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Microwave-assisted three component synthesis of novel bis-fused quinazolin-8(4*H*)-ones linked to aliphatic or aromatic spacer *via* amide linkages

Ibrahim M. Z. Fares, Ahmed E. M. Mekky, Ahmed H. M. Elwahy, and Ismail A. Abdelhamid

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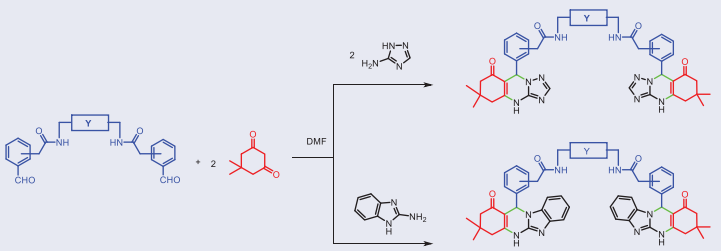
ABSTRACT

A novel series of bis(tetrahydro[1,2,4]triazolo[5,1-*b*]quinazolin-8-ones) and bis(tetrahydrobenzo[4,5]imidazo[2,1-*b*]quinazolinones) containing amide linkages were regionselectively prepared *via* a three-component reaction of bis(aldehydes) with dimedone and 3-amino-1,2,4-triazole (or 2-aminobenzimidazole) under conventional heating as well as under microwave irradiation.

GRAPHICAL ABSTRACT



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Amide linkages; bis-aldehydes; bis-benzo[4,5]imidazo[2,1-b]quinazolinones; bis-[1,2,4]triazolo[5,1-b]quinazolin-8-ones; multicomponent reactions

Introduction

Quinazolines and their derivatives represent one of the most interesting class of compounds because they exhibit a wide range of pharmacological activities including anti-bacterial,[1–3] analgesic,[4] anti-inflammatory,[5,6] anti-oxidant,[4,5] anti-tubercular,[1] anti-hypertensive,[7] anti-viral[8,9] and anti-cancer[10,11] activities. Some clinically used drugs that contain quinazoline and quinazolinone ring system, such as gefitinib (anticancer), letermovir (antiviral), and albaconazole (antifungal) are outlined in Figure 1.[12,13]

Among fused quinazolines, tetrahydro-[1,2,4]triazolo[5,1-*b*]quinazolinones and tetrahydrobenzo[4,5]imidazo[2,1-*b*]quinazolinones have received great interest due to their pharmaceutical applications.[14–23] In addition, multi-component reactions (MCRs) play a tremendous role in the synthesis of bioactive heterocyclic compounds.[24–28] Moreover, the growing attention in the synthesis of bis(heterocycles) has been reported as they exhibit bioactivity that include anticancer,[29–35] fungicidal and

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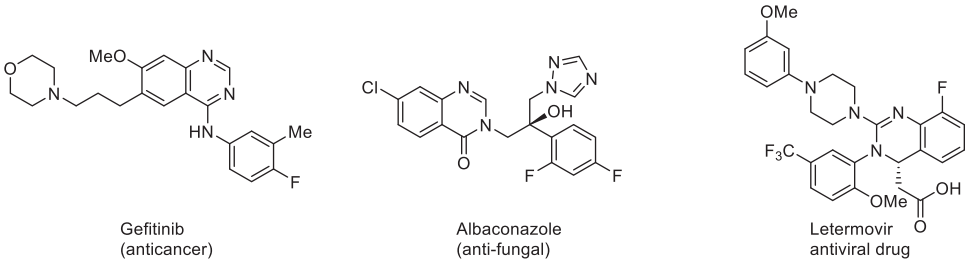
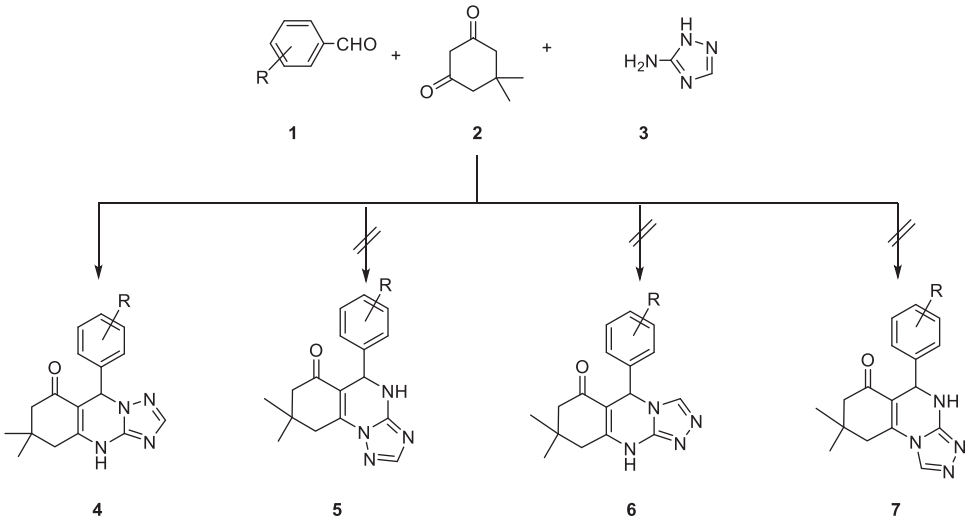


Figure 1. Some quinazoline/quinazolinone based drugs.

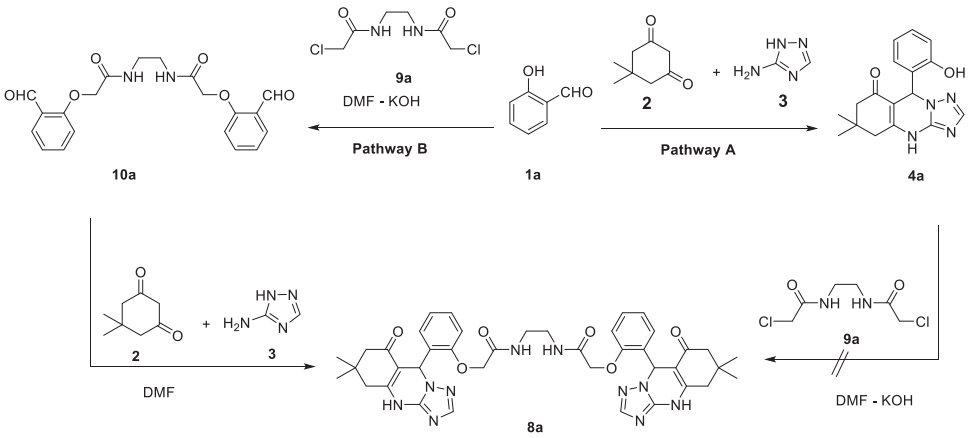


Scheme 1. Possible isomeric structures produced from a three-component reaction of aldehydes, dimedone and 4*H*-1,2,4-triazol-3-amine.

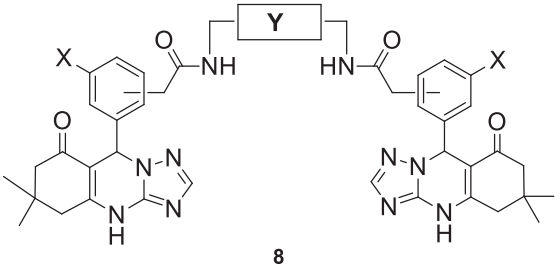
antibacterial properties.[36–39] They also have diverse applications as metal ligands,[40] chelating agents,[40] and electrical conducting materials.[41] Furthermore, the amide bond formation represent the most important transformation reactions in organic synthesis due to the availability of amides in natural products[42,43] and biologically active molecules.[42,44–46] In connection with these findings, and in conjunction to our interest in multicomponent reactions[29,47–49] as well as to the synthesis of bis(heterocycles)[22,29,31,49–55] we report herein, the synthesis of novel bis(tetrahydro[1,2,4]triazolo[5,1-*b*]quinazolin-8(4*H*)-one) and bis(tetrahydrobenzo[4,5]imidazo[2,1-*b*]quinazolinones) incorporating amide linkages.

Results and discussion

The popular protocol for the synthesis of tetrahydro[1,2,4]triazolo[5,1-*b*]quinazolin-8(4*H*)-ones **4** includes a three-component reaction of aldehydes **1**, dimedone **2** and 4 *H*-1,2,4-triazol-3-amine **3**. The reactions were carried out in different solvents[22,56,57] or under solvent free conditions[21,58] (Scheme 1). The reaction can logically afford several isomeric structures **4**–**7**. Unambiguous structural elucidation of the regioisomer **4**



Scheme 2. Attempted synthesis of **8a** using pathway A and pathway B.



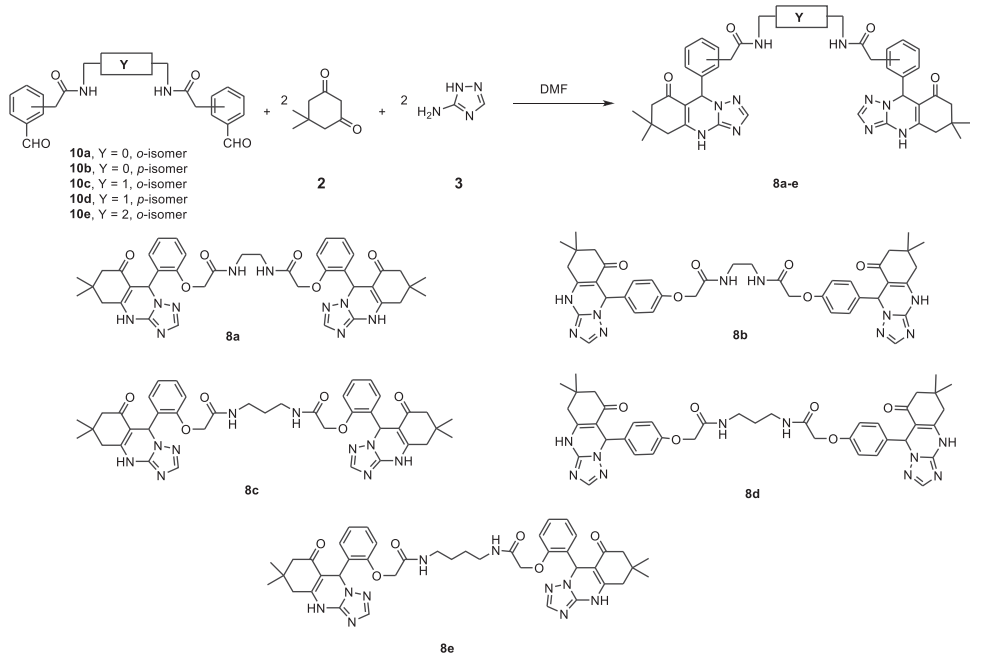
8

Figure 2. Structure of the target tetrahydro[1,2,4]triazolo[5,1-*b*]quinazolin-8(4*H*)-ones 8.

was done using DFT calculations, 2D-HMBC spectroscopy[22] as well as X-ray crystal structure elucidation.[58]

Our aim was to prepare the tetrahydro[1,2,4]triazolo[5,1-*b*]quinazolin-8(4*H*)-ones containing amide linkage of type **8** (Figure 2).

Two strategies were suggested for the synthesis of our target **8** (taking **8a** as an example). In the first strategy, the monopodal 9-(2-hydroxyphenyl)-6,6-dimethyl-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-*b*]quinazolin-8(4*H*)-one **4a**[23,59,60] was prepared *via* the cyclocondensation reaction of salicylaldehyde **1a** with both dimedone **2** and 4*H*-1,2,4-triazol-3-amine **3** in DMF at reflux. Unfortunately, the reaction of the potassium salt of **4a** with *N*,*N*′-(ethane-1,2-diyl)bis(2-chloroacetamide) **9a** in DMF at reflux, did not afford the corresponding bis-tetrahydro[1,2,4]triazolo[5,1-*b*]quinazolin-8(4*H*)-one linked to ethane core *via* amide linkage **8a**. The reaction gave instead an inseparable mixture of products that have not been characterized yet (Scheme 2, Pathway A). It is worthy that repeated attempts to react **4a** with **9** under different basic conditions to get pure sample of the target **8a** were also unsuccessful. We thus turned to pathway-B in which the *bis*-aldehyde **10a** has been firstly synthesized by the reaction of the potassium salt of 4-hydroxybenzaldehyde **1a** with *N*,*N*′-(ethane-1,2-diyl)bis(2-chloroacetamide) **9a** in DMF at reflux (Scheme 2, Pathway B). Subsequent reaction of the bis-aldehyde **10a** with two equivalents of both dimedone **2** and 4*H*-1,2,4-triazol-3-amine **3** in DMF at reflux resulted in the formation of the target compound **8a** in good yield. The structure



Scheme 3. Synthesis of bis(tetrahydro[1,2,4]triazolo[5,1-*b*]quinazolin-8(4*H*)-ones) **8a–e.**

of compound **8a** was established based on the spectral data. The IR spectra of compound **8a** indicated the presence of NH groups at 3387 cm^{-1}. In addition, it revealed the two carbonyl groups at 1675 and 1643 cm^{-1}. The ^1H NMR spectrum of **8a** featured two singlets integrated by 12 protons at δ 1.00 and 1.05 ppm assigned to four CH_3. In addition, the two singlet signals at 6.68 and 7.66 ppm are corresponding to H9 and triazole-H, respectively. The NH groups appeared as two broad singlets at δ 8.41 and 11.02 ppm, respectively. All other protons appear at their expected positions.

Subsequently, a series of bis(tetrahydro[1,2,4]triazolo[5,1-*b*]quinazolin-8(4*H*)-one) ring systems linked to alkane *via* amide linkages **8b–e** were prepared by reacting a variety of bis(aldehydes) **10a–e** with dimedone **2** and 4*H*-1,2,4-triazol-3-amine **3**. The bis(aldehydes) **10a–e** were prepared by the reaction of the appropriate bis(2-chloroacetamides) **9** with the potassium salt of *o*- or *p*-hydroxybenzaldehydes **1a,b** in DMF (Scheme 3).[61]

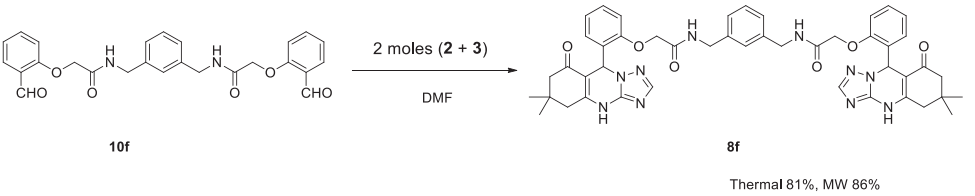
It is worth mentioning that, the synthesis of **8a–e** has been conducted using standard thermal conditions in DMF at reflux. When the same reactions were carried out under microwave irradiation, the reaction times were significantly decreased to 15 min and gave better yields (Table 1).

Interestingly, the bis(tetrahydro[1,2,4]triazolo[5,1-*b*]quinazolin-8(4*H*)-one) which is linked to benzene core *via* amide linkage **8f** was successfully prepared *via* the direct reaction of one mole of the bis-aldehyde **10f**[61] with two moles of both **2** and **3** under similar conditions (Scheme 4).

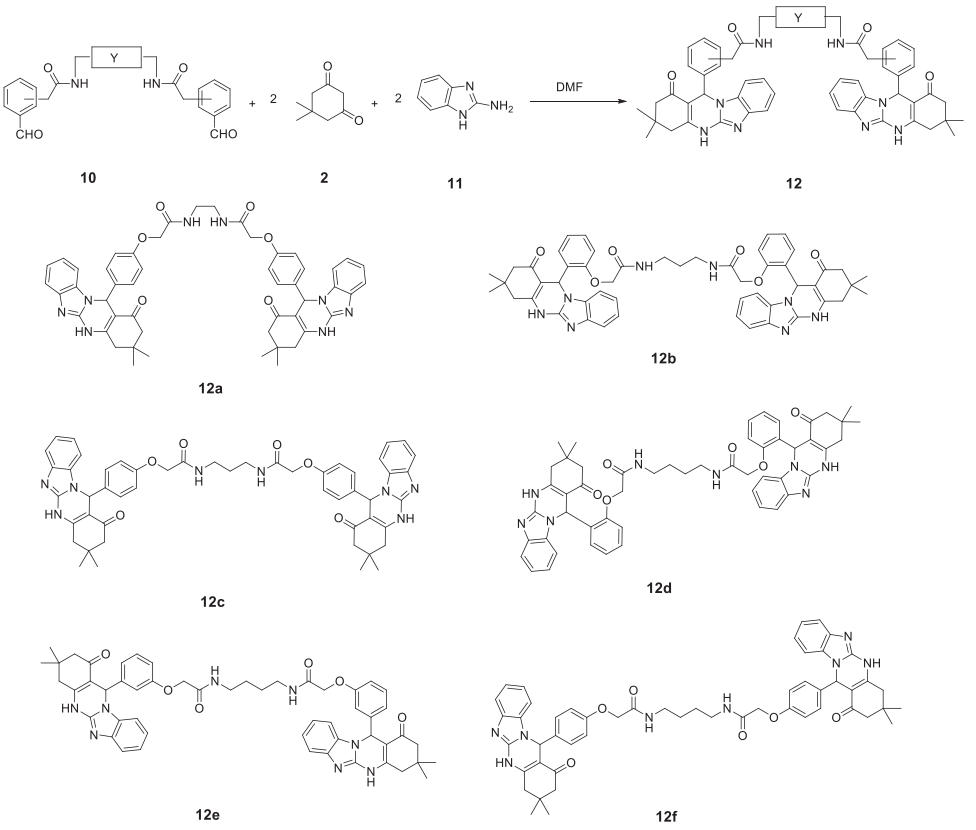
In a trial to expand the scope of this reaction, the replacement of 4*H*-1,2,4-triazol-3-amine by 2-aminobenzimidazole was investigated. Thus, under similar reaction conditions, the condensation of bis(aldehydes) **10** with both dimedone **2** and

Table 1. % Yield of **8a–e** obtained from thermal and microwave irradiation (MWI).

	Yield (%)	
Entry	Thermal heating	Microwave irradiation
8a	92	95
8b	90	94
8c	83	87
8d	85	90
8e	87	92



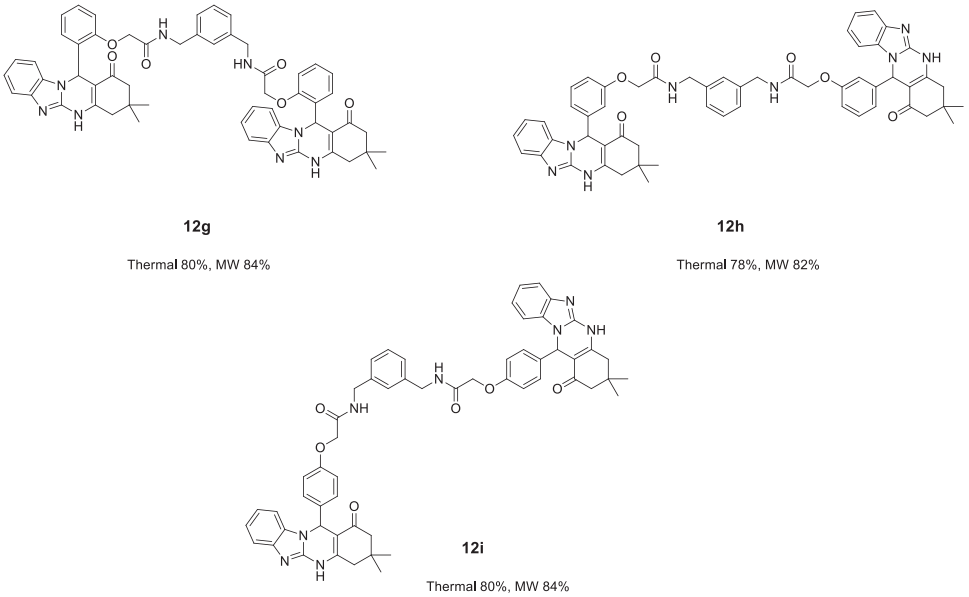
Scheme 4. Synthesis of bis(tetrahydro[1,2,4]triazolo[5,1-*b*]quinazolin-8(4*H*)-one) linked to benzene core *via* amide linkage **8f.**



Scheme 5. Synthesis of bis-tetrahydrobenzo[4,5]imidazo[2,1-*b*]quinazolinones linked to alkyl spacer *via* amide linkage (**12a–f**).

Table 2. % Yield of **12a–f** obtained from thermal and microwave irradiation (MWI).

	Yield (%)	
Entry	Thermal heating	Microwave irradiation
12a	86	90
12b	80	86
12c	89	92
12d	82	87
12e	90	93
12f	86	91



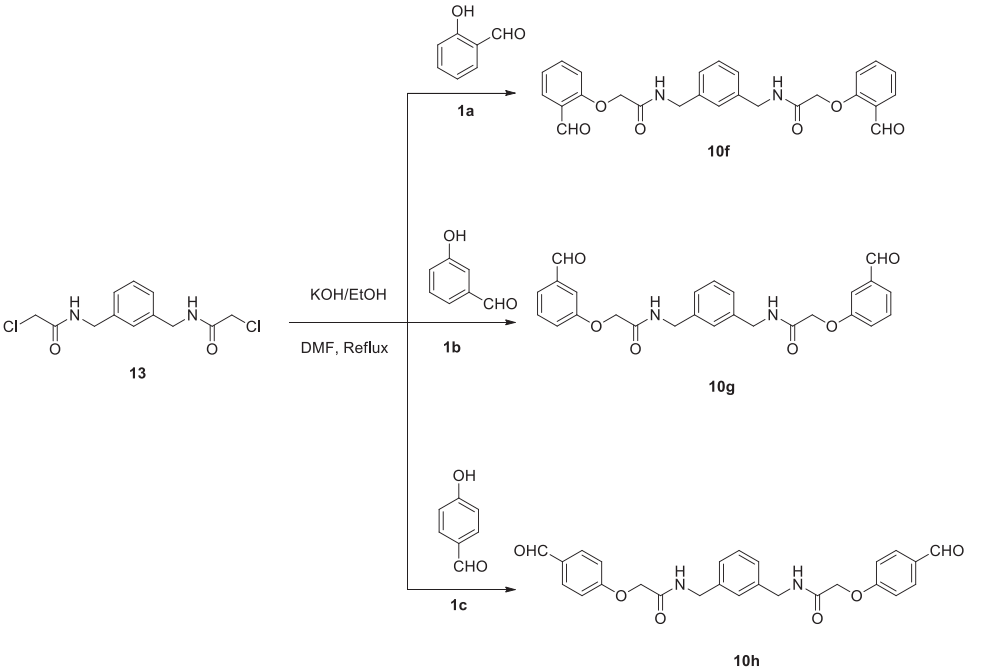
Scheme 6. Synthesis of bis-tetrahydrobenzo[4,5]imidazo[2,1-*b*]quinazolinones linked to benzene core *via* amide linkage (**12g–i**).

2-aminobenzimidazole **11** proceeded smoothly to give a new series of bis(tetrahydrobenzo[4,5]imidazo[2,1-*b*]quinazolinones) **12a-f** which are linked to alkyl spacer *via* amide linkage (Scheme 5). In a similar manner, and for the sake of comparison, the reactions were also done under microwave irradiation conditions (Table 2).

The same methodology was also applied for the synthesis of the corresponding bis(tetrahydrobenzo[4,5]imidazo[2,1-*b*]quinazolinones) **12g–i** which are linked to benzene core *via* amide linkages in good yields upon treatment of the appropriate bis(aldehydes) **10f–h**[61] with two equivalents of both **2** and **3** (Scheme 6).

The bis(aldehydes) **10f–h** were prepared by the reaction of *N,N′*-(1,3-phenylenebis(methylene))bis(2-chloroacetamide) **13** with the potassium salt of *o*-, *m*- or *p*-hydroxybenzaldehydes **1a–c** in DMF[61] (Scheme 7).

The structures of compounds **12** were established based on the spectral data. Thus, the IR spectra of compound **12h** as a representative example indicated the presence of an NH group at 3425 cm^{-1}. In addition, it revealed a carbonyl group at 1651 cm^{-1}. The ^{1}H NMR spectrum of **12h** indicated the presence of two singlets with 12 protons at



Scheme 7. Synthesis of the bis(aldehydes) (10f–h).

$\delta = 0.92$ ppm, and $\delta = 1.03$ ppm assigned to four CH_3 groups. Moreover, the singlet signal at $\delta = 6.36$ ppm is corresponding to H12. The NH group appeared as a broad singlet signal at $\delta = 11.08$ ppm. All other signals appeared at their expected positions.

Conclusion

We managed to synthesize a novel series of novel bis(tetrahydro[1,2,4]triazolo[5,1-b]quinazolin-8-ones) and bis(tetrahydrobenzo[4,5]imidazo[2,1-b]quinazolinones) containing amide linkages via a three-component reaction of bis(aldehydes) and dimedone with the respective 5-amino-1,2,4-triazole and 2-aminobenzimidazole. The structure of the newly synthesized regioisomers was confirmed based on spectroscopy.

Full experimental details and spectroscopic data (IR spectra, ^{1}H-NMR and MS) for compounds **8a–f**, **12a–i** can be found via the Supplementary Content section of this article's Web page

Experimental

General

Melting points were determined in open glass capillaries with a Gallenkamp apparatus. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3-300 and Shimaduz FTIR 8101 PC infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured using Bruker Ultrashield 400 MHz or Ascend 400 MHz (^{1}H: 400 MHz, ^{13}C: 100.6 MHz) instruments. Chemical shifts (δ) are referenced to residual solvent signals as internal standards. Mass spectra (EI) were obtained at 70 eV with a type Shimadzu GCMQP 1000 EX

spectrometer. Elemental analyses (CHN) were carried out at Hannover university, with an element Vario EL instrument with acetanilide as the standard. Analytical thin-layer chromatography was performed using pre-coated silica gel 60778 plates (Fluka), and the spots were visualized with UV light at 254 nm. Microwave experiments were carried out using a CEM Discover Labmate^{TM} microwave apparatus (300 W with ChemDriver^{TM} Software).

General procedure for the synthesis of compounds 8a–f

Method 'A' (conventional method)

A mixture of bis(aldehydes) **10** (1 mmol), dimedone **2** (2 mmol) and 4*H*-1,2,4-triazol-3-amine **3** (2 mmol) in DMF (5 mL) was heated at reflux for 1 h. The formed solid was filtered off, washed with ethanol, and recrystallized from proper solvent.

Method 'B' (microwave method)

A mixture of bis(aldehyde) **10** (1 mmol), dimedone **2** (2 mmol) and 4*H*-1,2,4-triazol-3-amine **3** (2 mmol) DMF (1 mL) was put in a 10-mL glass microwave reaction vessel containing a stirring bar. The reaction vessel was sealed with a cap and then placed into the microwave cavity. The microwave unit was adjusted to heat the reaction mixture to 160 °C under auto-generated pressure for 10 min. The reaction was accomplished and the vessel was cooled using a flow of compressed air. The crude material was filtered off, washed with ethanol, and recrystallized from proper solvent.

N,N′-(Ethane-1,2-diyl)bis(2-(4-(6,6-dimethyl-8-oxo-4,5,6,7,8,9-hexahydro-[1,2,4]triazolo[5,1-b]quinazolin-9-yl)phenoxy)acetamide) 8b

Colorless crystal [Ethanol/H_2O (3:1)]. *Mp* = 218–222 °C; IR (KBr, υ cm^{-1}): 3425 (NH), 1675,1639 (CO).[1]H NMR (400 MHz, DMSO-d_6): $\delta = 0.94$ (s, 6H, $2CH_3$), 1.01 (s, 6H, $2CH_3$), 1.96–2.16 (m, 4H, $2CH_2$), 2.52 (s, 4H, $2CH_2$), 3.17 (s, 4H, $2NCH_2$), 4.34–4.37 (m, 4H, $2OCH_2$), 6.13 (s, 2H, 2 pyrimidine-H), 6.83 (d, 4H, ArH, $J = 8.4$), 7.08 (d, 4H, ArH, $J = 8.4$), 7.63 (s, 2H, 2 triazole-H), 8.19 (*br.* s, 2H, 2NH), 11.12 (*br.* s, 2H, 2NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 27.4$, 28.9, 32.6, 38.5, 50.3, 57.7, 60.2, 67.3, 106.1, 114.9, 128.6, 135.0, 147.2, 150.5, 150.8, 157.6, 168.4, 193.4. Anal. For $C_{40}H_{44}N_{10}O_6$ (760.86) Calcd: C, 63.14; H, 5.83; N, 18.41. Found: C, 63.23; H, 5.35; N, 18.73%.

General procedure for the synthesis of compounds 12a–i

Method 'A' (conventional method)

A mixture of bis(aldehydes) **10** (1 mmol), dimedone **2** (2 mmol) and 2-aminobenzimidazole **11** (2 mmol) in DMF (5 mL) was heated at reflux for 1 h. The formed solid was filtered off, washed with ethanol, and recrystallized from proper solvent.

Method 'B' (microwave method)

A mixture of bis(aldehydes) **10** (1 mmol), dimedone **2** (2 mmol) and 2-aminobenzimidazole **11** (2 mmol) DMF (1 mL) was put in a 10-mL glass microwave reaction vessel

containing a stirring bar. The reaction vessel was sealed with a cap and then placed into the microwave cavity. The microwave unit was adjusted to heat the reaction mixture to 160 °C under auto-generated pressure for 10 min. The reaction was accomplished and the vessel was cooled using a flow of compressed air. The crude material was filtered off, washed with ethanol, and recrystallized from proper solvent.

N,N′-(Propane-1,3-diyl)bis(2-(2-(3,3-dimethyl-1-oxo-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-b]quinazolin-12-yl)phenoxy)acetamide) 12b

Colorless crystal [Acetic acid/Ethanol (10:1)]. *Mp* = 206–208 °C; IR (KBr, υ cm^{-1}): 3325 (NH), 1643 (CO). ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 0.94$ (s, 6H, $2CH_3$), 1.04 (s, 6H, $2CH_3$), 1.54–1.57 (m, 2H, CH_2), 2.04–2.26 (m, 4H, $2CH_2$), 2.50–2.59 (m, 4H, $2CH_2$), 3.05–3.15 (m, 4H, $2NCH_2$), 4.72 (*br*. s, 4H, $2OCH_2$), 6.82 (s, 2H, 2 pyrimidine-H), 6.83–7.37 (m, 16H, ArH), 8.16 (*br*. s, 2H, 2NH), 11.21 (*br*. s, 2H, 2NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 26.9$, 27.1, 29.0, 29.4, 32.7, 32.8, 36.6, 50.3, 67.6, 106.6, 109.8, 112.1, 117.4, 121.1, 121.6, 122.2, 122.3, 129.6, 130.4, 132.5, 142.1, 145.5, 151.7, 154.3, 168.1, 193.8. Anal. For $C_{51}H_{52}N_8O_6$ (873.03) Calcd: C, 70.17; H, 6.00; N, 12.84. Found: C, C, 70.03; H, 6.15; N, 12.64%.

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