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Original article

Synthesis and biological activity of dihydroimidazole and 3,4-dihydrobenzo[4,5]imidazo[1,2-*a*][1,3,5]triazins

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ABSTRACT

Reaction of 2-guanidinobenzimidazole with halogenated active methylenes and ketones gave dihydroimidazole and 3,4-dihydrobenzo[4,5]imidazo [1,2-*a*][1,3,5]triazin derivatives in very good yield. The anti-bacterial evaluation of the newly synthesized products against broad spectrum of bacteria was performed. Most of products showed high inhibitory effect. All compounds have been characterized based on IR, ^{1}H NMR, ^{13}C NMR and Mass spectra.

1. Introduction

The importance of dihydroimidazole units especially in biochemistry is recently increasing, since they are found in many biologically active compounds [1]. They are also used in organic synthesis as synthetic intermediates [2], chiral auxiliaries [3], and chiral ligands [4]. Dihydroimidazoles are reported to exhibit diverse biological and pharmacological properties. Examples of these include α-receptor stimulation, vasodepressor activity, α-adrenergic inhibition, and sympathomimetic, antihistaminic, histamine-like, and cholinomimetic activity [5,6]. Dihydroimidazoles, such as midaglizole, deriglidole, and efaroxan have been found to be potent antihyperglycemic agents [7].

1,3,5-triazin ring reported synthsised *via* heterocyclization of biguanides or their analogues using β-keto esters [8]. 1,3,5-triazin derivatives containing various amino groups at position 2, 4 or 6, such as tretamine, furazil and dioxadet, have been known as anti-cancer drugs [9]. Structural modifications consisting in the replacement of ethyleneimino moiety with either dialkylamino, alkoxy, alkylarylo or hydroxy groups led to discovery of novel chemotherapeutic agents [10–15]. Moreover, an anti-gastric ulcer agent that is commonly used in Japan, irsogladine (2-amino-1,3,5-triazin), was shown to possess antiangiogenic properties which result in anticancer effect of the drug [16,17].

As a part of our research program aimed at search for new synthesized dihydroimidazole and 2-amino-1,3,5-triazin derivatives in addition to screening of their inhibitory effect on different types of gram-positive and gram-negative bacteria.

2. Results and discussion

2-Guanidinobenzimidazole **1** was prepared by the cyclo-condensation of o-phenylendiamine with cyanoguanidine according to the method reported by King et al. [18] (Scheme 1).

Reaction of compound **1** with halogenated active methylenes such as phenacyl bromide, chloroacetate chloride, chloro acetone, ethyl bromoacetate, chloro acetonitril and bromo malononitril, in presence of a few drops of glacial acetic acid as a benign catalyst afforded the formation of dihydroimidazole drevatives **2**–**7** respectively (Scheme 2).

The reaction mechanism was proceeding *via* elimination of the corresponding hydrogen halide and elimination of either water molecules as in **2**–**4** or molecule of ethanol as in **5** while addition on cyano group resulted in ultimately the amino dihydroimidazoles **6** and **7**.

IR spectra of compounds **2**–**7** illustrated absorption peaks at range between 3381 and 3176 cm^{-1} corresponding to NH groups in

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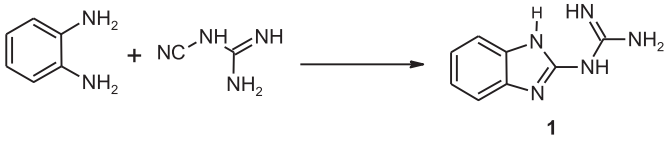


Scheme 1. Synthesis of 2-guanidinobenzimidazole.

dihydroimidazole ring and confirmed in ^{1}H NMR spectra as appeared as singlet peak between 9.74 and 10.23 ppm while CH of dihydroimidazole ring was observed between 5.64 and 6.71 ppm as singlet peak for compounds **2**–**7**. Mass spectra of compounds **2**–**7** gave molecular ion peaks at *m*/*z* 275, 233, 213, 215, 214 and 239 of compounds **2**–**7** respectively.

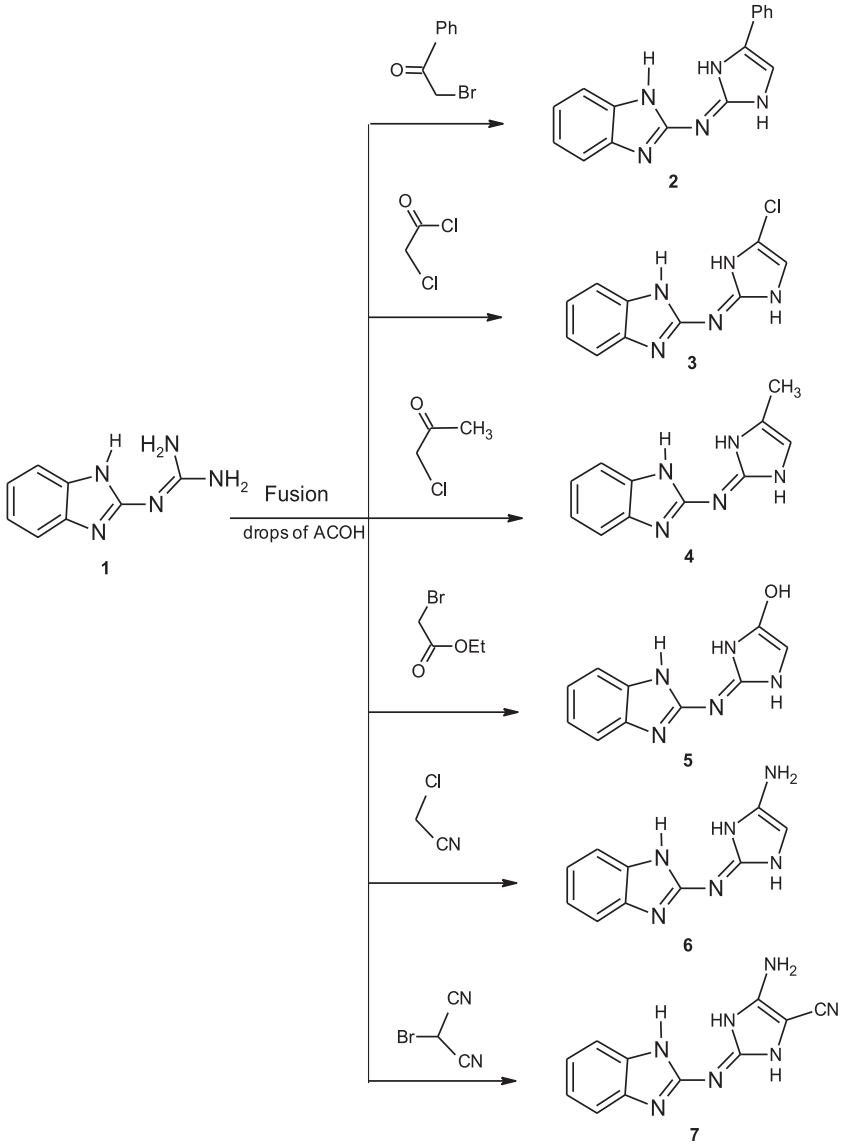
The reaction of 2-guanidinobenzimidazole **1** with ketones in ethanol proceeded *via* (5 + 1) heterocyclization and resulted in the formation of hitherto unknown 4-(het)aryl-3,4-dihydrobenzo [4,5] imidazo [1,2-a][1,3,5]triazin-2-amine **8**–**13** respectively.

The reaction of compound **1** with cyclopentanone, cyclohexanon, thiazolidione, pyrazolone, barbituric acid and camphor in ethanol and presence of a few drops of hydrochloric acid as a catalyst gave 4-(het)aryl-3,4-dihydrobenzo [4,5]imidazo [1,2-a] [1,3,5]triazin-2-amine **8**–**13** respectively rapidly and highly yielded (Scheme 3). Mass spectra of compounds **8**–**13** showed molecular ion peaks at *m*/*z* 241, 255, 274, 331, 285 and 309 respectively.

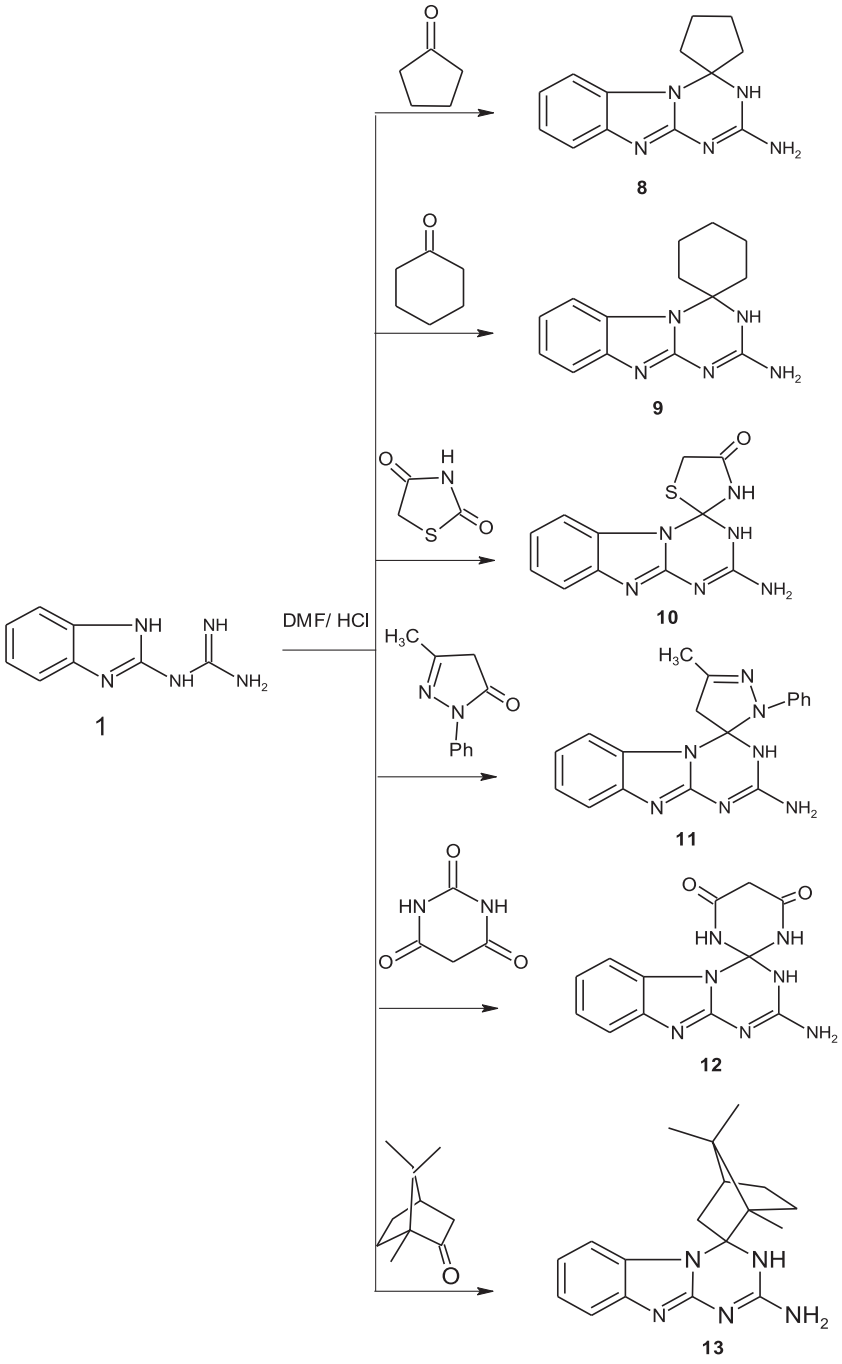
2.1. Anti-bacterial activity

The compounds were dissolved in DMSO. In order to ensure that the solvent per se had no effect on bacterial growth or enzymatic activity, negative control tests were performed using DMSO at the same concentrations.

The inhibitory effect of compounds **2**–**13** on the *in vitro* growth of broad spectrum of bacteria representing different types of gram-positive and gram-negative bacteria, namely *Bacillus cereus*, *Bacillus subtilis*, *Escherichia coli*, *Micrococcus luteus*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Micrococcus roseus* was evaluated using agar diffusion method (cup and plate method) [19–22]. DMSO was used as solvent control. All plates were incubated at 37 ± 0.5 °C for 24 h. The zone of inhibition of compounds was measured using cm scale. The results indicated in Table 1 revealed that compound **7** showed the highest inhibitory effect against all types of bacteria while compound **3** showed the lowest inhibitory



Scheme 2. Reaction of halogenated active methylenes with 2-guanidinobenzimidazole.



Scheme 3. Reaction of Ketones with 2-guanidinobenzimidazole.

effects against all types of bacteria (See Table 1). The results of triazin derivatives are shown in (Table 2). It seems that compound **10** exhibited the highest inhibitory effect against all types of bacteria while compound **13** showed the lowest inhibitory effects against all types of bacteria (See Table 2).

2.2. Experimental

All melting points are uncorrected and were recorded on Melt-Temp II melting point apparatus. IR spectra were measured as KBr pellets on a Shimadzu DR-8001 spectrometer. ^{1}H NMR spectra were recorded on a Varian Gemini at 280 MHz using TMS as an internal reference and DMSO-d_6 as a solvent. Mass spectra were performed on a Shimadzu GCMS-QP 1000 mass spectrometer at 70 ev. The elemental analyses were carried out on a Perkin–Elmer 240C Microanalyzer. All compounds were checked for their purity on TLC plates.

2.2.1. General procedure. 2–7

A mixture of compound **1** (50 mmol) and 10 ml of halogenated active methylenes such as phenacyl bromide, chloroacytel chloride, chloro acetone, ethyl bromoacetate, chloro acetonitril and bromo malononitril, in addition to few drops of catalytic glacial acetic acid was refluxed. The solid product was observed after reflux for further 1–4 h. After cooling down, the solid was collected by filtration, washed with cold ethanol and recrystalised from ethanol.

Table 1
Anti-bacterial evaluation results of dihydroimidazole compounds **2**–**7**.

Types of Bacteria	Compound **2**			Compound **3**			Compound **4**		
	Concentrations			Concentrations			Concentrations		
	10000 ppm	30000 ppm	50000 ppm	10000 ppm	30000 ppm	50000 ppm	10000 ppm	30000 ppm	50000 ppm
Bacillus cereus	0.6 cm	0.8 cm	0.9 cm	–	–	0.6 cm	0.6 cm	0.9 cm	1.2 cm
Bacillus subtilis	0.9 cm	1.1 cm	1.4 cm	0.6 cm	1.0 cm	1.4 cm	1.0 cm	1.3 cm	1.5 cm
Escherichia coli	0.4 cm	0.6 cm	0.8 cm	0.9 cm	1.3	1.8 cm	0.1 cm	0.4 cm	0.8 cm
Micrococcus luteus	–	–	0.3 cm	–	–	0.4 cm	0.6 cm	0.7 cm	0.8 cm
Staphylococcus aureus	–	0.5 cm	0.9 cm	–	0.5 cm	0.9 cm	–	0.3 cm	0.6 cm
Pseudomonas aeruginosa	0.4 cm	0.6 cm	1.1 cm	–	–	0.2 cm	–	0.4 cm	0.7 cm
Micrococcus roseus	0.3	0.8 cm	1.0 cm	–	0.3 cm	0.8 cm	0.5 cm	0.7 cm	0.9 cm
Types of Bacteria	Compound **5**			Compound **6**			Compound **7**		
	Concentrations			Concentrations			Concentrations		
	10000 ppm	30000 ppm	50000 ppm	10000 ppm	30000 ppm	50000 ppm	10000 ppm	30000 ppm	50000 ppm
Bacillus cereus	–	0.5 cm	1.0 cm	–	–	0.4 cm	0.6 cm	1.0 cm	1.4 cm
Bacillus subtilis	–	–	0.7 cm	–	–	0.6 cm	0.8 cm	1.1 cm	1.6 cm
Escherichia coli	0.6 cm	0.8 cm	1.3 cm	0.3 cm	0.8 cm	1.4 cm	0.8 cm	1.3 cm	1.9 cm
Micrococcus luteus	–	0.5 cm	0.9 cm	–	0.4 cm	0.8 cm	0.4 cm	0.7 cm	0.9 cm
Staphylococcus aureus	0.2 cm	0.7 cm	1.3 cm	0.4 cm	0.9 cm	1.5 cm	0.3 cm	0.7 cm	0.7 cm
Pseudomonas aeruginosa	0.5 cm	0.8 cm	1.1 cm	0.4 cm	0.7 cm	0.9 cm	0.6 cm	0.8 cm	0.9 cm
Micrococcus roseus	–	0.6 cm	0.8 cm	0.6 cm	0.8 cm	1.2 cm	0.4 cm	0.7 cm	0.9 cm

*2.2.1.1. N-[(2Z)-4-phenyl-1,5-dihydro-2H-imidazol-2-ylidene]-1,3-benzimidazol-2-amine (**2**).* Mp 155 °C, yield 88%; IR: cm^{-1} 3317, 3177(3NH); ^1H NMR: δ 09.75 (s,1H, NH), 7.71–7.01 (br,10H, 2 arom + NH), 6.66 (s,1H, CH), 6.18 (s,1H, NH); MS *m/z* (%): M^+ 275 (25.1), 198 (77.8), 166 (100), 149 (35.5), 123 (23.9), 96 (84.2); Anal.Calc. For $C_{16}H_{13}N_5$ (275.31): C(69.80%) H(4.76%) N(25.44%). Found: C(69.42%) H(4.24%) N(25.04%).

*2.2.1.2. N-[(2Z)-4-chloro-1,5-dihydro-2H-imidazol-2-ylidene]-1,3-benzimidazol-2-amine (**3**).* Mp 285 °C, yield 74%; IR: cm^{-1} 3378, 3209(3NH); ^1H NMR: δ 09.74 (s,1H, NH), 7.49–7.10 (br,5H, arom + NH), 6.65 (s,1H, CH), 06.12 (s,1H, NH); MS *m/z* (%): M^+ 235/233 (22.1), 198 (88.6), 167 (100), 123 (33.3), 96 (56.7); Anal.Calc. For $C_{10}H_8ClN_5$ (233.66): C(51.40%) H(3.45%) Cl(15.17) N(29.97%). Found: C(51.44%) H(3.28%) Cl(15.01) N(29.16%).

*2.2.1.3. N-[(2Z)-4-methyl-1,5-dihydro-2H-imidazol-2-ylidene]-1,3-benzimidazol-2-amine (**4**).* Mp 340 °C, yield 80%; IR: cm^{-1} 3322, 3188 (3NH); ^1H NMR: δ 10.23 (s,1H, NH), 7.49–7.10 (br,5H, arom + NH), 6.71 (s,1H, CH), 06.10 (s,1H, NH), 2.48 (s,3H, CH_3); MS *m/z* (%): M^+ 213 (23.4), 199 (29.9), 106 (80.6), 67 (100); Anal.Calc. For $C_{11}H_{11}N_5$ (213.24): C(61.96%) H(5.20%) N(32.84%). Found: C(61.56%) H(5.00%) N(32.23%).

*2.2.1.4. (2Z)-2-(1H-benzimidazol-2-ylimino)-2,3-dihydro-1H-imidazol-4-ol (**5**).* Mp 305 °C, yield 79%; IR: cm^{-1} 3458 (OH), 3288, 3176 (2NH); ^1H NMR: δ 11.14 (s,1H, OH), 10.07 (s,1H, NH), 7.51–7.05 (br,5H, arom + NH), 6.60 (s,1H, CH), 06.17 (s,1H, NH),; MS *m/z* (%): M^+ 215 (54.1), 198 (61.4), 175 (50.5), 163 (62.6), 82 (100); Anal.Calc. For $C_{10}H_9N_5O$ (215.21): C(55.81%) H(4.22%) N(32.54%). Found: C(55.88%) H(4.01%) N(32.03%).

*2.2.1.5. N-[(2Z)-4-amino-1,5-dihydro-2H-imidazol-2-ylidene]-1,3-benzimidazol-2-amine (**6**).* Mp 285 °C, yield 85%; IR: cm^{-1} 3381, 3233, 3177 (3NH,NH_2); ^1H NMR: δ 09.82 (s,1H, NH), 7.77–7.10 (br,5H, arom + NH), 06.16 (s,1H, NH), 5.64 (s,1H, CH), 4.77 (s,2H,

Table 2
Anti-bacterial evaluation results of 3,4-dihydrobenzo [4,5]imidazo [1,2-a] [1,3,5] triazins derivatives **8**–**13**.

Types of Bacteria	Compound **8**			Compound **9**			Compound **10**		
	Concentrations			Concentrations			Concentrations		
	10000 ppm	30000 ppm	50000 ppm	10000 ppm	30000 ppm	50000 ppm	10000 ppm	30000 ppm	50000 ppm
Bacillus cereus	–	0.5 cm	0.9 cm	–	0.4 cm	0.9 cm	0.6 cm	0.8 cm	1.1 cm
Bacillus subtilis	0.9 cm	1.2 cm	1.5 cm	0.7 cm	1.1 cm	1.3 cm	0.9 cm	1.3 cm	1.6 cm
Escherichia coli	1.2 cm	1.7 cm	2.0 cm	1.2 cm	1.5 cm	1.8 cm	–	0.5 cm	0.8 cm
Micrococcus luteus	0.7 cm	0.7 cm	1.2 cm	0.7 cm	0.7 cm	1.2 cm	–	0.3 cm	0.7 cm
Staphylococcus aureus	–	0.4 cm	0.6 cm	–	–	0.5 cm	0.3 cm	0.5 cm	0.8 cm
Pseudomonas aeruginosa	–	–	0.5 cm	–	0.4 cm	0.5 cm	0.5 cm	0.8 cm	1.1 cm
Micrococcus roseus	–	0.3 cm	0.8 cm	–	–	0.5 cm	0.4	0.7 cm	1.0 cm
Types of Bacteria	Compound **11**			Compound **12**			Compound **13**		
	Concentrations			Concentrations			Concentrations		
	10000 ppm	30000 ppm	50000 ppm	10000 ppm	30000 ppm	50000 ppm	10000 ppm	30000 ppm	50000 ppm
Bacillus cereus	–	–	0.4 cm	0.1 cm	0.4 cm	0.7 cm	–	–	0.4 cm
Bacillus subtilis	–	0.3 cm	0.9 cm	0.6 cm	1.0 cm	1.4 cm	0.3 cm	0.5 cm	0.6 cm
Escherichia coli	0.8 cm	1.3 cm	1.6 cm	0.8 cm	1.1 cm	1.5 cm	0.4 cm	0.9 cm	1.2 cm
Micrococcus luteus	0.5 cm	0.9 cm	1.1 cm	–	0.4 cm	0.6 cm	–	–	–
Staphylococcus aureus	–	–	0.4 cm	–	0.5 cm	0.8 cm	–	0.3 cm	0.8 cm
Pseudomonas aeruginosa	–	0.4 cm	0.6 cm	0.2 cm	0.6 cm	0.9 cm	–	–	–
Micrococcus roseus	–	0.3 cm	0.8 cm	0.1 cm	0.4 cm	0.7 cm	–	0.2 cm	0.5 cm

NH_2); MS *m/z* (%): M^+ 214 (44.1), 198 (52.2), 167 (60.3), 105 (33.2), 67 (100); Anal.Calc. For $C_{10}H_{10}N_6$ (214.23): C(56.07%) H(4.71%) N(39.23%). Found: C(56.14%) H(4.08%) N(39.01%).

*2.2.1.6. (2Z)-4-Amino-2-(1,3-benzimidazol-2-ylimino)-2,5-dihydro-1H-imidazole-5-carbonitrile (**7**).* Mp 330 °C, yield 73%; IR: cm^{-1} 3381, 3288, 3176 (2NH,NH_2), 2222(CN); ^1H NMR: δ 10.05 (s,1H, NH), 7.75–7.04 (br,5H, arom + NH), 06.19 (s,1H, NH), 5.23 (s,2H, NH_2); MS *m/z* (%): M^+ 240 (42.1), 198 (82.0), 172 (100), 148 (66.2), 105 (77.6); Anal.Calc. For $C_{11}H_{10}N_7$ (240.25): C(55.22%) H(3.79%) N(40.98%). Found: C(55.02%) H(3.59%) N(40.57%).

2.2.2. General procedure. 8–13

A mixture of compound **1** (50 mmol) and (50 mmol) cyclopentanone, cyclohexanon, thiazolidione, pyrazolone, barbituric acid and camphor in ethanol and presence of a few drops of hydrochloric acid as a catalyst was refluxed, solid products were observed after 5 h. After cooling down, the solid crystalline products were filtered, washed and recrystalised from ethanol.

*2.2.2.1. Cyclopentane – 3,4-dihydrobenzo [4,5]imidazo[1,2-a][1,3,5] triazin-2-amine **8**.* Yield 81%, mp = 310 °C; IR: cm^{-1} 3381, 3277, 3177 (NH_2,NH); ^1H NMR: δ 09.87 (s,1H, NH), 7.58–7.12 (m,4H, arom), 4.77 (br,2H, NH_2), 2.08 (s,4H, $2CH_2$), 1.90 (s,4H, $2CH_2$); ^{13}C NMR: δ 23.09, 36.74, 68.03, 110.63, 116.46, 122.68, 123.43,129.33, 141.30, 159.63, 160.44; MS *m/z* (%): M^+ 241 (38.1), 225 (66.5), 196 (34.2), 118 (88.1), 76 (100); Anal.Calc. For $C_{13}H_{15}N_5$ (241.30): C(64.71%) H(6.27%) N(29.02%). Found: C(64.44%) H(6.02%) N(28.94%).

*2.2.2.2. Cyclohexane – 3,4-dihydrobenzo [4,5]imidazo[1,2-a][1,3,5] triazin-2-amine **9**.* Yield 82%, mp = 285 °C; IR: cm^{-1} 3384, 3269, 3177 (NH_2,NH); ^1H NMR: δ 10.02 (s,1H, NH), 7.58–7.11 (m,4H, arom), 4.81 (br,2H, NH_2), 1.77–1.48 (m,10H, $5CH_2$); ^{13}C NMR: δ 21.91, 25.58, 36.04, 64.98, 110.55, 116.46, 122.68, 123.43, 129.01, 141.14, 159.68, 160.54; MS *m/z* (%): M^+ 255 (24.4), 239 (55.4), 167 (81. 1), 77 (100); Anal.Calc. For $C_{14}H_{17}N_5$ (255.32): C(65.86%) H(6.71%) N(27.43%). Found: C(65.20%) H(6.47%) N(27.05%).

*2.2.2.3. Thiazolidin-4-one – 3,4-dihydrobenzo [4,5]imidazo[1,2-a] [1,3,5]triazin-2-amine **10**.* Yield 79%, mp 265 °C; IR: cm^{-1} 3381, 3261, 3177 (NH_2,2NH), 1688 (CO); ^1H NMR: δ 10.15 (s,1H, NH), 7.60–7.10 (m,4H, arom), 6.83 (s,1H, NH), 4.80 (br,2H, NH_2), 3.98 (s,2H, CH_2); ^{13}C NMR: δ 32.12, 83.44, 106.40, 117.81, 123.60, 125.62, 141.45, 163.22, 169.83, 174.12; MS *m/z* (%): M^+ 274(25.4), 258 (39.1), 198 (88.7), 105 (100); Anal.Calc. For $C_{11}H_{10}N_6OS$ (274.30): C(48.17%) H(3.67%) N(30.64%) S(11.69%). Found: C(48.07%) H(3.32%) N(30.18%) S(11.48%).

*2.2.2.4. 3-Methyl-1-phenyl-1H-pyrazole – 3,4-dihydrobenzo [4,5] imidazo[1,2-a][1,3,5]triazin-2-amine **11**.* Yield 74%, mp = 282 °C; IR: cm^{-1} 3384, 3270, 3177 (NH_2,NH); ^1H NMR: δ 10.08 (s,1H, NH), 7.58–7.01 (m,9H, 2 arom), 4.61 (br,2H, NH_2), 3.17 (s,2H, CH_2), 2.24 (s,3H, $2CH_3$); ^{13}C NMR: δ 16.43, 38.17, 86.46, 108.78, 116.24, 122.74, 122.50, 124.19, 124.78, 126.19, 126.80, 139.18, 142.80, 155.29, 155.93, 157.44; MS *m/z* (%): M^+ 331 (22.8), 316 (60. 2), 204 (44.5), 119 (58.6), 77 (100); Anal.Calc. For $C_{18}H_{17}N_7$ (331.38): C(65.24%) H(5.17%) N(29.59%). Found: C(65.09%) H(5.01%) N(29.18%).

*2.2.2.5. Barbaturic acid – 3,4-dihydrobenzo [4,5]imidazo[1,2-a] [1,3,5]triazin-2-amine **12**.* Yield 88%, mp 340 °C; IR: cm^{-1} 3387, 3264, 3175 (NH_2,3NH), 1688 (CO), 1679 (CO); ^1H NMR: δ 10.24 (s,1H, NH), 9.68 (s,2H, 2NH), 7.58–7.07 (m,4H, arom), 5.26 (br,2H, NH_2), 3.24 (s,2H, CH_2); ^{13}C NMR: δ 53.50, 61.89, 104.00, 116.13, 122.23, 123.24, 124.20, 140.83, 157.95, 161.81, 170.33; MS *m/z* (%): M^+ 285 (27.47), 261 (31.1), 242 (100), 185(20.2), 77 (35.1); Anal.Calc. For $C_{12}H_{11}N_7O_2$(285.26):C(50.53%) H(3.89%) N(34.37%). Found: C(50.22%) H(3.77%) N(34.13%).

*2.2.2.6. Camphor – 3,4-dihydrobenzo [4,5]imidazo[1,2-a][1,3,5]triazin-2-amine **13**.* Yield 71%, mp = 360 °C; IR: cm^{-1} 3374, 3235, 3167 (NH, NH_2); ^{13}C NMR: δ 9.02, 22.77, 26.55, 30.18, 32.36, 35.27, 36.34, 53.39, 80.45, 109.87, 116.36, 122.84, 123.45, 128.80, 140.77, 158.17, 161.98; MS *m/z* (%): M^+ 309 (28.55), 288 (67.24), 167 (56.9), 76 (100); Anal.Calc. For $C_{19}H_{23}N_5O$ (309.41): C(67.63%) H(6.87%) N(20.76%). Found: C(67.35%) H(6.32%) N(20.01%).

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