2.21 (m, 4H, 2 CH_2), 2.57–2.63 (m, 4H, 2 CH_2), 4.12 (br s, 4H, $OCH_2CH_2CH_2CH_2CH_2O$), 6.56 (s, 2H, 2 CH), 6.78 – 7.93 (m, 26H, ArH), 8.54 (s, 2H, 2 pyrazole-H5), 11.47 (br s, 2H, 2 NH). Anal. Calcd. for $C_{67}H_{62}N_{10}O_4$ (1071.3): C, 75.12; H, 5.83; N, 13.07; found: C, 75.01; H, 5.99; N, 12.98%.

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References

[1] Fathalla, M.; Lawrence, C. M.; Zhang, N.; Sessler, J. L.; Jayawickramarajah, J. *Chem. Soc. Rev*. **2009**, *38*, 1608–1620. DOI: 10.1039/b806484a.
[2] Sivakova, S.; Rowan, S. J. *Chem. Soc. Rev*. **2005**, *34*, 9–21. DOI: 10.1039/b304608g.
[3] Parker, J. B.; Bianchet, M. A.; Krosky, D. J.; Friedman, J. I.; Amzel, L. M.; Stivers, J. T. *Nature* **2007**, *449*, 433–437. DOI: 10.1038/nature06131.
[4] Okamoto, A. *Org. Biomol. Chem*. **2009**, *7*, 21–26. DOI: 10.1039/B813595A.
[5] McCarthy, O.; Musso-Buendia, A.; Kaiser, M.; Brun, R.; Ruiz-Perez, L. M.; Johansson, N. G.; Pacanowska, D. G.; Gilbert, I. H. *Eur. J. Med. Chem*. **2009**, *44*, 678–688. DOI: 10.1016/J.EJMECH.2008.05.018.
[6] Nair, V.; Chi, G.; Shu, Q.; Julander, J.; Smee, D. F. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 1425–1427. DOI: 10.1016/J.BMCL.2009.01.031.
[7] Samanta, A.; Leonidas, D. D.; Dasgupta, S.; Pathak, T.; Zographos, S. E.; Oikonomakos, N. G. *J. Med. Chem*. **2009**, *52*, 932–942. DOI: 10.1021/jm800724t.
[8] Rico-Gómez, R.; López-Romero, J. M.; Hierrezuelo, J.; Brea, J.; Loza, M. I.; Pérez-González, M. *Carbohydr. Res*. **2008**, *343*, 855–864. DOI: 10.1016/J.CARRES.2008.01.011.
[9] Thureau, P.; Ancian, B.; Viel, S.; Thévand, A. *Chem. Commun*. **2006**, *2006*, 200. DOI: 10.1039/B513580J.
[10] Tucci, F. C.; Zhu, Y.-F.; Guo, Z.; Gross, T. D.; Connors, P. J.; Gao, Y.; Rowbottom, M. W.; Struthers, R. S.; Reinhart, G. J.; Xie, Q.; et al. *J. Med. Chem*. **2004**, *47*, 3483–3486. DOI: 10.1021/JM049791W.
[11] Sutherlin, D. P.; Sampath, D.; Berry, M.; Castanedo, G.; Chang, Z.; Chuckowree, I.; Dotson, J.; Folkes, A.; Friedman, L.; Goldsmith, R.; et al. *J. Med. Chem*. **2010**, *53*, 1086–1097. DOI: 10.1021/jm901284w.
[12] Bansal, R.; Kumar, G.; Gandhi, D.; Young, L. C.; Harvey, A. L. *Eur. J. Med. Chem*. **2009**, *44*, 2122–2127. DOI: 10.1016/J.EJMECH.2008.10.01
[13] Drabczyńska, A.; Müller, C. E.; Schiedel, A.; Schumacher, B.; Karolak-Wojciechowska, J.; Fruziński, A.; Zobnina, W.; Yuzlenko, O.; Kieć-Kononowicz, K. *Bioorg. Med. Chem*. **2007**, *15*, 6956–6974. DOI: 10.1016/J.BMC.2007.07.051.
[14] Agarwal, A.; Chauhan, P. M. S. *Tetrahedron Lett*. **2005**, *46*, 1345–1348. DOI: 10.1016/j.tetlet.2004.12.109.
[15] Thakur, A. J.; Saikia, P.; Prajapati, D.; Sandhu, J. S. *Synlett* **2001**, *2001*, 1299–1301. DOI: 10.1055/s-2001-16036.

[16] Shi, D.-Q.; Niu, L.-H.; Yao, H.; Jiang, H. *J. Heterocyclic Chem.* **2009**, *46*, 237–242. DOI: 10.1002/jhet.57.
[17] Edjlali, L.; Khanamiri, R. H.; Abolhasani, J. *Monatsh. Chem.* **2015**, *146*, 1339–1342. DOI: 10.1007/s00706-014-1368-5.
[18] Shi, D.-Q.; Ni, S.-N.; Yang, F.; Shi, J.-W.; Dou, G.-L.; Li, X.-Y.; Wang, X.-S.; Ji, S.-J. *J. Heterocycl. Chem.* **2008**, *45*, 693. DOI: 10.1002/jhet.5570450310.
[19] Tanifum, E. A.; Kots, A. Y.; Choi, B.-K.; Murad, F.; Gilbertson, S. R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3067–3071. DOI: 10.1016/J.BMCL.2009.04.024.
[20] Tu, S.; Fang, F.; Li, T.; Zhu, S.; Zhang, X. *J. Heterocycl. Chem.* **2005**, *42*, 707–710. DOI: 10.1002/jhet.5570420436.
[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: 10.10/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*, 4891–4898. 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] Jardosh, H. H.; Patel, M. P. *Eur. J. Med. Chem.* **2013**, *65*, 348–359. DOI: 10.1016/j.ejmech.2013.05.003.
[29] Khan, N. S.; Khan, P.; Ansari, M. F.; Srivastava, S.; Hasan, G. M.; Husain, M.; Hassan, M. I. *Mol. Pharm.* **2018**, *15*, 4173–4189. DOI: 10.1021/acs.molpharmaceut.8b00566.
[30] Basha, S. J.; Mohan, P.; Yeggoni, D. P.; Babu, Z. R.; Kumar, P. B.; Rao, A. D.; Subramanyam, R.; Damu, A. G. *Mol. Pharm.* **2018**, *15*, 2206–2223. DOI: 10.1021/acs.molpharmaceut.8b00041.
[31] Nqoro, X.; Tobeka, N.; Aderibigbe, B. A. *Molecules* **2017**, *22*, 2268. DOI: 10.3390/molecules22122268.
[32] Marco-Contelles, J.; León, R.; de Los Ríos, C.; Guglietta, A.; Terencio, J.; López, M. G.; García, A. G.; Villarroya, M. *J. Med. Chem.* **2006**, *49*, 7607–7610. DOI: 10.1021/jm061047j.
[33] Shaveta; Mishra, S.; Singh, P. *Eur J. Med. Chem.* **2016**, *124*, 500–536. Elsevier Masson SAS November 29, pp DOI: 10.1016/j.ejmech.2016.08.039.
[34] Abdelgawad, M. A.; Bakr, R. B.; Azouz, A. A. *Bioorg. Chem.* **2018**, *77*, 339–348. DOI: 10.1016/j.bioorg.2018.01.028.
[35] 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.
[36] Romagnoli, R.; Baraldi, P. G.; Carrion, M. D.; Cruz-Lopez, O.; Cara, C. L.; Balzarini, J.; Hamel, E.; Canella, A.; Fabbri, E.; Gambari, R.; et al. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2022–2028. DOI: 10.1016/j.bmcl.2009.02.038.
[37] Candeias, N. R.; Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P. *Chem. Rev.* **2010**, *110*, 6169–6193. DOI: 10.1021/cr100108k.
[38] Shiri, M. *Chem. Rev.* **2012**, *112*, 3508–3549. DOI: 10.1021/cr2003954.
[39] Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083–3135. DOI: 10.1021/cr100233r.
[40] Brauch, S.; van Berkel, S. S.; Westermann, B. *Chem. Soc. Rev.* **2013**, *42*, 4948–4962. DOI: 10.1039/c3cs35505e.
[41] Isambert, N.; Duque, M. d M. S.; Plaquevent, J.-C.; Génisson, Y.; Rodriguez, J.; Constantieux, T. *Chem. Soc. Rev.* **2011**, *40*, 1347–1357. DOI: 10.1039/C0CS00013B.

[42] Abdella, A. M.; Mohamed, M. F.; Mohamed, A. F.; Elwahy, A. H. M.; Abdelhamid, I. A. *J. Heterocyclic Chem.* **2018**, *55*, 498–507. DOI: 10.1002/jhet.3072.
[43] Abdelmoniem, A. M.; Ghozlan, S. A. S.; Abdelmoniem, D. M.; Elwahy, A. H. M.; Abdelhamid, I. A. *J. Heterocyclic Chem.* **2017**, *54*, 2844–2849. DOI: 10.1002/jhet.2890.
[44] Salama, S. K.; Mohamed, M. F.; Darweesh, A. F.; Elwahy, A. H. M.; Abdelhamid, I. A. *Bioorg. Chem.* **2017**, *71*, 19–29. DOI: 10.1016/J.BIOORG.2017.01.009.
[45] Hebishy, A. M. S.; Abdelhamid, I. A.; Elwahy, A. H. M. *Arkivoc* **2018**, *2018*, 97–108. DOI: 10.24820/ark.5550190.p010.367.
[46] Elnagdi, M. H.; Al-Awadi, N. A.; Abdelhamid, I. A. *Adv. Heterocycl. Chem.* **2009**, *97*, 1. DOI: 10.1016/S0065-2725(08)00201-8.
[47] Abdelhamid, I. A.; Darweesh, A. F.; Elwahy, A. H. M. *Tetrahedron Lett.* **2015**, *56*, 7085–7088. DOI: 10.1016/j.tetlet.2015.11.015.
[48] Sanad, S. M. H.; Kassab, R. M.; Abdelhamid, I. A.; Elwahy, A. H. M. *Heterocycles* **2016**, *92*, 910. DOI: 10.3987/COM-16-13441.
[49] Mohamed, M. F.; Darweesh, A. F.; Elwahy, A. H. M.; Abdelhamid, I. A. *RSC Adv.* **2016**, *6*, 40900–40910. DOI: 10.1039/C6RA04974E.
[50] Abdelmoniem, A. M.; Abdella, A. M.; Elwahy, A. H. M.; Abdelhamid, I. A. *Arkivoc* **2020**, *2020*, 136–149. DOI: 10.24820/ark.5550190.p011.357.
[51] Abdella, A. M.; Elwahy, A. H. M.; Abdelhamid, I. A. *Curr. Org. Synth.* **2016**, *13*, 601. DOI: 10.2174/1570179413999151211115100.
[52] Diab, H. M.; Abdelhamid, I. A.; Elwahy, A. H. M. *Synlett* **2018**, *29*, 1627–1633. DOI: 10.1055/s-0037-1609967.
[53] Darweesh, A. F.; Salama, S. K.; Abdelhamid, I. A.; Elwahy, A. H. M. *J. Heterocyclic Chem.* **2021**, *58*, 315–328. DOI: 10.1002/jhet.4170.
[54] Darweesh, A. F.; Salama, S. K.; Abdelhamid, I. A.; Elwahy, A. H. M. *Synth. Commun.* **2021**, *51*, 471–484. DOI: 10.1080/00397911.2020.1837170.
[55] Sanad, S. M. H.; Hawass, M. A. E.; Elwahy, A. H. M.; Abdelhamid, I. A. *Synth. Commun.* **2020**, *50*, 1982–1992. DOI: 10.1080/00397911.2020.1761395.
[56] Sinkkonen, J.; Ovcharenko, V.; Zelenin, K. N.; Bezhan, I. P.; Chakchir, B. A.; Al-Assar, F.; Pihlaja, K. *Eur. J. Org. Chem.* **2002**, *2002*, 2046. DOI: 10.1002/1099-0690(200207)2002:13<2046::AID-EJOC2046>3.0.CO;2-C.
[57] Alagarsamy, V.; Pathak, U. S. *Bioorg. Med. Chem.* **2007**, *15*, 3457–3462. DOI: 10.1016/j.bmc.2007.03.007.
[58] Alagarsamy, V.; Revathi, R.; Meena, S.; Ramaseshu, K. V.; Rajasekaran, S.; De Clerco, E. *Indian J. Pharm. Sci.* **2004**, *66*, 459.
[59] Ziarani, G. M.; Badiei, A.; Aslani, Z.; Lashgari, N. *Arab. J. Chem.* **2015**, *8*, 54–61. DOI: 10.1016/j.arabjc.2011.06.020.
[60] Chen, L. H.; Chung, T. W.; Narhe, B. D.; Sun, C. M. *ACS Comb. Sci.* **2016**, *18*, 162–169. DOI: 10.1021/acscombsci.5b00186.
[61] Reddy, M. V.; Reddy, G. C. S.; Jeong, Y. T. *RSC Adv.* **2015**, *5*, 11423–11432. DOI: 10.1039/b000000x.