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Synthesis of Novel Fused Pyrimidines and Imidazoles as Potential Analgesics from 2-Amino-4-substituted-*s*-triazino[1,2-a]-benzimidazoles

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ABSTRACT

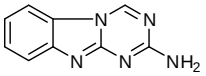
The synthesis of novel fused pyrimidines and imidazole derivatives from 2-amino-*s*-triazino[1,2-a]benzimidazoles **2a-e** and **3a-c** was successfully carried out by a ring annelation reaction in a very good yield. Compound **3c** was screened for analgesic activity against acetic acid irritation and has shown protection equal to the reference drug (diclofenac sodium). The acute toxicity study revealed that compound **3c** is safe up to 300 mg/kg and there is no sign and symptoms of toxicity and mortality for 72 hours.

Key words: 2-Guanidinobenzimidazoles, cyclocondensation, fused pyrimidines, fused imidazoles, analgesic activity.

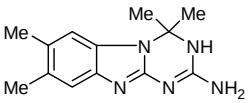
INTRODUCTION

Azole class of drugs, particularly fused imidazole occupy a prominent place in medicinal chemistry because of their broad spectrum of pharmacological activities such as anti-inflammatory, analgesic, anticancer, antiulcer, antimicrobial, antiviral, pesticidal and anti-arrhythmic activities[1-4]. Omeprazole, mebendazole and abendazole are well known drugs in the market which contain fused imidazole as active core moiety.

1,3,5-Triazine (*s*-triazines) derivatives, which synthesized via heterocyclic-zation of bigunaidines or their analogues using ²-keto ester[5] such as Tretamines, Furazil and Dioxadet, have been known as anticancer drugs[6]. Moreover, an anti-gastric ulcer agent that is commonly used in Japan, irsogladine (2-amino-1,3,5-triazine), was shown to possess antiangiogenic properties which result in the anticancer effect of the drug[7]. It was reported[8] that compounds having the core structure of s-triazino[1,2-a]benzimidazole**(A)** with particular reference to 2-amino-4,4,7,8-tetramethyl-3,4-dihydro-*s*-triazino[1,2-a]benzimid-azole **(B)**, have demons-trated inhibitory activity against the plasmodial DHER.



A



B

Pyrimidines and fused pyrimidines, being an integral part of DNA and RNA, play an essential role in several biological processes. They also have considerable chemical and pharmacological importance, particularly, as nucleoside antibiotics, antibacterial, cardiovascular as well agrochemical and veterinary products[9]. Various pyrimidine derivatives showed analgesic, antiarrhythmic and anticancer activities[10], as well anti-inflammatory, antiparkinsonian and androgenic anabolic activities[11].

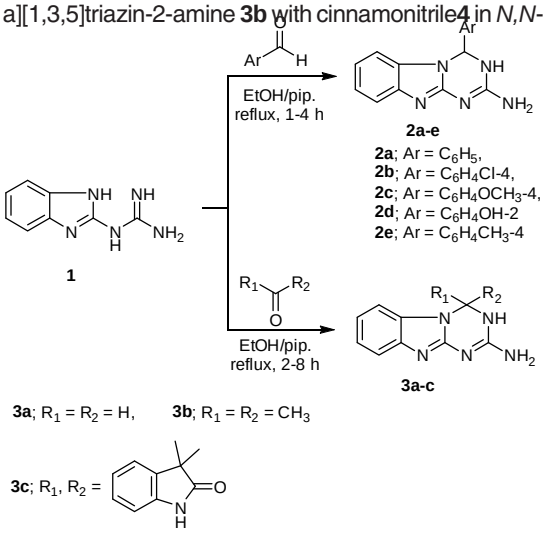
Encouraged by the above observations and in continuation of our work for the syntheses of biologically active heterocyclic lead compounds[2,3,12,13], a new series of fused pyrimidines**(8, 13, 15a-f, 19a-d)** and fused imidazoles**(20a,b)** were synthesized with a view to explore the possibility of achieving a new class of heterocylic compounds possessing potent analgesic activity.

RESULTS AND DISCUSSION

Chemistry

The reaction sequence used to synthesize the target compounds is illustrated in Schemes 1-6. The key intermediate, 2-guanidino-benzimidazole **(1)** was prepared by cyclocondensation of *o*-phenylenediamine with dicyandiamide in acidic medium[14] under reflux temperature. The synthesis of 3,4-dihydro[1,3,5]triazino[1,2-a]-benzimidazole-2-amines through a base catalyzed cyclization of 2-guanidinobenz-imidazole **(1)** with benzaldehyde was first reported by Nagarajan*et al* in 1970[15]. Using a variety of aromatic aldehydes and ketones in the presence of piperidine as a catalyst, we have prepared 4-aryl-3,4-dihydro[1,3,5]triazino[1,2-a]benzimidazole-2-amines **2a-e & 3a-c** (Scheme 1); as a starting material in our study to capitalize on the biological potential of these new heterocyclic systems.

It has been found that, the treatment of 4,4-dimethyl-3,4-dihydrobenzo[4,5]-imidazo[1,2-a][1,3,5]triazin-2-amine **3b** with cinnamonitrile**4** in *N,N*-

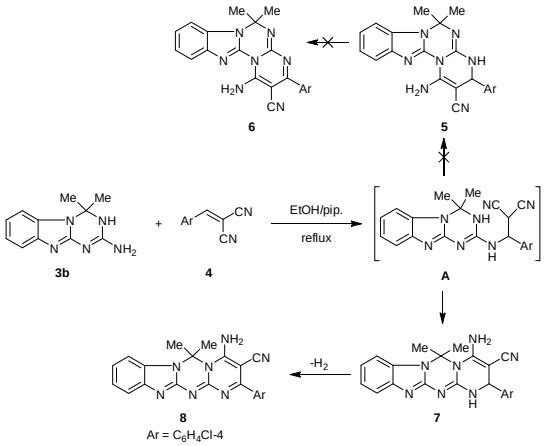


Scheme 1

dimethylf-ormamide at reflux temperature in the presence of trimethylamine as a catalyst gave the novel 4-amino-2-(4-chlorophenyl)-6,6-dimethyl-6H-benzo[4,5]imidazo[1,2-a]-pyrimido-[2,1-d][1,3,5]triazine-3-carbonitrile **8** (Scheme 2). The two other possible structures **5&6** were excluded upon the elemental analyses and spectral data. The infrared and the ^{1}HNMR spectra were in complete agreement with the structure of compound **8**. The infrared spectra of compound **8** showed the presence of the NH_2 group at 3380, 3146 cm^{-1} and Ca"N at 2210 cm^{-1}. The ^{1}H NMR spectrum (DMSO-d_6) revealed a singlet at 1.96 ppm due to two methyl groups and a singlet at 6.49 ppm which was assigned to the NH_2 protons, in addition to the presence of aromatic protons 7.23-7.64 ppm. The reaction occurs *via* an initial formation of the *Michael* adduct **A** from the Michael addition of amino exocyclic in 2-aminotriazinobenz-imidazole derivative **3b** to the activated double bond in compounds**4**. The

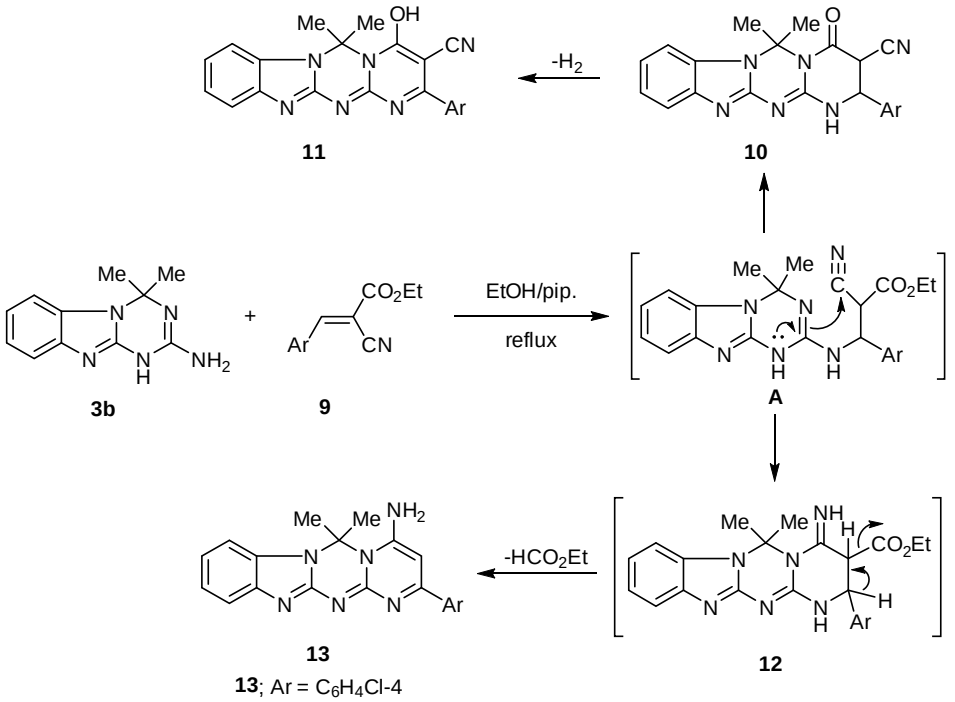
latter adduct undergo cyclization to give the non-isolable intermediate **7** followed by aromatization *via* loss of H_2 molecule **[16]** to give compounds **8**.

As an extension of such synthetic route, the behavior of **3b** toward ethyl α-cyanocinnamate**9** was also investigated. The reaction of compound **3b** with ethyl α-cyanocinnamate**9** in refluxing *N,N*-dimethylformamide in the presence of trimethyl-amine as a catalyst gave the corresponding 2-(4-chlorophenyl)-6,6-dimethyl-6H-benzo[4,5]-imidazo[1,2-a]pyrimido[2,1-d][1,3,5]triazin-4-amine **13** rather than the compound **11** (Scheme 3). Evidence for the structure of compounds **13** included the infrared spectra which revealed absorption bands for the NH_2 and C=O groups and the absence of the absorption band of carbonitrile group. The infrared spectrum of compound **13** displayed the absorption bands for NH_2 at 3350, 3170 cm^{-1}, aliphatic-CH at 2970 cm^{-1}, C=O at 1666 cm^{-1}, C=N at 1615 cm^{-1}. The ^{1}HNMR spectra of the reaction product displayed the absence of the lack of signals characteristic for ethyl protons. The ^{1}HNMR spectrum (DMSO-d_6) of this revealed a singlet at 1.84 ppm assigned for two geminal methyl protons, a singlet at 5.84 assigned for methine-H, a singlet at 7.95 ppm assigned for amino group, in addition to the presence of aromatic protons at 6.76-7.61 ppm in the spectrum.



Scheme 2

The treatment of compounds **2a-d, 3a-c** with ethyl cyanoacetate in *N,N*-dimethylformamide at reflux temperature gave the novel 4-amino-benzo[4,5]-imidazo[1,2-a]pyrimido[2,1-d][1,3,5]triazin-2(1H)-ones **15a-f** (Scheme 4). Theoretically, the cyclization reaction of 2-amino-4-aryl-3,4-dihydro[1,3,5]triazino-



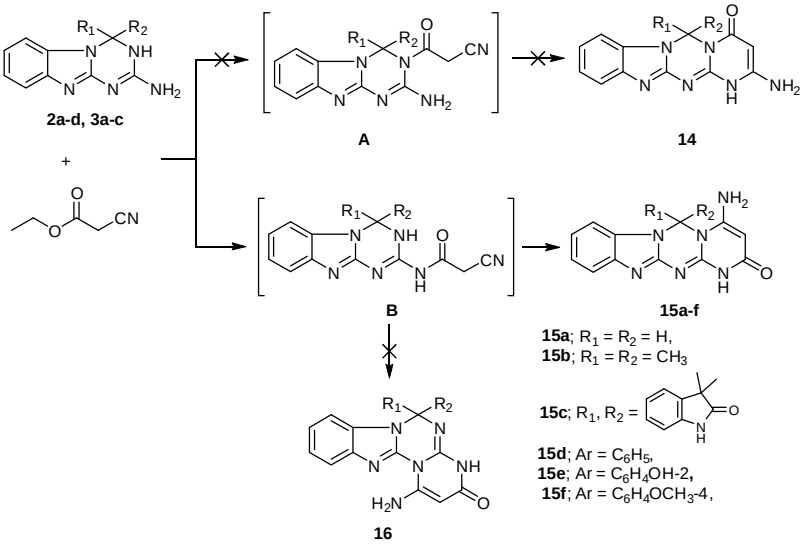
Scheme 3

[1,2-a]benzimidazoles**2a-d, 3a-d** with ethyl cyano acetate may proceed in several ways. The most probable approaches include:

1) The initial attack of endocyclic N-3 of 2-amino-4-aryl-3,4-dihydro[1,3,5]triazino-[1,2-a]benzimidazoles **2a-d,3a-c** with ethyl cyanoacetate followed by intramolecular cyclization of the presumable intermediate **A** with formation of the heterocyclic system **14**.
2) The initial attack of exocyclic amino group nitrogen of 2-amino-4-aryl-3,4-dihydro[1,3,5] triazino [1,2-a]benzimidazoles**2a-d, 3a-c** with ethyl cyanoacetate followed by ring closure of the presumable intermediate **B** to *N*-3 or *N*-1 with formation of the heterocyclic system **15** or **16**, respectively.

The structures of compounds **15a-f** were elucidated by the elemental analyses and spectral data. For example, the infrared spectrum of compounds **15a-f** exhibited the absorption bands of NH_2, NH between 3400-3110 cm^{-1}, carbonyl group from 1690-1658 cm^{-1}. The ^{1}HNMR spectrum (DMSO-d_6) of compound **15a** revealed a singlet at 5.49 ppm assigned for $N(CH_2)$, 5.90 ppm for pyrimidine-H, 6.03 ppm for NH_2, a singlet at 7.62 assigned for NH, in addition to the presence of aromatic protons at 7.13-7.45 ppm. Also, the ^{1}HNMR spectrum of compound **15b** displayed a singlet at 1.90 ppm assigned for two germinal methyl protons, a singlet at 8.69 ppm assigned ofNH, in addition to the presence of aromatic protons at 7.09-7.72 ppm.

Also, the reaction of **2c-e, 3a,b** with ethyl acetoacetate led to the formation of condensation product which may be formulated as 4-methyl-6-aryl-6H-benzo[4,5]-imidazo[1,2-a]pyrimido[2,1-d][1,3,5]triazin-2(1H)-ones **19a-d** (Scheme 5). The other possible structure **18** was excluded according to previously reported data[17]. The elemental and spectral analysis of the isolated products was

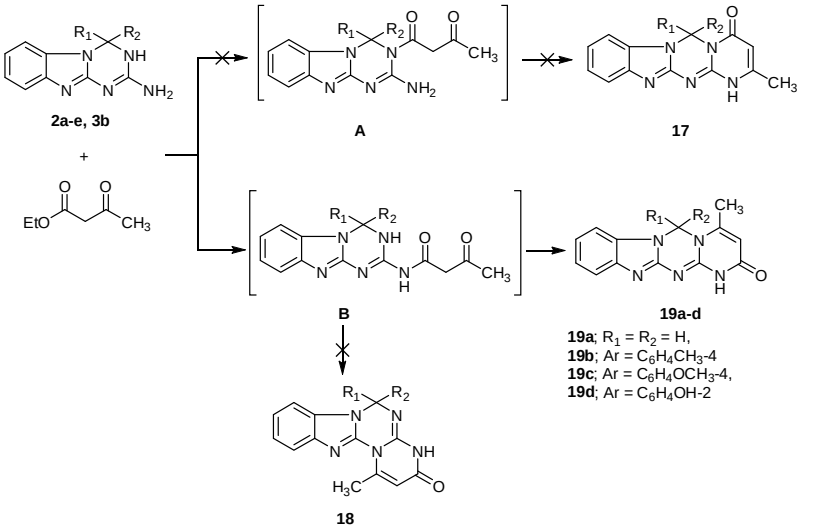


Scheme 4

consistent with both structures **19a-d** (cf. Experimental). The ir spectrum of compound **19b** exhibited absorption bands at 3130 for NH, 2971 cm^{-1} for aliphatic-CH, 1689 cm^{-1} for carbonyl group. The ^{1}HNMR spectrum (DMSO-d_6) of compound **19b** two singlets at 2.13, 2.38 ppm assigned for two methyl protons, two singlets at 5.52, 5.67 ppm assigned for pyrimdine-H, and triazine-H, respectively, a singlet at 7.87 assigned for NH, in addition to the presence of aromatic protons at 6.98-7.45 ppm in the spectrum. ^{13}CNMR spectrum (DMSO-d_6) of compound **19b** displayed signal at 165.12 ppm assigned for carbonyl group, 159.31, 157.02, 150.38 ppm for C=N groups, 64.91 ppm assigned for triazine-C, and 20.63, 14.08 ppm assigned for 2 methyl carbon's, in addition to aromatic carbons at 148.84-109.73 ppm.

Finally, the cyclocondensation of 2-amino-4-aryl-3,4-dihydro[1,3,5]triazino-[1,2-a]benzimidazoles with benzoin gave 2,3-diphenyl-3H,5H-

benzo[4,5]imidazo-[1,2-a]imidazo[2,1-d][1,3,5]triazines **20a,b** andthe other possible structure 5-aryl-1,2-diphenyl-1,5-dihydrobenzo[4,5]imidazo[1,2-a]-imidazo[1,2-c][1,3,5]triazines **21a,b** was excluded according to previously reported data[17] (Scheme 6). The infrared spectrum of compound **20a**

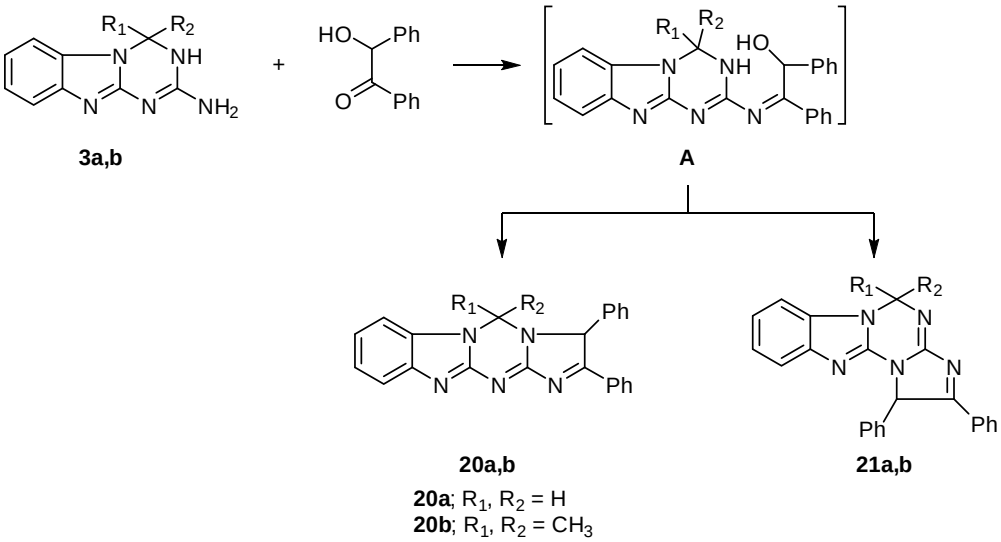


Scheme 5

exhibited absorption bands at 2971 cm^{-1} for aliphatic-CH, 1610 cm^{-1} for C=N. the ^{1}HNMR spectrum (DMSO-d_6) of compound **20b** displayed a singlet at 1.92 ppm assigned for two geminal methyl protons, a singlet at 5.38 ppm assigned for imidazole-H, in addition to the presence of aromatic protons at 6.87-7.78 ppm.

Pharmacology

A preliminary pharmacological screening of compound **3c** for analgesic activity was carried out adopting acetic acid induced writhing test[18]. The results were expressed as mean ± SEM and statistical comparisons were made by conducting one way ANOVA ($p<0.05$) (table 1).



Scheme 6

The results from table 1 indicate that compound **3c** either in oral dose 20mg/kg or oral dose 40mg/kg and the reference drug (diclofenac sodium) in oral 20mg/kg give a significant reduction in the number of writhes compared to the control which administered in oral dose 10 ml/kg in 2% aqueous gum acacia. Also, from table 1 the results of percentage inhibition indicate that there is no significance difference between the treated groups (71.28% inhibition of compound **3c** in comparison to 72.70% of diclofenac sodium). These results are in accordance to the reported data[19,20] that acetic acid induces pain sensation through prostaglandin (PG) biosynthesis and hence the writhing response is associated with increased level of PGE_2 and $PGE_{2\pm}$.

On the light of the above data we can surmise that compound **3c** produce its analgesic effect by the interference with prostaglandin synthesis.

The acute toxicity study of compound **3c** was performed on the basis of OECD/OCDE

Table 1: Effect of synthesized drug on acetic acid induced writhing in mice

Group	Dose	Number of writhing (Mean ±SEM)	Percent inhibition
Group-I	Control (10 ml/kg 2% aqueous gum)	28.20 ± 6.20	-
Group-II	positive control (diclofenac sodium 20 mg/kg, oral)	7.70 ± 2.10 *↓	72.70
Group-III	Synthesized compound (20 mg/kg, oral)	11.60 ± 4.34 *↓	58.87
Group-IV	Synthesized compound (40 mg/kg, oral)	8.10 ± 2.61 *↓	71.28

One way ANOVA ($P < 0.05$)*↓ Significant reduction

Table 2(a): The acute oral toxicity for the control Group: 2% Aqueous gum solution

No.	Wt. (g)	Physiological alterations (hours) Grooming			Hyperactivity			Sedation			Resp. Arrest			Convulsions			Increased M.A			Decreased M.A			Death (hours)
		1 hr	24 hrs	72 hrs	1 hr	24 hrs	72 hrs	1 hr	24 hrs	72 hrs	1 hr	24 hrs	72 hrs	1 hr	24 hrs	72 hrs	1 hr	24 hrs	72 hrs	1 hr	24 hrs	72 hrs	
1	29g	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2	31g	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3	29g	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 2(b): The acute oral toxicity for the group administered the synthesized compound (300mg\kg)

No.	Wt. (g)	Physiological alterations (hours) Grooming			Hyperactivity			Sedation			Resp. Arrest			Convulsions			In
		1 hr	24 hrs	72 hrs	1 hr	24 hrs	72 hrs	1 hr	24 hrs	72 hrs	1 hr	24 hrs	72 hrs	1 hr	24 hrs	72 hrs	1 hr
1	27g	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2	29g	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3	28g	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

The results of table 2 (A & B) reveals that there is no toxicity observed for the compound **3d** at the dose level of 300 mg/kg up to 72 hours. So, LD_{50} of compound 3d will be more than 300mg/kg body weight

guidelines No: 423[21] in a dose level of 300 mg/kg body weight, and the behavioral and physiological effects[22] were recorded.

EXPERIMENTAL

All melting points are uncorrected. IR spectra (KBr) were measured on Shimadzu 440 spectrometer, ^{1}HNMR and ^{13}CNMR spectra were obtained in DMSO-$d_6$on a Varian Gemini 600 MHz spectrometer using TMS as internal standard; chemical shifts are reported as (ppm). Elemental analyses were carried out at the Department of Chemistry, Faculty of Science, King Abdul-Aziz University, Jeddah 21589, KSA. Antimicrobial screening was carried out in Microbiology Department, Faculty of Pharmacy, Northern Border University, Rafhaa, KSA. Compounds **2a-e**, **3a-c** were prepared according to reported procedure[23]. *2-Amino-3H-spiro[benzo[4,5]-imidazo[1,2-a][1,3,5]triazine-4,3'-indolin]-2'-one* ***3c;*** yield (81%); m.p: 310-312ºC; ir (potassium bromide, cm^{-1}): 3384, 3272, 3180 (NH_2/NH), 1670 (C=O), 1615 (C=N); ^{1}H-NMR (600 MHz, DMSO-d_6): ´ 6.78 (s, 2H, NH_2), 7.08-7.63 (m, 8H, Ar-H), 8.31, 11.66 (2s, 2H, 2NH); Anal. Calcd. for $C_{16}H_{12}N_6O$: C, 63.15; H, 3.97; N, 27.62. Found: C, 63.03; H, 3.86; N, 27.45.

4-Amino-2-(4-chlorophenyl)-6,6-dimethyl-6H-benzo[4,5]imidazo[1,2-a]pyrimido-[2,1-d][1,3,5]triazine-3-carbonitrile 8.

A solution of **3b** (0.01 mole), 2-(4-chlorobenzylidene)malononitrile (0.01 mole) and triethylamine (0.5 mL) in *N,N*-dimethylformamide (30 ml) was refluxed for 4 hours. The precipitated solid was filtered on hot and recrystallized from dioxane to give compound **8** as yellow crystals, yield (70%); m.p: 300-302ºC; ir (potassium bromide, cm^{-1}): 3380, 3146 (NH_2), 2970 (CH-aliph.), 2210 (C≡N), 1580 (C=N); ^{1}H-NMR (600 MHz, DMSO-d_6): δ 1.96 (s, 6H, 2 CH_3), 7.97 (s, 2H, NH_2), 7.23-7.64 (m, 8H, Ar-H); Anal. Calcd. for $C_{21}H_{16}ClN_7$: C, 62.77; H, 4.01; N, 24.40. Found: C, 62.62; H, 3.92; N, 24.32.

2-(4-chlorophenyl)-6,6-dimethyl-6H-benzo[4,5]-imidazo[1,2-a]pyrimido[2,1-d]-[1,3,5]triazin-4-amine13.

A solution of **3b** (0.01 mole), 2-(4-chlorobenzylidene)malononitrile (0.01 mole) and triethylamine (0.5 mL) in *N,N*-dimethylformamide (30 ml) was refluxed for 6 hours. The solid that obtained on cooling was collected by filtration and recrystallized from acetic acid to give compound **13** as yellow crystals, yield (66%); m.p: 297-299ºC; ir (potassium bromide, cm^{-1}): 3350, 3170 (NH_2), 2970 (CH-aliph.), 1666 (C=O), 1615 (C=N); ^{1}H-NMR (600 MHz, DMSO-d_6): δ 1.84 (s, 6H, 2 CH_3), 5.84 (s, 1H, CH), 6.76-7.61 (m, 8H, Ar-H), 7.95 (s, 2H, NH_2); Anal. Calcd. for $C_{20}H_{17}ClN_6$: C, 63.74; H, 4.55; N, 22.30. Found: C, 63.62; H, 4.42; N, 22.20.

Synthesis of Benzo[4,5]imidazo[1,2-a]pyrimido [2,1-d] [1,3,5]triazin-2(1H)-ones15a-f

General *procedure:* A solution of **2a-d and/ or 3a-c** (0.01 mole), ethyl cyanoacetate (0.01 mole) in *N,N*-dimethylformamide (30 ml) was refluxed for 8 hours. The solid that obtained on cooling was collected by filtration and recrystallized from proper solvent to give compounds **15a-f.**

4-Amino-6H-benzo[4,5]imidazo[1,2-a]pyrimido [2,1-d] [1,3,5]triazin-2(1H)-one 15a.

Yield (72%); acetic acid (yellow crystals); m.p: 308-310ºC; ir (potassium bromide, cm^{-1}): 3310, 3130 (NH_2), 2876 (CH-aliph.), 1668 (C=O), 1619 (C=N); ^{1}H-NMR (600 MHz, DMSO-d_6): δ 5.49 (s, 2H, N(CH_2)), 5.90 (s, 1H, CH), 6.03 (s, 2H, NH_2), 7.13-7.45 (m, 4H, Ar-H), 7.62 (s, 1H, NH); Anal. Calcd. for $C_{12}H_{10}N_6O$: C, 56.69; H, 3.96; N, 33.05. Found: C, 56.57; H, 4.01; N, 32.92.

4-Amino-6,6-dimethyl-6H-benzo[4,5]imidazo[1,2-a]pyrimido[2,1-d][1,3,5]triazin-2(1H)-one 15b

Yield (78%); DMF (faint yellow crystals); m.p: 312-314ºC; ir (potassium bromide, cm^{-1}): 3350, 3170 (NH_2), 2970 (CH-aliph.), 1670 (C=O), 1615 (C=N); ^{1}H-NMR (600 MHz, DMSO-d_6): δ 1.90 (s, 6H, 2CH_3), 6.47 (s, 1H, CH), 7.09-7.72 (m, 6H, Ar-H + NH_2), 8.69 (s, 1H, NH), Anal. Calcd. for $C_{14}H_{14}N_6O$: C, 59.56; H, 5.00; N, 29.77. Found: C, 59.44; H, 4.88; N, 29.63.

4-Aminospiro[benzo[4,5]imidazo[1,2-a]pyrimido [2,1-d][1,3,5]triazine-6,3'-indo-line]-2,2'(1H)-dione15c

Yield (71%); dioxane (brown crystals); m.p: 300-301ºC; ir (potassium bromide, cm^{-1}): 3420, 3244, 3150 (NH_2/NH), 2970 (CH-aliph.), 1690, 1669 (C=O), 1608 (C=N); ^{1}H-NMR (600 MHz, DMSO-d_6): δ 6.48 (s, 1H, CH), 7.95 (s, 2H, NH_2), 6.94-7.96 (m, 8H, Ar-H), 8.65 (s, 1H, NH), 10.09 (s, 1H, NH), 12.48 (s, 1H, NH); Anal. Calcd. for $C_{19}H_{13}N_7O_2$: C, 61.45; H, 3.53;

N, 26.40. Found: C, 61.50; H, 3.47; N, 26.29.

4-Amino-6-phenyl-6H-benzo[4,5]imidazo[1,2-a]pyrimido[2,1-d][1,3,5]triazin-2(1H)-one15d

Yield (68%); acetic acid (white crystals); m.p: 286-288ºC; ir (potassium bromide, cm^{-1}): 3415, 3230 (NH_2), 2986 (CH-aliph.), 1658 (C=O), 1620 (C=N); ^{1}H-NMR (600 MHz, DMSO-d_6): δ 5.98 (s, 1H, CH), 6.41 (s, 1H, CH), 7.21-7.48 (m, 9H, Ar-H), 7.96 (s, 2H, NH_2), 12.51 (hump, 1H, NH); Anal. Calcd. for $C_{18}H_{14}N_6O$: C, 65.44; H, 4.27; N, 25.44. Found: C, 65.34; H, 4.20; N, 25.31.

4-Amino-6-(2-hydroxyphenyl)-6H-benzo[4,5] imidazo[1,2-a]pyrimido[2,1-d][1,3,5]-triazin-2(1H)-one 15e

Yield (65%); DMF (brown crystals); m.p: 302-304ºC; ir (potassium bromide, cm^{-1}): 3328, 3220 (NH_2), 2970 (CH-aliph.), 1670 (C=O), 1622 (C=N); ^{1}H-NMR (600 MHz, DMSO-d_6): δ 5.88 (s, 1H, CH), 6.23 (s, 1H, CH), 7.14-7.52 (m, 8H, Ar-H), 7.86 (s, 2H, NH_2), 12.66 (hump, 2H, NH, OH); Anal. Calcd. for $C_{18}H_{14}N_6O_2$: C, 62.42; H, 4.07; N, 24.27. Found: C, 62.28; H, 4.00; N, 24.18.

4-Amino-6-(4-methoxyphenyl)-6H-benzo[4,5] imidazo[1,2-a]pyrimido[2,1-d][1,3,5]-triazin-2(1H)-one 15f

Yield (69%); dioxane (white crystals); m.p: 305-306ºC; ir (potassium bromide, cm^{-1}): 3415, 3178 (NH_2), 2970 (CH-aliph.), 1671 (C=O), 1620 (C=N); ^{1}H-NMR (600 MHz, DMSO-d_6): δ 3.74 (s, 3H, OCH_3), 6.08 (s, 1H, CH), 6.47 (s, 1H, CH), 6.63-7.35 (m, 10H, Ar-H+NH_2), 8.22 (s, 1H, NH); Anal. Calcd. for $C_{19}H_{16}N_6O_2$: C, 63.33; H, 4.48; N, 23.32. Found: C, 63.40; H, 4.33; N, 23.20.

Synthesis of Benzo[4,5]imidazo[1,2-a]pyrimido [2,1-d] [1,3,5]triazin-2(1H)-ones19a-e

General procedure: A solution of **2a-d and/ or 3a-c** (0.01 mole), ethyl acetoacetate (0.01 mole) in *N,N*-dimethylformamide (30 ml) was refluxed for 6 hours. The solid that obtained on cooling was collected by filtration and recrystallized from proper solvent to give compounds **19a-d.**

4-Methyl-6H-benzo[4,5]imidazo[1,2-a]pyrimido [2,1-d][1,3,5]triazin-2(1H)-one 19a.

Yield (64%); acetic acid (white crystals); m.p: 308-310ºC; ir (potassium bromide, cm^{-1}): 3150 (NH), 2970 (CH-aliph.), 1668 (C=O), 1636 (C=N); ^{1}H-NMR (600 MHz, DMSO-d_6): δ 2.14 (s, 3H, CH_3), 5.54 (s, 1H, CH), 5.94 (s, 2H, $N(CH_2)$), 6.03 (s, 2H, NH_2), 7.09-7.46 (m, 4H, Ar-H), 12.21 (s, 1H, NH); Anal. Calcd. for $C_{13}H_{11}N_5O$: C, 61.65; H, 4.38; N, 27.65. Found: C, 61.49; H, 4.26; N, 27.51.

4-Methyl-6-(p-tolyl)-6H-benzo[4,5]imidazo[1,2-a]pyrimido[2,1-d][1,3,5]triazin-2(1H)-one 19b

Yield (60%); DMF (yellow crystals); m.p: 305-307ºC; ir (potassium bromide, cm^{-1}): 3130 (NH), 2971 (CH-aliph.), 1689 (C=O), 1645 (C=N); ^{1}H-NMR (600 MHz, DMSO-d_6): δ 2.13 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 5.52 (s, 1H, CH), 5.67 (s, 1H, CH), 6.98-7.45 (m, 8H, Ar-H), 7.87 (s, 1H, NH); ^{13}C-NMR (600 MHz, DMSO-d_6): ´ 14.08, 20.63, 59.28, 109.73, 115.99, 120.20, 121.09, 122.22, 126.19, 126.24, 129.35, 130.95, 134.08, 136.65, 139.08, 141.88, 148.84, 150.38, 157.02, 159.31, 165.12. Anal. Calcd. for $C_{20}H_{17}N_5O$: C, 69.96; H, 4.99; N, 20.40. Found: C, 69.83; H, 5.05; N, 20.33.

6-(4-Methoxyphenyl)-4-methyl-6H-benzo[4,5] imidazo[1,2-a]pyrimido[2,1-d][1,3,5]-triazin-2(1H)-one19c

Yield (81%); DMF (yellow crystals); m.p: 298-300ºC; ir (potassium bromide, cm^{-1}): 3182 (NH), 2970 (CH-aliph.), 1657 (C=O), 1622 (C=N); ^{1}H-NMR (600 MHz, DMSO-d_6): δ 2.13 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 5.66 (s, 1H, CH), 5.67 (s, 1H, CH), 6.86-7.38 (m, 8H, Ar-H), 7.87 (s, 1H, NH); Anal. Calcd. for $C_{20}H_{17}N_5O_2$: C, 66.84; H, 4.77; N, 19.49. Found: C, 66.67; H, 4.58; N, 19.36.

6-(2-Hydroxyphenyl)-4-methyl-6H-benzo[4,5] imidazo[1,2-a]pyrimido[2,1-d][1,3,5]-triazin-2(1H)-one19d.

Yield (73%); DMF (brown crystals); m.p: 304-306ºC; ir (potassium bromide, cm^{-1}): 3423 (OH), 3210 (NH), 2974 (CH-aliph.), 1657 (C=O), 1610 (C=N); ^{1}H-NMR (600 MHz, DMSO-d_6): δ 2.19 (s, 3H, CH_3), 5.54 (s, 1H, CH), 6.13 (s, 1H, CH), 7.09-7.39 (m, 8H, Ar-H), 11.52 (s, 1H, NH), 12.43 (s, 1H, OH); Anal. Calcd. for $C_{19}H_{15}N_5O_2$: C, 66.08; H, 4.38; N, 20.28. Found: C, 66.15; H, 4.26; N, 20.12.

Synthesis of *Benzo[4,5]imidazo[1,2-a]imidazo [2,1-d] [1,3,5]triazines*20a,b

General procedure: A solution of **3a,b** (0.01 mole), 2-hydroxy-1,2-diphenylethan-1-one (0.01 mole)

in acetic acid (30 ml) was refluxed for 6 hours. The solid that obtained on cooling was collected by filtration and recrystallized from proper solvent to give compounds **20a,b.**

2,3-Diphenyl-3H,5H-benzo[4,5]imidazo[1,2-a]imidazo[2,1-d][1,3,5]triazine20a

Yield (64%); dioxane (yellow crystals); m.p: 277-278ºC; ir (potassium bromide, cm^{-1}): 3120 (NH), 2971 (CH-aliph.), 1610 (C=N); ^{1}H-NMR (600 MHz, DMSO-d_6): δ 6.22 (s, 2H, N(CH_2), 7.19-7.57 (m, 14H, Ar-H), 7.97 (s, 1H, NH); Anal. Calcd. for $C_{23}H_{17}N_5$: C, 76.01; H, 4.72; N, 19.27. Found: C, 75.85; H, 4.55; N, 19.15.

5,5-Dimethyl-2,3-diphenyl-3H,5H-benzo[4,5] imidazo[1,2-a]imidazo[2,1-d][1,3,5]-triazine 20b

Yield (67%); dioxane (yellow crystals); m.p: 281-283ºC; ir (potassium bromide, cm^{-1}): 3142 (NH), 2970 (CH-aliph.), 1630 (C=N); ^{1}H-NMR (600 MHz, DMSO-d_6): δ 1.92 (s, 6H, $2CH_3$), 5.38 (s, 1H, CH), 6.87-7.78 (m, 14H, Ar-H); Anal. Calcd. for $C_{25}H_{21}N_5$: C, 76.70; H, 5.41; N, 17.89. Found: C, 76.61; H, 5.29; N, 17.68.

Analgesic activity

Mice of either sex (25–30 g) obtained from the animal house at the faculty of pharmacy, Northern Border University were used for this study. The animals were fasted overnight and water *ad libitum*. The animals were divided into 4 groups, each group containing 10 mice:

Group 1 control (10 ml/kg 2% aqueous gum, oral).
Group 2 positive control (diclofenac sodium 20 mg/kg, oral).
Group 3 Synthesized compound (20 mg/kg, oral).
Group 4 Synthesized compound (40 ml/kg, oral).

Assessment of Analgesic activity

Acetic acid-induced writhing test

The animals were divided into 4 groups with 10 albino mice in each group. Treatment schedule is mentioned in table 1:

Test samples and 2% aqueous gum administered orally 30 minutes prior to *intraperitoneal* (*i.p*) administration of 1.0 % v/v acetic acid (0.1 ml/10 g). Diclofenac sodium administered orally 15 minutes prior to acetic acid. The number of writhes was recorded for 15 minutes commencing just 5 minutes after *i.p* administration of acetic acid[18-20]. The percentage protection was calculated as follows:

X_1-X_2/X_1 . 100
X_1 = No. of writhing in control group
X_2 = No. of writhing in treated group

Acute toxicity study

The acute toxicity study of compound **3**c was performed according to OECD/OCDE guidelines No: 423 and a dose of 300 mg/kg body weight was used[21]. Two groups, each of 3 mice, group-1 is control (animals weighted and administered 10 ml/kg, 2% aqueous gum solution orally) and group-2 administered 300mg/kg of the drug orally (OECD guidelines 423). Animals were observed individually after dosing at 1 hour, 24 hours and 72 hours for behavioral and physiological effects and the observations were recorded[21,22].

CONCLUSION

Several novel fused pyrimidines and imidazoles derived from 2-amino-*s*-triazino[1,2-benzimidazoles were synthesized. The preliminary pharmacological screening for analgesic activity of these compounds revealed that they possess potent analgesic activity. Compound **3c** possesses a potent analgesic activity equal that of diclofenac sodium (Voltraen). These results indicate that the new compounds may represent a novel analgesic and hence they are ideally suited for further study and could be developed as lead compounds in novel class of analgesics.

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