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Synthesis, and antibacterial activities of novel 1,3,4a,9-tetraza-4*H*-fluoren-2-amines incorporating phenoxy-*N*-arylacetamide, pyrazole, and 2-(4-(1-phenyl-1*H*-pyrazol-3-yl) phenoxy)-*N*-arylacetamide moieties

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Abstract

A ring annelation reaction was used to successfully prepare benzo[4,5]imidazo[1,2-*a*][1,3,5]triazines (Systematic Name: 1,3,4a,9-tetraza-4*H*-fluoren-2-amines) tethered to phenoxy-*N*-arylacetamide, pyrazole, and 2-(4-(1-phenyl-1*H*-pyrazol-3-yl)phenoxy)-*N*-arylacetamide moieties utilizing 1-(1*H*-benzo[*d*]imidazol-2-yl)guanidine and the proper aldehydes as precursors. 2-(Phenylamino)ethyl fragment of compound **7** was cleaved off and compound **8** was formed. The constitutions of the novel compounds were confirmed based on spectral data. The antibacterial activity was evaluated for the prepared compounds against two gram-negative and two gram-positive bacteria. Among them, compound **12b** (inhibition zone 16 ± 0.7 mm) was the most promising against *S. aureus* compared to Gentamycin (15 ± 0 mm). Also, compounds **5a** and **5d** exerted comparable antibacterial activity (inhibition zones 13 ± 1.4 and 13 ± 2.1 mm), respectively to Gentamycin against *S. aureus*. Minimum inhibitory concentration (MIC) evaluation against *S. aureus* showed that compound **12b** had the lowest MIC value (78.1 µg/mL).

Keywords Ring annelation, 1-(1*H*-benzo[*d*]imidazol-2-yl)guanidine, 1,3,4a,9-tetraza-4*H*-fluoren-2-amines, phenoxy-*N*-arylacetamide, *Trans* esterification, Antibacterial activity

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Introduction

Benzimidazoles are the fundamental component of a wide range of biochemical and medicinal substances with varying chemical and pharmacological properties. Numerous derivatives of benzimidazoles have a variety of biological characteristics, including antitumor [1–6], antifungal [7, 8], antiviral [9–11], antihistaminic [12–14] antibacterial [15, 16], and anticonvulsant activity [17, 18]. Representative examples of drugs containing benzimidazole moiety are depicted in Fig. 1 (compounds **I** [19–21], **II** [22–24], **III** [25–27]).

Moreover, triazines are benzene-like six-membered planar structures having three nitrogen atoms [28]. The triazine scaffold is the most well-known heterocycle, with a wide spectrum of biological activity [28–31]. There are three triazine isomers, namely, 1,2,4-triazine, 1,2,3-triazine, and 1,3,5-triazine. 1,3,5-Triazine is the most studied due to its distinct chemical structure and medicinal capabilities [30, 31]. For example, 1,3,5-triazine-thiazolidine-dione **IV** [30] has been reported as a DPP-4 inhibitor with antibacterial activity targeting the S1 pocket for the treatment of type 2 diabetes [30] (Fig. 1). Also, triazine dimer **V** [31] has been reported as an antileishmanial agent (Fig. 1) [31].

Besides, it was noted that compounds with acetamide linkages as core structures have drawn a lot of interest because of their possible therapeutic applications, including anticancer [32, 33], haemolytic [34], antioxidant [35], antitubercular [36], antiurease [34], antimicrobial [34, 37, 38], anti-inflammatory [39], anticonvulsant [40], analgesic [38, 39], anti-COVID-19 [41], and antituberculosis [42].

Moreover, pyrazoles, a five-membered heterocycle with two neighboring nitrogen atoms, are the fundamental structures found in a variety of compounds with diverse biological activities such as anticancer [43, 44], anti-inflammatory [45, 46], antimicrobial [46, 47], antioxidant [48, 49], and anticonvulsant [50] activities. Furthermore, bis-heterocycles, which consist of two bioactive heterocycles linked by a flexible linker, have been reported to possess plant growth regulative, anticancer, antibacterial, and fungicidal properties [51–55]. They can also be used as chelating agents, electrical conducting compounds [56], and metal ligands [57].

Fluorene is one example of a polyaromatic hydrocarbon (PAH), an essential precursor used in manufacturing as a component of plastics, insecticides, resins, dyes, and medications [58–60]. It was found that replacing one or more carbon atoms with heteroatoms results in significant alterations of its biological activity [61, 62]. Thus, in continuation of our interest in the synthesis of bioactive heterocycles [63–87], we aim to prepare hybrid heterocycles based on 1,3,4a,9-tetraza-4*H*-fluoren-2-amines tethered phenoxy-*N*-arylacetamide, and pyrazole moiety.

Results and discussion

According to the preceding general procedure, the reaction of *o*-phenylenediamine **1** with cyanoguanidine **2** in a refluxing water-HCl mixture produces 1-(1*H*-benzo[*d*] imidazol-2-yl)guanidine **3** (Scheme 1).

The reaction of 1-(1*H*-benzo[*d*]imidazol-2-yl) guanidine **3** with 2-(4-formylphenoxy)-*N*-arylacetamides **4a-d** in ethanol in the presence of piperidine as a basic catalyst leads to the formation of

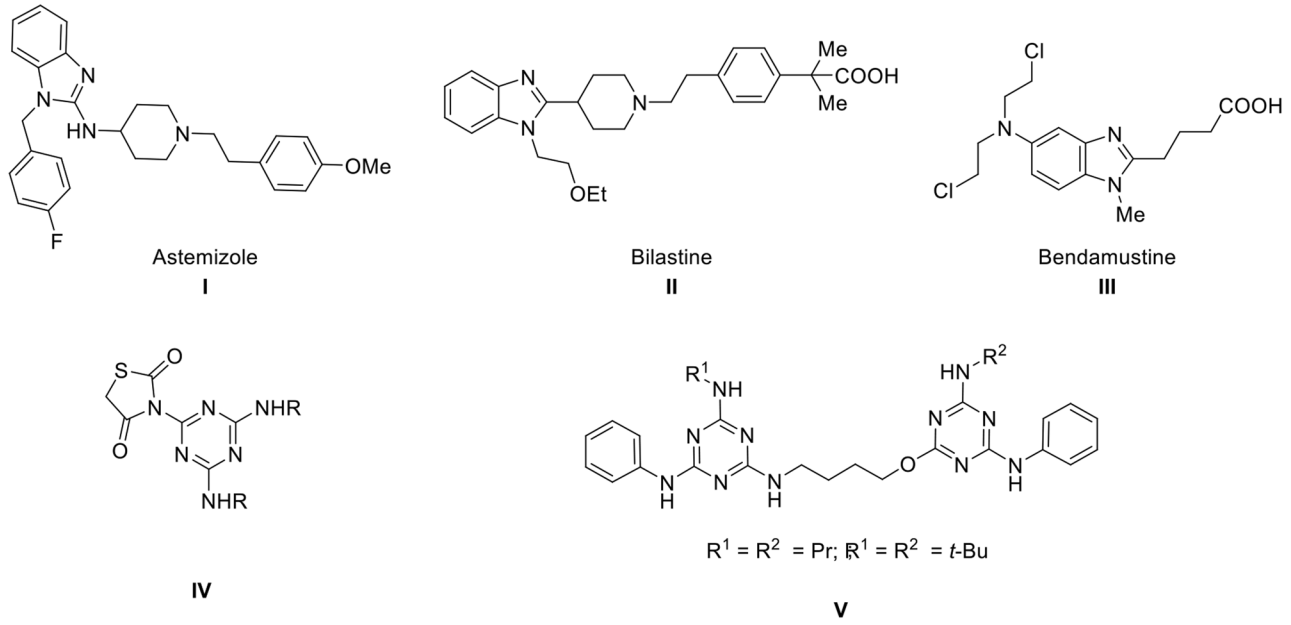
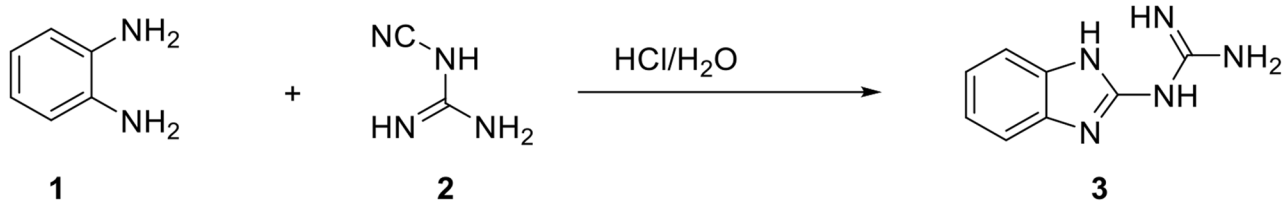
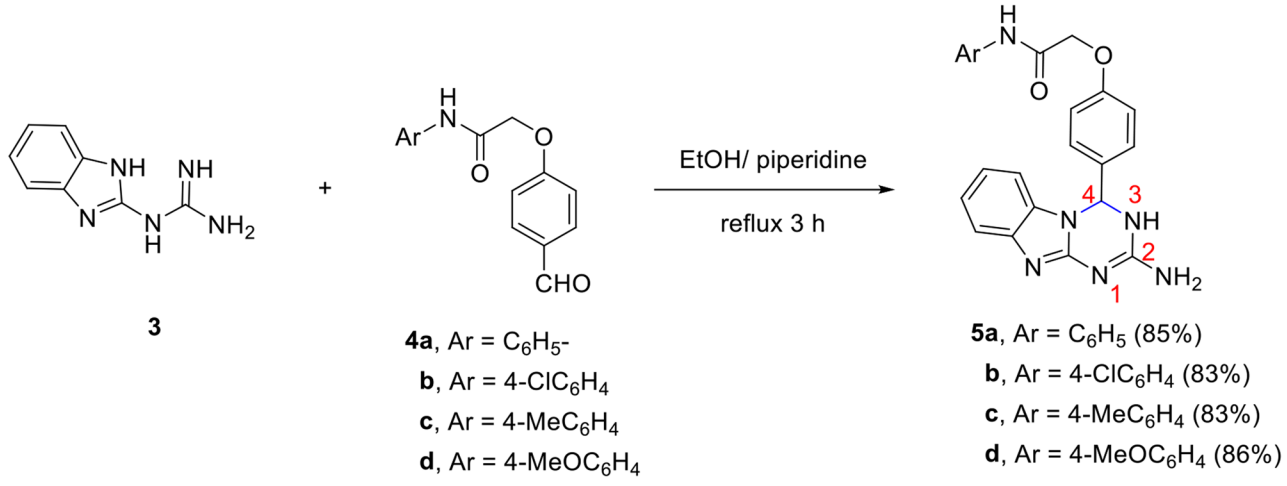


Fig. 1 Some drugs containing benzimidazole or [1,3,5]triazine cores



Scheme 1 Synthesis of 1-(1*H*-benzo[*d*]imidazol-2-yl)guanidine **3**



Scheme 2 Synthesis of 2-(4-(dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazin-4-yl)phenoxy)-*N*-arylacetamides **5a-d**

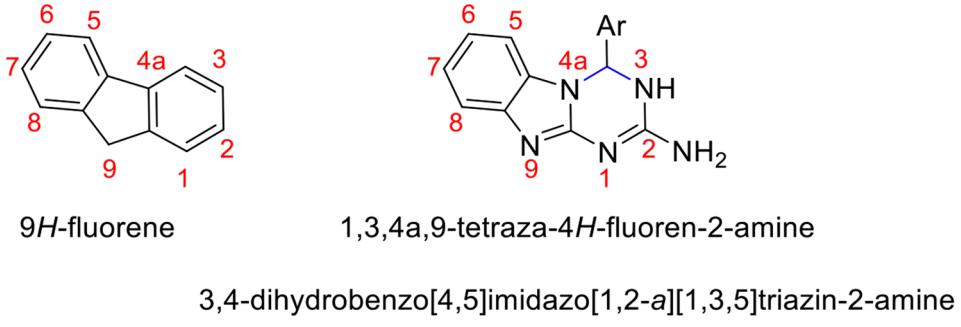


Fig. 2 Structures of 9*H*-fluorene and1,3,4a,9-tetraza-4*H*-fluoren-2-amines **5**

2-(4-(2-amino-3,4-dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazin-4-yl)phenoxy)-*N*-phenylacetamides **5a-d** in which the benzo[4,5]imidazo[1,2-*a*][1,3,5]triazine moiety is linked to phenoxy-*N*-arylacetamide moieties (Scheme 2).

The constitution of the formed products was proved based on spectral data. For example, the mass spectrum of **5a** revealed a molecular ion peak at m/z 412. The IR spectrum of compound **5a** showed characteristic N-H stretching bands at $\bar{\nu}$ 3449 and 3325 cm^{-1} and a strong absorption band at $\bar{\nu}$ 1674 cm^{-1} for the carbonyl group. The ^{1}H NMR spectrum displayed a singlet at δ 4.69 ppm for OCH_2 protons besides a multiplet at δ 6.68–7.62 ppm integrated for 14 protons corresponding to the aromatic protons and *H*-4. It also demonstrated three singlet signals (exchangeable with D_2O) at δ 6.39 (2 H), 7.98 (1H), and 10.06 (1H) ppm assigned to NH_2 and 2 NH protons. In addition, the ^{13}C NMR showed peaks at δ 65.6 and 67.1 ppm for aliphatic carbons OCH_2 and *C*-4 as well as a characteristic peak at δ 166.4 for the amide group. Peaks of the aromatic carbons appear at their appropriate position.

Compounds **5** can be seen as 1,3,4a,9-tetraza-4*H*-fluoren-2-amines, as illustrated in Fig. 2. It has been observed that replacing one or more carbon atoms of a carbocyclic molecule with heteroatoms results in significant alterations of its biological activity [88–91].

However, the formed dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazine could exist in three tautomeric structures, namely 3,4-dihydro- **5**, 1,4-dihydro- **5(I)**, and

4,10-dihydro- **5(II)** tautomeric forms, the 3,4-dihydro-isomer is predominant in the crystal form, as indicated in related work [92] (Fig. 3).

On the other hand, trials to prepare the benzo[4,5]imidazo[1,2-*a*][1,3,5]triazines **7** which are linked to benzoyloxyacetamide *via* the direct reaction of **3** with 2-oxo-2-(phenylamino)ethyl 4-formylbenzoate derivatives **6a-d** under the same condition of absolute ethanol at reflux in presence of a catalytic amount of piperidine did not succeed. Instead, in all these examples, only ethyl 4-(2-amino-3,4-dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazin-4-yl)benzoate **8** was obtained as the sole product (Scheme 3).

Compound **8** was formed due to the transesterification of the initially formed **7a-d** as indicated in the following mechanism. The nucleophilic attack of ethanol to the carbonyl ester of **7** leads to the tetrahedral intermediate **9** that was deprotonated in the presence of a basic catalyst (piperidine) into the intermediate **10** that affords the final isolable product **8** (Scheme 4).

The chemical constitution of compound **8** was undoubtedly confirmed by the aid of spectral tools and elemental analysis. The mass spectrum showed a molecular ion peak at *m/z* 335, consistent with the proposed structure. The IR spectrum revealed the presence of a characteristic absorption band at $\bar{\nu}$ 1713 cm^{-1} for the ester carbonyl stretch, and broad absorption bands at $\bar{\nu}$ 3418 and 3248 cm^{-1} for NH_2 and NH group. The ^1H NMR further confirmed the transesterification as it showed the absence of any peaks for OCH_2 and amide N*H* protons. Instead, ethoxy protons appeared as a characteristic triplet and quartet at δ 1.26 and 4.25 ppm (p*J* = 7.2 Hz). NH_2 and NH protons gave peaks at δ 6.42 (2 H) and 8.09 (1H) ppm, respectively. Other peaks for aromatic protons and H-4 exist in their expected position. ^{13}C NMR spectrum showed peaks for carbons of ethoxy group at δ 14.2 and 61.1 ppm. It revealed also peaks at δ 65.4 ppm for C-4, and at δ 165.3 ppm for ester carbonyl. Peaks of other aromatic carbons appeared as expected.

To achieve the concept of molecular hybridization, we attempt to introduce the biologically active pyrazole ring into the structure of 1,3,4a,9-tetraza-4*H*-fluoren-2-amines (benzo[4,5]imidazo[1,2-*a*][1,3,5]triazines). For this purpose, 1-phenyl-3-aryl-1*H*-pyrazole-4-carbaldehydes **11a-c** were chosen as starting materials and were allowed to react with **3** in ethanol at reflux in the presence of a few drops of piperazine. Interestingly, benzo[4,5]imidazo[1,2-*a*][1,3,5]triazines **12a-c** which are linked to a pyrazole moiety at position-4 has been generated in good yields (Scheme 5).

The chemical composition of the products was verified by the different spectral tools. For example, the mass spectrum of **12b** (Ar = 4-MeC_6H_4) demonstrated a molecular ion peak at *m/z* 419 which fits with the proposed structure. The IR spectrum of compound **12** showed absorption bands at $\bar{\nu}$ 3546 and 3325 cm^{-1} for NH_2 and NH stretching vibration. The ^1H NMR indicated the presence of a signal at δ 2.24 ppm for methyl protons, a doublet at δ 6.57 ppm for *H*-4, a characteristic signal at δ 9.03 ppm for pyrazole-*H*5, and two singlet signals at δ 7.04 (2 H), 9.48 (1H) ppm for NH_2 and N*H*, respectively. Signals for the aromatic protons appear at their appropriate position. The ^{13}C NMR spectrum showed characteristic peaks at δ 20.9 and 59.9 ppm for methyl and C-4, respectively. Peaks for other carbons appear in their expected position.

Stimulated by the previously mentioned results, we broadened the scope of this reaction to include the synthesis of 1,3,4a,9-tetraza-4*H*-fluoren-2-amines **14a-d** that are linked to 2-(4-(1-phenyl-1*H*-pyrazol-3-yl)phenoxy)-*N*-arylacetamide moieties at position-4 in good yields by the direct reaction of the appropriate 2-(4-(4-formyl-1-phenyl-1*H*-pyrazol-3-yl)phenoxy)-*N*-arylacetamides **13a-d** with the corresponding mole equivalent of **3** (Scheme 6).

The chemical structure of the resulting compounds **14a-d** was confirmed based on spectral analyses. For instance, the mass spectrum of **14a** indicated a

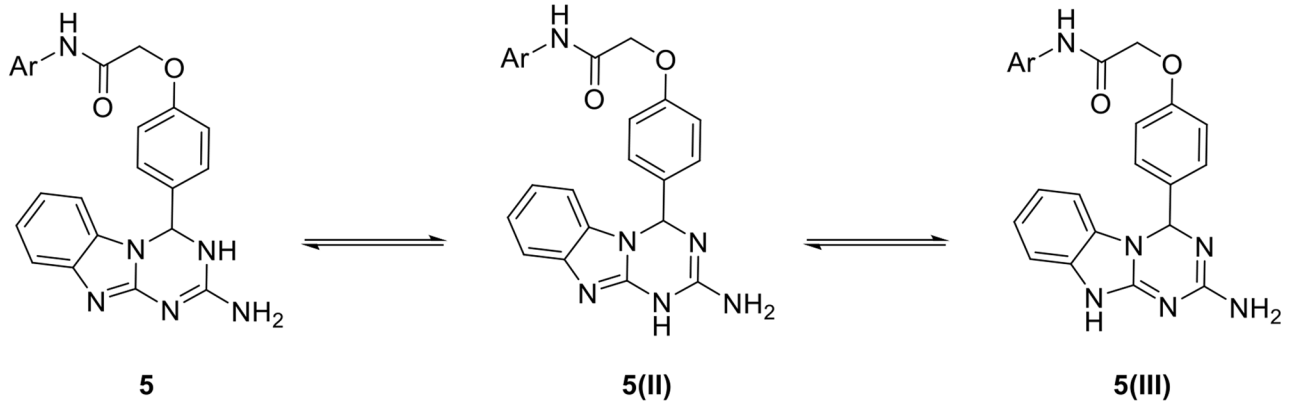
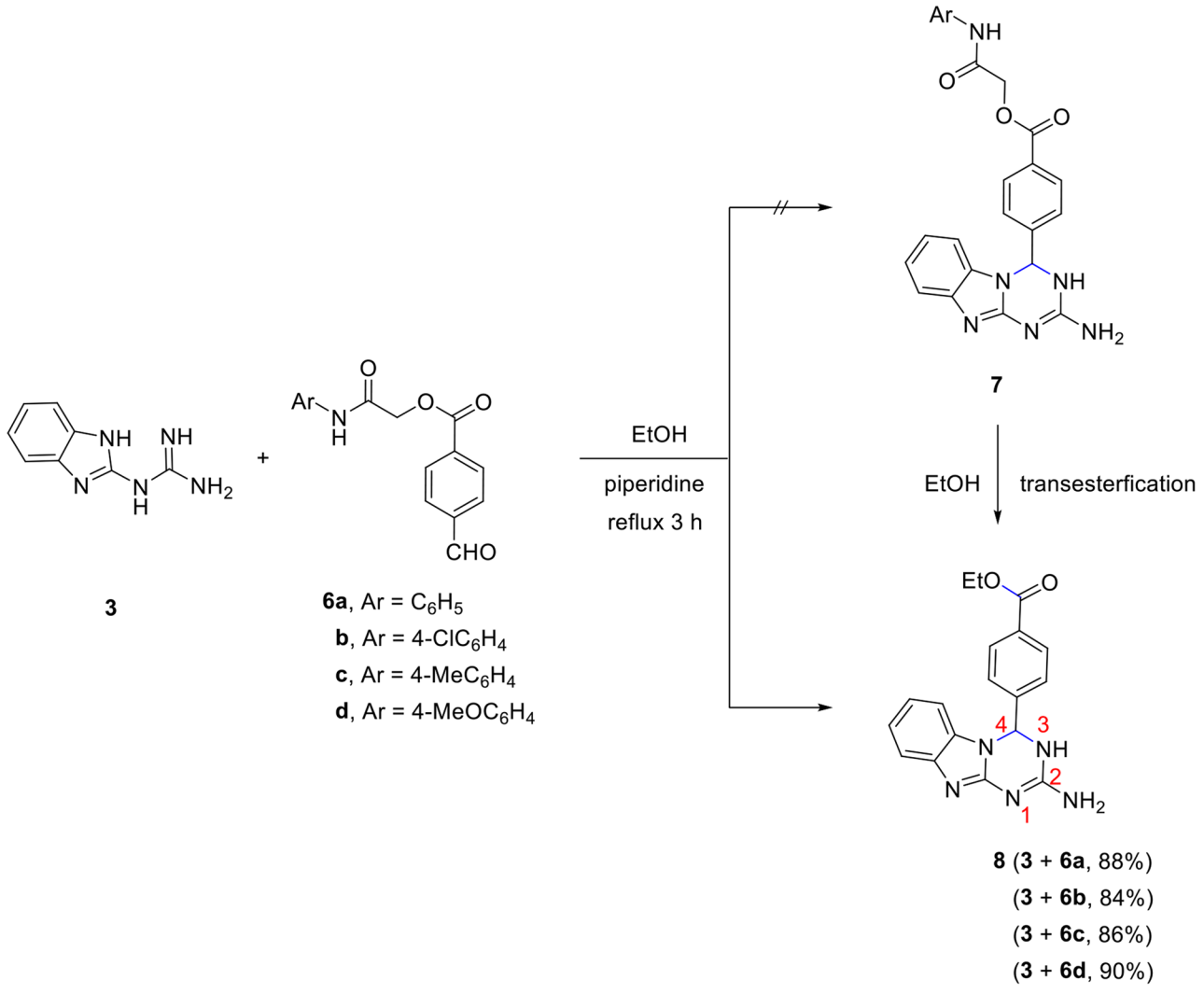
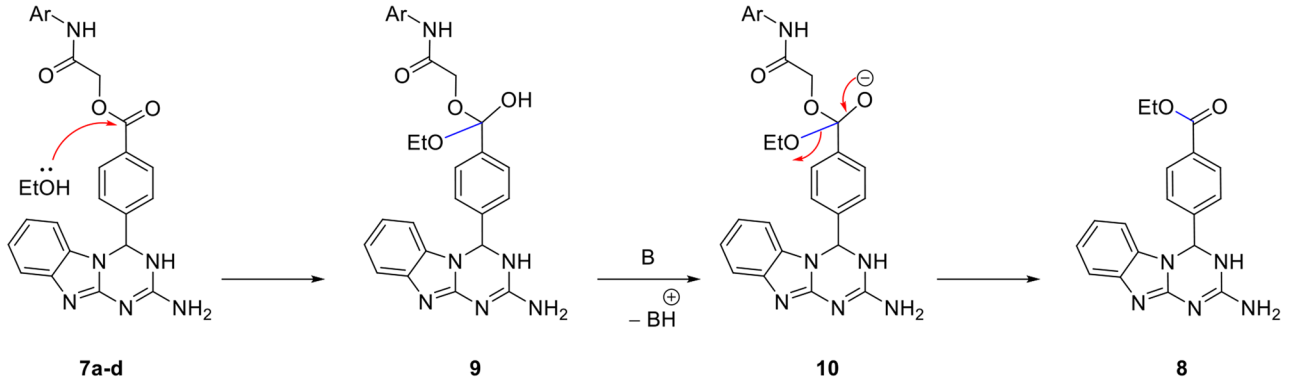


Fig. 3 Isomeric structures of [4,5]imidazo[1,2-*a*][1,3,5]triazines **5**

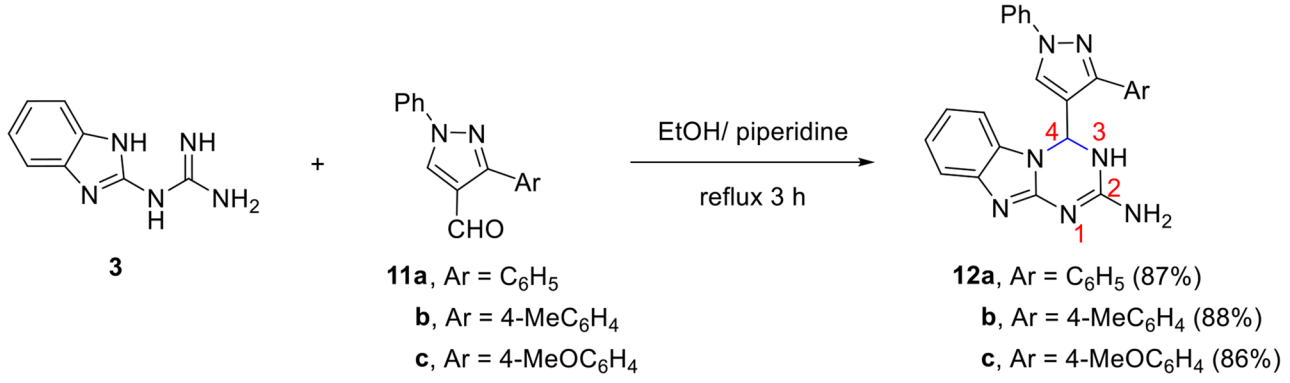


Scheme 3 Synthesis of ethyl 4-(2-amino-3,4-dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazin-4-yl)benzoate **8**

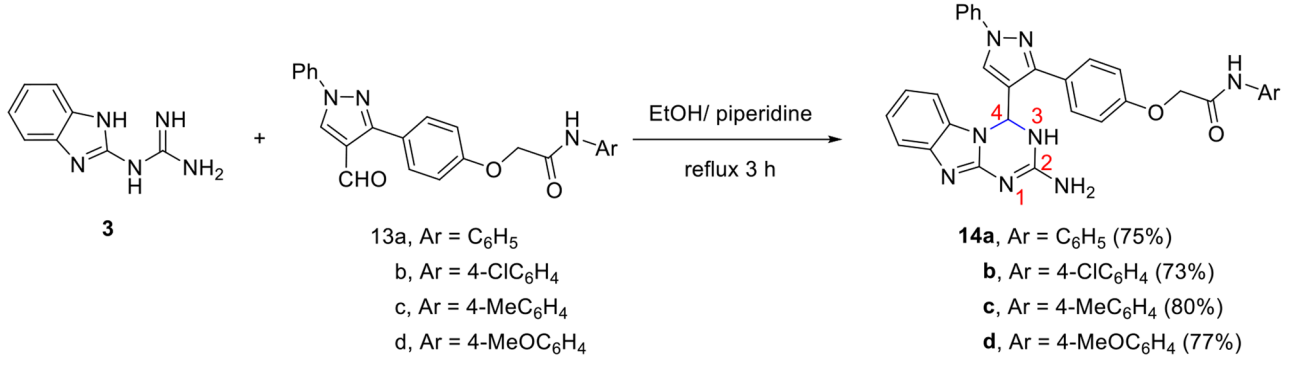


Scheme 4 Unexpected formation of ethyl 4-(2-amino-3,4-dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazin-4-yl)benzoate **8**

molecular-ion peak at *m/z* 554 which is relative to the proposed structure. The IR spectrum showed characteristic absorption bands at $\bar{\nu}$ 3549, 3325, 1674 cm^{-1} for NH_2, NH, and amide C = O, respectively. The ^1H NMR spectrum displayed two characteristic singlets at δ 4.79 and 9.08 ppm for OCH_2 and pyrazole-*H*5, respectively. It showed further multiplets at δ 6.93–7.99 ppm integrated for 21 protons for the amino group, *H*-4, and aromatic



Scheme 5 Synthesis of pyrazole-containing 1,3,4a,9-tetraza-4*H*-fluoren-2-amines **12a-c**



Scheme 6 Synthesis of 1,3,4a,9-tetraza-4*H*-fluoren-2-amines **14a-d** that are linked to 2-(4-(1-phenyl-1*H*-pyrazol-3-yl)phenoxy)-*N*-arylacetamide moieties

Table 1 Antibacterial activity of the synthesized compounds at a concentration of 10 mg/mL. The data was mean ± standard deviation (SD) of two separate experiments performed in triplicats

Inhibition zone diameter (mm) ± SD at 10 mg/mL				
Sample	**S. aureus**	**B. subtilis**	**E. coli**	***P.* aeruginosa**
5a	13 ± 1.4	14 ± 0	NA	14 ± 0
5b	NA	NA	NA	NA
5c	12 ± 0	NA	NA	13 ± 1.4
5d	13 ± 2.1	16 ± 0.7	NA	16 ± 0.7
8	10 ± 0	NA	NA	NA
12a	NA	14 ± 0	NA	NA
12b	16 ± 0.7	14 ± 1.4	NA	14 ± 1.4
12c	NA	NA	NA	NA
14a	NA	NA	NA	NA
14b	NA	NA	NA	NA
14c	NA	NA	NA	NA
14d	NA	NA	NA	10 ± 0
Gentamycin	15 ± 0	20 ± 1.4	20 ± 2.1	21 ± 0
5% DMSO	0.0	0.0	0.0	0.0

(Gentamycin, 10 µg/disc) was positive control for gram-positive and gram-negative bacteria. *NA: No activity

protons, as well as two D_2O-exchangeable singlets at δ 8.67 and 10.12 ppm for the two N*H* groups. The ^{13}C NMR spectrum shows peaks at δ 67.1 and 166.5 ppm for OCH_2 and amide *C* = O. Other peaks are present in close agreement with the proposed structure.

Antibacterial activity

Agar well diffusion assay was used to assess the antibacterial activity of all the prepared compounds against *Staphylococcus aureus* (*S. aureus*) and *Bacillus subtilis* (*B. subtilis*) (gram-positive bacteria), *Escherichia coli* (*E. coli*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) (gram-negative bacteria). The results showed that compounds **5a, 5d**, and **12b** were promising against *S. aureus* with the inhibition zones of 13 ± 1.4, 13 ± 2.1, and 16 ± 0.7 mm, respectively, and the most effective one was compound **12b** compared to Gentamycin (15 ± 0 mm) (Table 1). Concerning *B. subtilis*, compounds **5a, 5d, 12a**, and **12b** showed moderate activity with the inhibition zones of 14 ± 0, 16 ± 0.7, 14 ± 0, and 14 ± 1.4 mm, respectively, compared to Gentamycin (20 ± 1.4). Compound **5d** had the strongest action against *P. aeruginosa* (16 ± 0.7 mm), compared to Gentamycin (21 ± 0 mm). Compounds **5a, 5c**, and **12b** had moderate activity, whereas compound **14d** had the lowest activity (10 ± 0 mm) against *P. aeruginosa* compared to Gentamycin. All the synthesized

Table 2 The effect of different concentrations (10-0.0195 mg/mL) of **5a, 5c, 5d, 8**, and **12b** on *S. Aureus*. The data was the mean of duplicate results ± standard deviation (SD)

Concentration (mg/mL)	S. aureus (Inhibition zone (mm) ± SD)				
	5a	5c	5d	8	12b
10	14 ± 1.4	12 ± 0	12.5 ± 2.1	10 ± 0	15.5 ± 0.7
5	13 ± 0.7	11 ± 0	10 ± 0.7	10 ± 0	14 ± 0
2.5	12 ± 0	11 ± 0	10 ± 0	9 ± 0.7	13 ± 1
1.25	11 ± 0	10 ± 0.7	9 ± 0	9 ± 0.7	13 ± 0
0.625	0	9 ± 0	0	0	12 ± 1
0.3125	0	0	0	0	12 ± 0.8
0.1563	0	0	0	0	11.5 ± 0
0.0781	0	0	0	0	11 ± 0
0.0391	0	0	0	0	0
0.0195	0	0	0	0	0

Table 3 Minimum inhibitory concentration (MIC) of compounds **5a, 5c, 5d, 8**, and **12b** against *S. Aureus*

Compound	S. aureus
	MIC (µg/mL)
5a	1250
5c	625
5d	1250
8	1250
12b	78.1

compounds had no action against *E. coli*. So, the most promising results were shown against *S. aureus* compared to Gentamycin. Therefore, *S.aureus* strain was chosen for further MIC evaluation. Tables 2 and 3; Fig. 4 showed the results of MIC determination. It was found that compound **12b** had the lowest MIC value (78.1 µg/mL).

Structure-activity relationship

Figure 5 shows a design for the prepared series of benzo[4,5]imidazo[1,2-*a*][1,3,5]triazines **5,12**, and **14**.

The structure-activity relationship demonstrated that the derivatives **5a-d** and **12a-c** performed better than the derivatives **14a-d**. Compound **5d**, which included a 4-methoxyphenyl group (an electron-donating group), had the highest antibacterial activity against *S. aureus,P. aeuroginosa*, and *B. subtilis* among the **5a-d** derivatives. Compound **5a**, which included an unsubstituted phenyl group, had a moderate action against *S. aureus,P. aeruginosa* and *B. subtilis*. The *p*-tolyl group (electron-donating group) in derivative **5c** demonstrated modest antibacterial activity against *S. aureus* and *P. aeruginosa*. On the other hand, derivative **5b** with 4-chlorophenyl moiety (electron-withdrawing group) reduced antibacterial efficacy against the tested bacterial strains. The unsubstituted phenyl group in **12a** demonstrated moderate activity against *B. subtilis*, whereas derivative **12b** with *p*-tolyl group exhibited promising action against *S. aureus* and moderate activity against *B. subtilis* and *P. aeruginosa*, respectively. Compound **12c**, on the other hand, had decreased activity against all the strains tested. Among compounds **14a-d**, only **14d** containing a 4-methoxyphenyl group was effective. It showed limited efficacy against *P. aeruginosa*.

Conclusion

We have described an effective method for creating novel annelated 1,3,4a,9-tetraza-4*H*-fluoren-2-amines ring systems incorporating phenoxy-*N*-arylacetamide, and pyrazole moieties. The reaction involves reacting one-mole equivalent of 1-(1*H*-benzo[*d*]imidazol-2-yl) guanidine with one-mole equivalent of the appropriate aldehydes. We concluded that compound **5d**'s promising action against *S. aureus* and *P. aeruginosa*, as well as its modest activity against *B. subtilis*, might be attributed to its inhibition of the MurG enzyme, as indicated by our molecular docking studies. Furthermore, the promising efficacy of compounds **5a** and **5c** against *S. aureus* might be attributed to their inhibitory action on bacterial tyrosyl tRNA synthetase and MurG.

Supplementary file Compounds **5a** is represented here as a representative example. Full experimental details of all compounds and spectral data are represented in the supplementary file.

"Experimental

"Melting points were measured with using a Stuart melting point apparatus and were uncorrected. The IR spectra were recorded using Vector 22 FTIR-spectrophotometer (Brucker, Germany) as KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 as a solvent with Mercury VXR-300 NMR spectrometer (Varian, USA) operating at 300 MHz and 75 MHz, using TMS as an internal standard. Chemical shifts were reported as δ values in ppm. Mass spectra were recorded with GCMS-QP-1000 EX mass spectrometer (Shimadzu, Japan) in EI (70 eV) model. The elemental analyses were performed using CHNS-932 Vario elemental analyzer (LECO, USA) at the Micro Analytical Centre, Cairo University".

General method for the synthesis of compounds 5a-d, 8, 12a-c and 14a-d

"A solution of 1-(1*H*-benzo[*d*]imidazol-2-yl)guanidine (**3**) (175 mg, 1 mmol) and the appropriate aldehyde (**4a-d**), **(6a-d), (11a-c), or (13a-d)** (1 mmol) in ethanol (10 mL) containing piperidine (2 drops) was heated at reflux for 3 h. The reaction mixture is allowed to cool to ambient temperature. A precipitate is formed which is subsequently filtered, washed with ethanol, and recrystallized from EtOH\dioxane (3:1, v/v) mixture to give the titled compound".

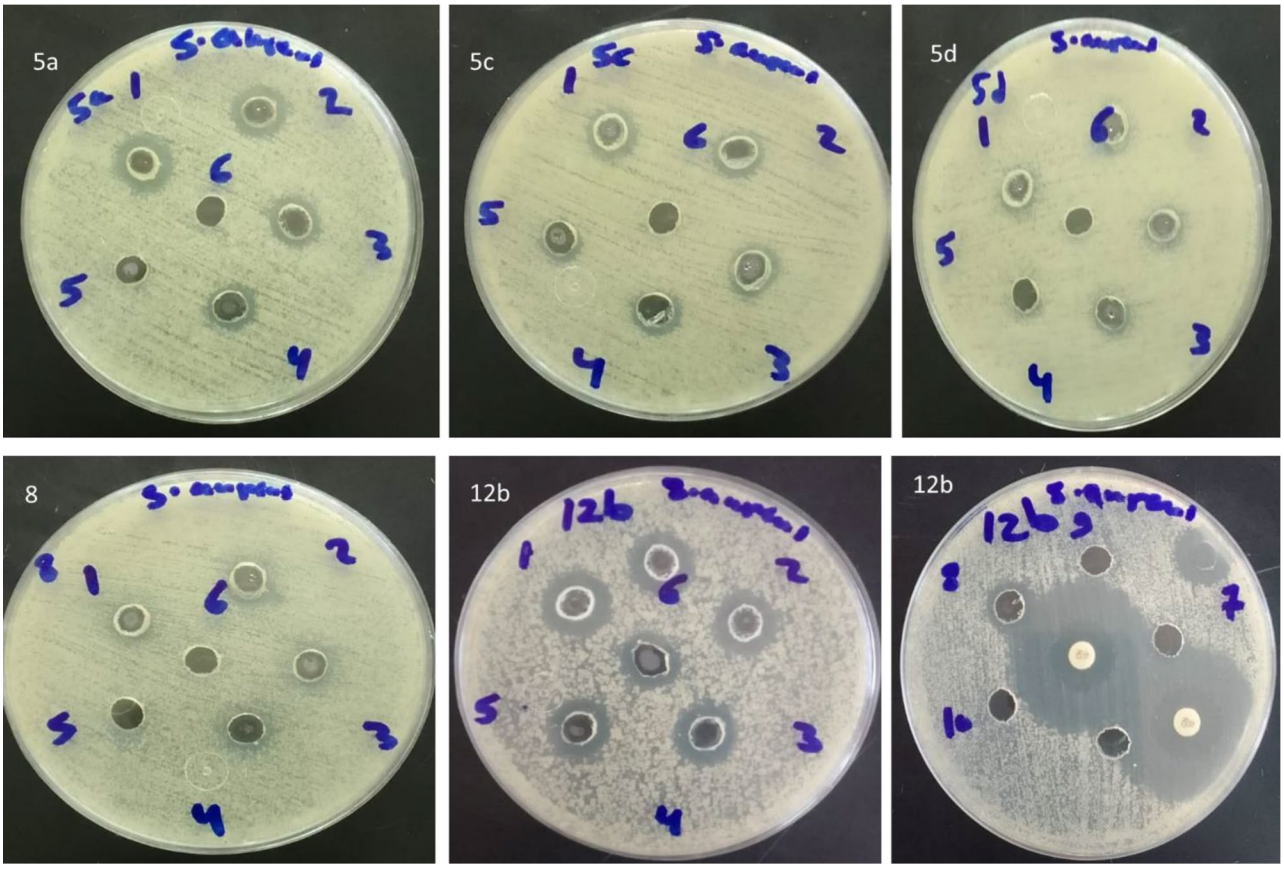


Fig. 4 Agar well diffusion assay for estimating the MIC of compounds **5a, 5c, 5d, 8** and **12b** against *S. aureus*. The range of serial dilution concentrations was 1 = 10 mg/mL to 10 = 0.0195 mg/mL. CN10 means Gentamycin positive control

2-(4-(2-Amino-3,4-dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5] triazin-4-yl)phenoxy)-*N*-phenylacetamide (5a)

Colorless powder (350 mg, 85%); Mp 235–237 °C; IR (KBr): $\bar{\nu}$ 3449 (NH_2), 3325 (2N*H*), 1674 (C = O), 1605 (C = N), 1520 (C = C) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.69 (s, 2 H, OCH_2), 6.39 (s, 2 H, NH_2, D_2O exchangeable), 6.70 (d, *J* = 6.9 Hz, 2 H, Ar-*H*), 6.78 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 6.93 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 7.02 (d, *J* = 8.6 Hz, 2 H, Ar-*H*), 7.08 (d, *J* = 8.4 Hz, 1H, *H*4), 7.22 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.26–7.36 (m, 4 H, Ar-*H*), 7.61 (d, *J* = 8.6 Hz, 2 H), 7.98 (br s, 1H, N*H*, D_2O exchangeable), 10.06 (s, 1H, N*H*, D_2O exchangeable) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 65.6, 67.1, 108.4, 115.0, 115.9, 119.0, 119.8, 120.9, 123.7, 127.8, 128.8, 131.2, 133.2, 138.4, 143.1, 153.5, 155.4, 158.4, 166.4 ppm; MS (EI, 70 eV): *m/z* (%) 412]M^+[; Anal. Calcd for $C_{23}H_{20}N_6O_2$: C, 66.98; H, 4.89; N, 20.38. Found: C, 66.83; H, 4.70; N, 20.18%.

2-(4-(2-Amino-3,4-dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5] triazin-4-yl)phenoxy)-*N*-(4-chlorophenyl)acetamide (5b)

Pale yellow powder (370 mg, 83%); Mp 200–202 °C; IR (KBr): $\bar{\nu}$ 3448 (NH_2), 3320 (2N*H*), 1670 (C = O), 1600 (C = N), 1519 (C = C) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.69 (s, 2 H, OCH_2), 6.34 (s, 2 H, NH_2, D_2O exchangeable), 6.69 (d, *J* = 7.2 Hz, 2 H, Ar-*H*), 6.76 (t, *J* = 7.2 Hz, 1H, Ar-*H*), 6.91 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 7.01 (d, *J* = 8.7 Hz, 2 H, Ar-*H*), 7.22 (d, *J* = 7.7 Hz, 1H, *H*4), 7.32 (d, *J* = 8.8 Hz, 2 H, Ar-*H*), 7.36 (d, *J* = 8.9 Hz, 2 H, Ar-*H*), 7.65 (d, *J* = 8.9 Hz, 2 H, Ar-*H*), 7.92 (s, 1H, N*H*, D_2O exchangeable), 10.20 (s, 1H, N*H*) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 65.9, 67.3, 108.3, 114.6, 116.0, 118.6, 120.1, 120.7, 121.1, 128.1, 129.7, 131.7, 132.6, 133.4, 135.2, 143.4, 154.9, 158.8, 166.6 ppm; MS (EI, 70 eV): *m/z* (%) 446]M^+[Anal. Calcd for $C_{23}H_{19}ClN_6O_2$: C, 61.82; H, 4.29; N, 18.81. Found: C, 61.66; H, 4.11; N, 18.64%.

2-(4-(2-Amino-3,4-dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5] triazin-4-yl)phenoxy)-*N*-(*p*-tolyl)acetamide (5c)

Colorless powder (354 mg, 83%); Mp 204–206 °C; IR (KBr): $\bar{\nu}$ 3448 (NH_2), 3328 (2N*H*), 1677 (C = O), 1609 (C = N), 1520 (C = C) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.25 (s, 3 H, CH_3), 4.66 (s, 2 H, OCH_2), 6.38 (s, 2 H, NH_2, D_2O exchangeable), 6.69 (d, *J* = 6.6 Hz, 2 H, Ar-*H*), 6.76 (t, *J* = 7.3 Hz, 1H, Ar-*H*), 6.92 (t, *J* = 7.1 Hz, 1H, Ar-*H*), 7.01 (d, *J* = 8.1 Hz, 2 H, Ar-*H*), 7.11 (d, *J* = 7.6 Hz, 2 H, Ar-*H*), 7.21 (d, *J* = 7.6 Hz, 1H, *H*4), 7.33 (d, *J* = 8.2 Hz,

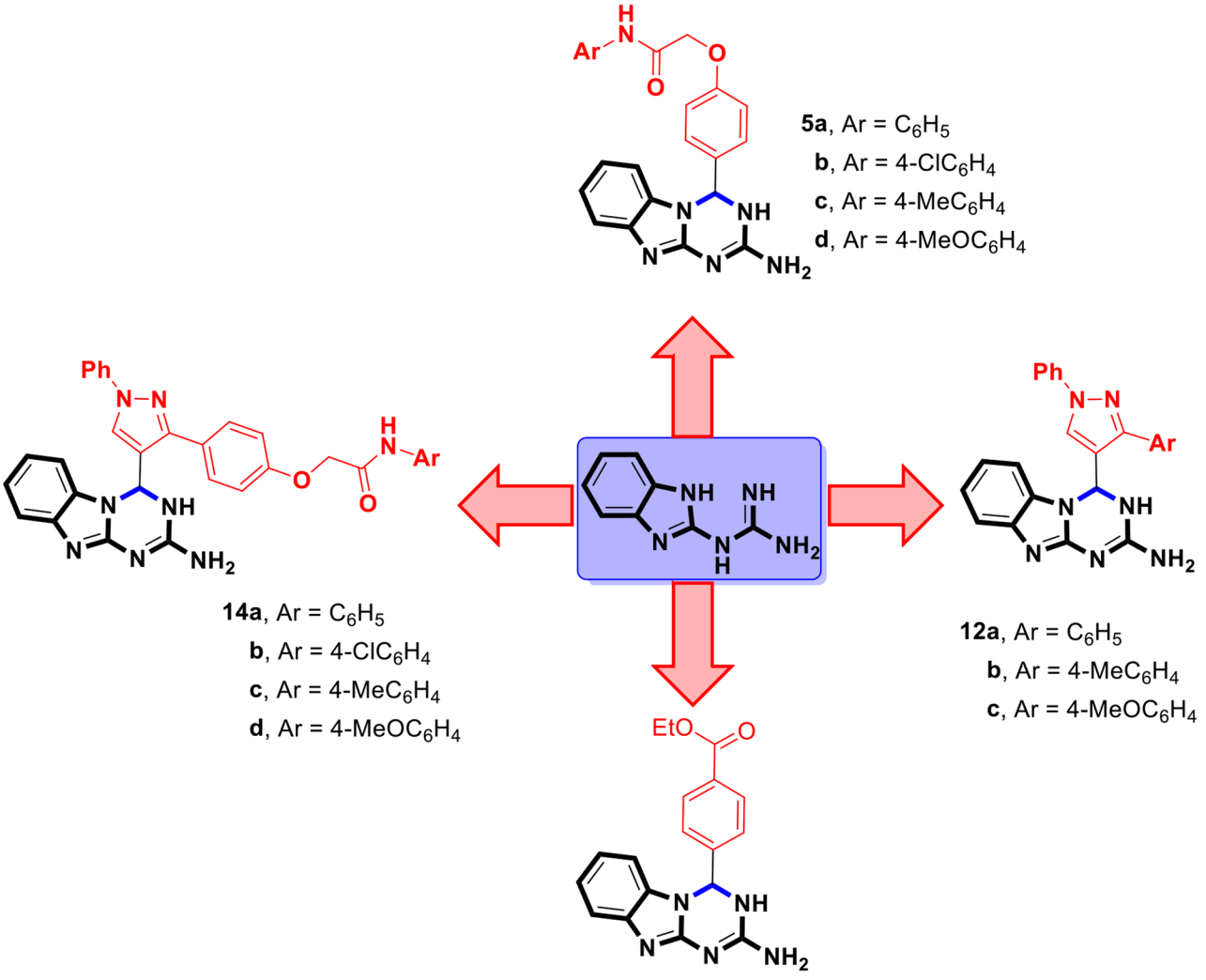


Fig. 5 A general structure of the prepared benzo[4,5]imidazo[1,2-*a*][1,3,5]triazines **5**,**12**, and **14**

2 H), 7.49 (d, *J* = 7.8 Hz, 2 H, Ar-*H*), 7.96 (br s, 1H, N*H*, D_2O exchangeable), 9.96 (s, 1H, N*H*, D_2O exchangeable) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.5, 65.5, 67.1, 108.3, 115.0, 115.9, 118.9, 119.9, 120.5, 120.8, 127.7, 129.1, 131.3, 132.7, 133.2, 135.9, 143.4, 155.4, 158.4, 166.1 ppm; MS (EI, 70 eV): *m/z* (%) 426]M$^+$[Anal. Calcd for $C_{24}H_{22}N_6O_2$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.39; H, 5.02; N, 19.53%.

2-(4-(2-Amino-3,4-dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazin-4-yl)phenoxy)-*N*-(4-methoxyphenyl)acetamide (5d)

Grey powder (380 mg, 86%); Mp 240–242 °C; IR (KBr): $\bar{\nu}$ 3448 (NH_2), 3330 (2N*H*), 1678 (C = O), 1608 (C = N), 1522 (C = C) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.72 (s, 3 H, OCH_3), 4.65 (s, 2 H, OCH_2), 6.37 (s, 2 H, NH_2, D_2O exchangeable), 6.69 (d, *J* = 6.2 Hz, 2 H, Ar-*H*), 6.77 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 6.88 (d, *J* = 8.2 Hz, 2 H, Ar-*H*), 6.93 (d, *J* = 7.5 Hz, 1H, Ar-*H*), 7.02 (d, *J* = 7.9 Hz, 2 H, Ar-*H*), 7.21 (d, *J* = 7.7 Hz, 1H, *H*4), 7.33 (d, *J* = 8.1 Hz, 2 H, Ar-*H*), 7.51 (d, *J* = 8.7 Hz, 2 H, Ar-*H*), 7.95 (s, 1H, N*H*, D_2O exchangeable), 9.91 (s, 1H, N*H*, D_2O exchangeable) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 58.1, 65.5, 69.1, 108.3, 115.0, 115.5, 116.0, 119.8, 120.1, 120.8, 129.1, 131.7, 132.3, 133.4, 135.9, 144.3, 154.5, 158.4, 160.3, 167.4 ppm; MS (EI, 70 eV): *m/z* (%) 442]M$^+$[Anal. Calcd for $C_{24}H_{22}N_6O_3$: C, 65.15; H, 5.01; N, 18.99. Found: C, 64.97; H, 4.87; N, 18.82%.

Ethyl 4-(2-amino-3,4-dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazin-4-yl)benzoate (8)

Wite powder (295 mg, 88%); Mp 208–210 °C; IR (KBr): h$\bar{\nu}$ 3418 (NH_2), 3248 (N*H*), 1713 (C = O), 1628 (C = N), 1528 (C = C) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.28 (t, *J* = 7.2 Hz, 3 H, $COOCH_2CH_3$), 4.29 (q, *J* = 7.2 Hz, 2 H, $COOCH_2CH_3$), 6.42 (s, 2 H, NH_2, D_2O exchangeable), 6.74 (d, *J* = 7.5 Hz, 1H, *H*4), 6.79 (t, *J* = 7.4 Hz, 1H, Ar-*H*), 6.84 (s, 1H, *H*4), 6.94 (t, *J* = 7.4 Hz, 1H, Ar-*H*), 7.24 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.48 (d, *J* = 7.9 Hz, 2 H, Ar-*H*), 7.96

(d, *J* = 7.7 Hz, 2 H, Ar-*H*), 8.09 (s, 1H, N*H*, D_2O exchangeable) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.2, 61.1, 65.4, 108.5, 116.1, 119.3, 121.4, 126.6, 128.7, 130.0, 130.7, 131.1, 143.2, 145.3, 155.2, 165.3 ppm; MS (EI, 70 eV): *m/z* (%) 335]M^+[. Anal. Calcd for $C_{18}H_{17}N_5O_2$: C, 64.47; H, 5.11; N, 20.88. Found: C, 64.33; H, 4.95; N, 20.70%.

4-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-3,4-dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazin-2-amine (12a)

Colorless powder (352 mg, 87%); Mp 280–282 °C; IR (KBr): $\bar{\nu}$ 3540 (NH_2), 3325 (N*H*), 1604 (C = N), 1520 (C = C) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 6.40 (d, *J* = 7.9 Hz, 1H, *H*4), 6.51(s, 2 H, NH_2, D_2O exchangeable), 6.69 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 6.88 (d, *J* = 7.2 Hz, 2 H, Ar-*H*), 7.15 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.33 (t, *J* = 7.4 Hz, 1H, Ar-*H*), 7.41 (d, *J* = 6.6 Hz, 2 H, Ar-*H*), 7.50 (t, *J* = 7.7 Hz, 3 H, Ar-*H*), 7.65 (d, *J* = 7.6 Hz, 2 H, Ar-*H*), 7.90 (d, *J* = 8.0 Hz, 2 H, Ar-*H*), 8.25 (br s, 1H, N*H*, D_2O exchangeable), 8.76 (s, 1H, pyrazole-*H*5) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 62.6, 111.2, 118.1, 118.5, 119.2, 122.9, 123.8, 127.0, 128.0, 128.2, 128.9, 129.2, 129.4, 129.6, 130.2, 137.6, 139.5, 150.5, 151.4, 157.7 ppm; MS (EI, 70 eV): *m/z* (%) 405]M^+[Anal. Calcd for $C_{24}H_{19}N_7$: C, 71.09; H, 4.72; N, 24.18. Found: C, 70.96; H, 4.56; N, 24.04%.

4-(1-Phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)-3,4-dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazin-2-amine (12b)

Wite powder (369 mg, 88%); Mp 295–297 °C; IR (KBr): h $\bar{\nu}$ 3546 (NH_2), 3325 (N*H*), 1604 (C = N), 1525 (C = C) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.34 (s, 3 H, CH_3), 6.58 (d, *J* = 7.9 Hz, 1H, *H*4), 7.04 (s, 2 H, NH_2, D_2O exchangeable), 7.17 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.23 (d, *J* = 7.6 Hz, 2 H, Ar-*H*), 7.33 (d, *J* = 7.9 Hz, 3 H, Ar-*H*), 7.43 (d, *J* = 8.0 Hz, 2 H, Ar-*H*), 7.52 (t, *J* = 7.7 Hz, 3 H, Ar-*H*), 7.89 (d, *J* = 8.2 Hz, 2 H, Ar-*H*), 9.03 (s, 1H, pyrazole-*H*5), 9.48 (br s, 1H, N*H*, D_2O exchangeable) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.9, 59.9, 110.2, 111.7, 118.5, 119.2, 122.9, 123.8, 127.0, 128.0, 128.2, 128.9, 129.2, 129.4, 129.7, 130.1, 138.2, 139.0, 150.8, 151.2, 156.7 ppm; MS (EI, 70 eV): *m/z* (%) 419]M^+[Anal. Calcd for $C_{25}H_{21}N_7$: C, 71.58; H, 5.05; N, 23.37. Found: C, 71.43; H, 4.95; N, 23.18%.

4-(3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-3,4-dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazin-2-amine (12c)

Colorless powder (374 mg, 86%); Mp 287–289 °C; IR (KBr): $\bar{\nu}$ 3549 (NH_2), 3325 (N*H*), 1674 (C = O), 1605 (C = N), 1528 (C = C) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.78 (s, 3 H, OCH_3), 6.50 (d, *J* = 7.6 Hz, 1H, *H*4), 6.92 (s, 2 H, NH_2, D_2O exchangeable), 6.97 (d, *J* = 8.3 Hz, 2 H, Ar-*H*), 7.07 (d, *J* = 7.5 Hz, 1H, Ar-*H*), 7.13 (s, 2 H, Ar-*H*), 7.27 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.35 (d, *J* = 8.1 Hz, 1H, Ar-*H*), 7.50 (d, *J* = 6.1 Hz, 4 H, Ar-*H*), 7.88 (d, *J* = 8.1 Hz, 2 H, Ar-*H*), 8.37 (s, 1H, N*H*, D_2O exchangeable), 8.87 (s, 1H, pyrazole-*H*5) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.4, 61.8, 110.5, 111.9, 118.4, 119.2, 122.9, 123.8, 127.2, 128.16, 128.18, 128.9, 129.3, 129.4, 129.7, 138.0, 138.6, 150.6, 151.2, 156.7, 159.4 ppm; MS (EI, 70 eV): *m/z* (%) 435]M^+[Anal. Calcd for $C_{25}H_{21}N_7O$: C, 68.95; H, 4.86; N, 22.51. Found: C, 68.79; H, 4.69; N, 22.39%.

2-(4-(4-(2-Amino-3,4-dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazin-4-yl)-1-phenyl-1*H*-pyrazol-3-yl)phenoxy)-*N*-phenylacetamide (14a)

White powder (415 mg, 75%); Mp 240–242 °C; IR (KBr): $\bar{\nu}$ 3549 (NH_2), 3325 (N*H*), 1674 (C = O), 1605 (C = N), 1528 (C = C) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.79 (s, 2 H, OCH_2), 6.92 (s, 1H, *H*4), 7.09–7.18 (m, 3 H, NH_2, Ar-*H*), 7.35 (s, 4 H, Ar-*H*), 7.54 (s, 4 H, Ar-*H*), 7.67 (d, *J* = 18.5 Hz, 5 H, Ar-*H*), 7.99 (s, 4 H, Ar-*H*), 8.67 (s, 1H, N*H*, D_2O exchangeable), 9.08 (s, 1H, pyrazole-*H*5), 10.12 (s, 1H, N*H*, D_2O exchangeable) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 67.2, 71.5, 110.5, 115.1, 115.7, 116.3, 119.0, 119.8, 120.6, 122.5, 123.9, 124.9, 127.3, 128.6, 128.9, 129.8, 130.0, 130.3, 138.4, 139.0, 142.8, 152.7, 153.6, 158.4, 160.2, 166.5.ppm; MS (EI, 70 eV): *m/z* (%) 554]M^+[Anal. Calcd for $C_{32}H_{26}N_8O_2$: C, 69.30; H, 4.73; N, 20.20. Found: C, 69.12; H, 4.57; N, 20.01%.

2-(4-(4-(2-Amino-3,4-dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazin-4-yl)-1-phenyl-1*H*-pyrazol-3-yl)phenoxy)-*N*-(4-chlorophenyl)acetamide (14b)

Yellow powder (430 mg, 73%); Mp 180–182 °C; IR (KBr): $\bar{\nu}$ 3549 (NH_2), 3325 (N*H*), 1670 (C = O), 1604 (C = N), 1525 (C = C) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.79 (s, 2 H, OCH_2), 6.59 (d, *J* = 8.8 Hz, 1H, *H*4), 7.12 (t, *J* = 8.9 Hz, 3 H, NH_2, Ar-*H*), 7.39 (td, *J* = 12.3, 8.3 Hz, 5 H, Ar-*H*), 7.55 (d, *J* = 7.9 Hz, 2 H, Ar-*H*), 7.58–7.66 (m, 2 H, Ar-*H*), 7.69 (d, *J* = 8.8 Hz, 2 H, Ar-*H*), 7.95 (dd, *J* = 12.7, 8.6 Hz, 5 H, Ar-*H*), 9.27 (s, 1H, pyrazole-*H*5), 9.97 (s, 1H, N*H*, D_2O exchangeable), 10.28 (s, 1H, N*H*, D_2O exchangeable) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 66.9, 70.7, 108.9, 114.86, 114.93, 115.4, 115.9, 118.3, 118.9, 119.2, 119.9, 121.1, 125.0, 126.6, 129.1, 129.4, 129.5, 130.3, 131.1, 133.5, 135.8, 138.6, 143.3, 150.3, 158.1, 166.3 ppm;.MS (EI, 70 eV): *m/z* (%) 589]M^+[Anal. Calcd for $C_{32}H_{25}ClN_8O_2$: C, 65.25; H, 4.28; N, 19.02. Found: C, 65.05; H, 4.15; N, 18.86%.

2-(4-(4-(2-Amino-3,4-dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazin-4-yl)-1-phenyl-1*H*-pyrazol-3-yl)phenoxy)-*N*-(*p*-tolyl)acetamide (14c)

Colorless powder (454 mg, 80%); Mp 193–195 °C; IR (KBr): $\bar{\nu}$ 3549 (NH_2), 3325 (N*H*), 1672 (C = O), 1604 (C = N), 1527 (C = C) cm^{-1}; ^1H NMR (300 MHz,

DMSO-d_6) δ 2.26 (s, 3 H, CH_3), 4.72 (s, 2 H, OCH_2), 6.29 (s, 2 H, NH_2, D_2O exchangeable), 6.41 (d, J = 7.8 Hz, 1H, *H*4), 6.79–6.92 (m, 3 H, Ar-*H*), 7.06–7.20 (m, 5 H, Ar-*H*), 7.30–7.35 (m, 1H, Ar-*H*), 7.46–7.55 (m, 5 H, Ar-*H*), 7.64 (d, J = 7.2 Hz, 1H, Ar-*H*), 7.90 (d, J = 9.1 Hz, 2 H, Ar-*H*), 8.70 (s, 1H, N*H*, D_2O exchangeable), 9.15 (s, 1H, pyrazole-*H*5), 10.02 (s, 1H, N*H*, D_2O exchangeable) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.5, 67.2, 70.7, 108.4, 114.8, 114.9, 115.9, 118.3, 119.0, 119.2, 119.8, 120.8, 125.2, 126.6, 129.1, 129.5, 129.6, 129.7, 130.1, 131.5, 132.7, 135.8, 139.1, 143.3, 150.4, 158.0, 166.1 ppm; MS (EI, 70 eV): *m/z* (%) 568]M$^+$[Anal. Calcd for $C_{33}H_{28}N_8O_2$: C, 69.70; H, 4.96; N, 19.71. Found: C, 69.59; H, 4.81; N, 19.58%.

2-(4-(4-(2-Amino-3,4-dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazin-4-yl)-1-phenyl-1*H*-pyrazol-3-yl)phenoxy)-*N*-(4-methoxyphenyl)acetamide (14d)

Grey powder (450 mg, 77%); Mp 182–184 °C; IR (KBr): $\bar{\nu}$ 3549 (NH_2), 3325 (N*H*), 1674 (C = O), 1605 (C = N), 1528 (C = C) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.72 (s, 3 H, OCH_3), 4.70 (s, 2 H, OCH_2), 6.30 (s, 2 H, NH_2, D_2O exchangeable), 6.41 (d, J = 7.3 Hz, 1H, *H*4), 6.70 (d, J = 7.6 Hz, 1H, Ar-*H*), 6.88 (t, J = 4.5 Hz, 4 H, Ar-*H*), 7.04–7.11 (m, 2 H, Ar-*H*), 7.44–7.68 (m, 8 H, Ar-*H*), 7.89 (d, J = 8.2 Hz, 2 H, Ar-*H*), 8.70 (s, 1H, N*H*, D_2O exchangeable), 9.28 (s, 1H, pyrazole-*H*5), 9.95 (s, 1H, N*H*, D_2O exchangeable) ppm; MS (EI, 70 eV): *m/z* (%) 584]M$^+$[Anal. Calcd for $C_{33}H_{28}N_8O_3$: C, 67.80; H, 4.83; N, 19.17. Found: C, 67.61; H, 4.67; N, 18.99%.

Antibacterial assay

The antibacterial activity of the prepared compounds was assessed by using the agar well diffusion assay. The antibacterial activity was screened against two gram-positive bacteria *Staphylococcus aureus* (ATCC 6538) and *Bacillus subtilis* (DSM 1088) as well as two gram-negative bacteria *Pseudomonas aeruginosa* (ATCC 10145) and *Escherichia coli* (ATCC 8739). Dimethyl sulfoxide (DMSO) was used to make a solution of 10 mg/mL of each synthesized compound. The nutrient agar medium was poured on the plates and let to be cooled to 45 °C. 10^5-10^6 colony forming unit (CFU) per mL from an overnight bacterial culture was cultured on nutrient agar plates. Then, 6 mm wells were created in the nutritional medium using sterile metallic bores. After that, 20 µL of each tested compound (10 mg/mL) was added to the prepared well. Herein, the negative control was 5% DMSO and the results were compared to standard Gentamycin (10 µg/disc) and Clindamycin (2 µg/disc) (positive controls). The inhibition zone diameter in (mm) was measured using a calliper after the incubation of the plates at 37 °C for (18–24) hours. The experiment was repeated twice and in each time was done in triplicates. The minimum inhibition concentration (MIC) of compounds **5a, 5c, 5d, 8** and **12b** was determined against *S. aureus*. A serial dilution method with concentrations ranging from 10 to 0.0195 mg/mL was utilized. The MIC is the lowest concentration of the target drug that can inhibit the growth of the studied bacteria.

Supplementary Information

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Supplementary Material 1

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Author contributions

R.E.A. suggested the research plan, carried out the laboratory work, participated in data analysis, shared in writing the original draft of the manuscript, and followed up the experimental work. A.H.M.E., A.M.A., and I.A.A. suggested the research plan, and shared in writing the original draft of the manuscript. N.S.I carried out the biological activity work, participated in data analysis, and shared in writing the original draft of the manuscript. All authors gave final approval for publication.

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Data availability

All data generated or analyzed during this study are included in this published article and its supplementary information file. Data available at request (Ismail A. Abdelhamid, ismail_shafy@yahoo.com, ismail_shafy@cu.edu.eg).

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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