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. Omeprazole, mebendazole and abendazole are well-known drugs in the market which contain fused imidazole as active core moiety.

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.
1,3,5-Triazine (s-triazines) derivatives, which synthesized via heterocyclic-zation of biguanidines or their analogues using \( \text{\textsuperscript{2}} \)-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]benzimidazole\(^{(B)}\), have demonstrated inhibitory activity against the plasmodial DHER.

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 as agrochemical and veterinary products\(^9\). Various pyrimidine derivatives showed analgesic, antiarrhythmic and anticancer activities\(^10\), as well as 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 heterocyclic 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 \( \text{\textsuperscript{2}} \)-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 \( \text{N,N} \)-dimethylformamide 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 spectra of compound \(8\) showed the presence of the \( \text{NH}_{2} \) group at 3380, 3146 cm\(^{-1}\) and Ca"N at 2210 cm\(^{-1}\). The \( 1\text{H} \) 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 \( \text{NH}_{2} \) 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 $\alpha$-cyanocinnamate 9 was also investigated. The reaction of compound 3b with ethyl $\alpha$-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.

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]triazeno-
[1,2-a]benzimidazoles 2a-d, 3a-d with ethyl cyanoacetate 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, NH between 3400-3110 cm⁻¹, carbonyl group from 1690-1658 cm⁻¹. The ¹HNMR spectrum (DMSO-d₆) of compound 15a revealed a singlet at 5.49 ppm assigned for N(CH₃), 5.90 ppm for pyrimidine-H, 6.03 ppm for NH₂, a singlet at 7.82 assigned for NH, in addition to the presence of aromatic protons at 7.13-7.45 ppm. Also, the ¹HNMR 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 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 ¹HNMR spectrum (DMSO-d₆) 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. The ¹³CNMR spectrum (DMSO-d₆) 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 and the 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 data17 (Scheme 6). The infrared spectrum of compound 20a 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 test18. The results were expressed as mean ± SEM and statistical comparisons were made by conducting one way ANOVA (p<0.05) (table 1).
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\textsuperscript{19,20} that acetic acid induces pain sensation through prostaglandin (PG) biosynthesis and hence the writhing response is associated with increased level of PGE\textsubscript{2} and PGE\textsubscript{2α}.

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

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

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

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

<table>
<thead>
<tr>
<th>N o.</th>
<th>Wt. (g)</th>
<th>Grooming</th>
<th>Hyperactivity</th>
<th>Sedation</th>
<th>Resp.</th>
<th>Convulsion</th>
<th>Increased Activity</th>
<th>Decreased Activity</th>
<th>Sedation</th>
<th>Death</th>
<th>Resp.</th>
<th>Convulsion</th>
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</table>

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

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\textsubscript{50} of compound 3d will be more than 300mg/kg body weight.
on the dose level of 300 mg/kg body weight, and the behavioral and physiological effects were recorded.

**EXPERIMENTAL**

All melting points are uncorrected. IR spectra (KBr) were measured on Shimadzu 440 spectrometer, 1HNMR and 13CNMR spectra were obtained in DMSO-d6 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. 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 (NH2/NH), 1670 (C=O), 1615 (C=N); 1H-NMR (600 MHz, DMSO-d6): δ 6.78 (s, 2H, NH2), 7.08-7.63 (m, 8H, Ar-H), 8.31, 11.66 (2s, 2H, 2NH); Anal. Calcd. for C16H12N6O: C, 63.15; H, 3.97; N, 27.62. Found: C, 63.03; H, 3.86; N, 27.45.


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), 2970 (CH-aliph.), 1666 (C=O), 1615 (C=N); 1H-NMR (600 MHz, DMSO-d6): δ 1.84 (s, 6H, 2 CH3), 5.84 (s, 1H, CH), 6.76-7.61 (m, 8H, Ar-H), 7.95 (s, 2H, NH2); Anal. Calcd. for C20H17ClN6: 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)-ones 15a-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.


Yield (78%); acetic acid (yellow crystals); m.p: 308-310ºC; ir (potassium bromide, cm⁻¹): 3310, 3130 (NH), 2876 (CH-aliph.), 1668 (C=O), 1619 (C=N); 1H-NMR (600 MHz, DMSO-d6): δ 6.78 (s, 2H, NH2), 7.08-7.63 (m, 8H, Ar-H), 7.95 (s, 1H, CH), 6.03 (s, 2H, NH2), 7.13-7.45 (m, 4H, Ar-H), 7.62 (s, 1H, NH); Anal. Calcd. for C12H10N6O: 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 (77%); DMF (faint yellow crystals); m.p: 312-314ºC; ir (potassium bromide, cm⁻¹): 3310, 3130 (NH), 2876 (CH-aliph.), 1668 (C=O), 1619 (C=N); 1H-NMR (600 MHz, DMSO-d6): δ 5.49 (s, 2H, N(CH2)), 5.90 (s, 1H, CH), 6.03 (s, 2H, NH2), 7.13-7.45 (m, 4H, Ar-H), 7.62 (s, 1H, NH); Anal. Calcd. for C13H18N6O: C, 56.69; H, 3.96; N, 33.05. Found: C, 56.57; H, 4.01; N, 32.92.

4-Aminospiro[benzo[4,5]imidazo[1,2-a]pyrimido[2,1-d][1,3,5]triazin-6,3'-indo-line]-2,2'(1H)-dione 15c.

Yield (71%); dioxane (brown crystals); m.p: 300-301ºC; ir (potassium bromide, cm⁻¹): 3420, 3244, 3150 (NH/NH), 2970 (CH-aliph.), 1608 (C=N); 1H-NMR (600 MHz, DMSO-d6): δ 6.47 (s, 1H, CH), 7.95 (s, 2H, CH), 6.47 (s, 1H, CH), 7.09-7.72 (m, 6H, Ar-H + NH), 8.69 (s, 1H, NH), Anal. Calcd. for C19H13N7O2: C, 59.56; H, 5.00; N, 29.77. Found: C, 59.44; H, 4.88; N, 29.63.

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 (71%); DMF (faint yellow crystals); m.p: 312-314ºC; ir (potassium bromide, cm⁻¹): 3350, 3170 (NH), 2970 (CH-aliph.), 1670 (C=O), 1615 (C=N); 1H-NMR (600 MHz, DMSO-d6): δ 1.90 (s, 6H, 2CH3), 6.47 (s, 1H, CH), 6.47 (s, 1H, CH), 7.09-7.72 (m, 6H, Ar-H + NH), 8.69 (s, 1H, NH), Anal. Calcd. for C19H13N7O2: 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]triazin-6,3'-indo-line]-2,2'(1H)-dione 15c.

Yield (71%); dioxane (brown crystals); m.p: 300-301ºC; ir (potassium bromide, cm⁻¹): 3420, 3244, 3150 (NH/NH), 2970 (CH-aliph.), 1609, 1669 (C=O), 1608 (C=N); 1H-NMR (600 MHz, DMSO-d6): δ 6.48 (s, 1H, CH), 7.95 (s, 2H, CH), 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 C19H13N7O2: C, 61.45; H, 3.53.

4-Amino-6-phenyl-6H-benzo[4,5]imidazo[1,2-a]pyrimido[2,1-d][1,3,5]triazin-2(1H)-one 15d
Yield (68%); acetic acid (white crystals); m.p: 286-288°C; ir (potassium bromide, cm⁻¹): 3415, 3230 (NH₂), 2986 (CH-aliph.), 1658 (C=O), 1200 (C=N); ¹H-NMR (600 MHz, DMSO-d₆): δ 5.98 (s, 1H, CH), 6.41 (s, 1H, CH), 7.21-7.48 (m, 9H, Ar-H), 7.96 (s, 2H, NH₂), 12.51 (hump, 1H, NH); Anal. Calcd. for C₁₈H₁₄N₆O: 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: 302-304°C; ir (potassium bromide, cm⁻¹): 3328, 3220 (NH₂), 2970 (CH-aliph.), 1670 (C=O), 1622 (C=N); ¹H-NMR (600 MHz, DMSO-d₆): δ 5.88 (s, 1H, CH), 6.23 (s, 1H, CH), 7.14-7.52 (m, 8H, Ar-H), 7.86 (s, 2H, NH₂), 12.66 (hump, 2H, NH, OH); Anal. Calcd. for C₁₈H₁₄N₆O₂: 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: 306-308°C; ir (potassium bromide, cm⁻¹): 3415, 3178 (NH₂), 2970 (CH-aliph.), 7.14-7.52 (m, 10H, Ar-H+NH₂), 8.22 (s, 1H, NH); Anal. Calcd. for C₁₉H₁₆N₆O₂: 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)-ones 19a-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: 308-310°C; ir (potassium bromide, cm⁻¹): 3150 (NH), 2970 (CH-aliph.), 1668 (C=O), 1636 (C=N); ¹H-NMR (600 MHz, DMSO-d₆): δ 2.14 (s, 3H, CH₃), 5.54 (s, 1H, CH), 5.94 (s, 2H, N(CH₂)), 6.03 (s, 2H, NH₂), 7.09-7.46 (m, 4H, Ar-H), 12.21 (s, 1H, NH); Anal. Calcd. for C₁₃H₁₁N₅O: 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: 305-307°C; ir (potassium bromide, cm⁻¹): 3130 (NH), 2971 (CH-aliph.), 1689 (C=O), 1645 (C=N); ¹H-NMR (600 MHz, DMSO-d₆): δ 2.13 (s, 3H, CH₃), 2.38 (s, 3H, CH₃), 5.52 (s, 1H, CH), 5.67 (s, 1H, CH), 6.98-7.45 (m, 8H, Ar-H), 7.87 (s, 1H, NH); ¹³C-NMR (600 MHz, DMSO-d₆): ´ 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 C₂₀H₁₇N₅O: 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)-one 19c
Yield (81%); DMF (yellow crystals); m.p: 298-300°C; ir (potassium bromide, cm⁻¹): 3182 (NH), 2970 (CH-aliph.), 1657 (C=O), 1622 (C=N); ¹H-NMR (600 MHz, DMSO-d₆): δ 2.19 (s, 3H, CH₃), 3.70 (s, 3H, OCH₃), 7.09-7.46 (m, 10H, Ar-H+NH₂), 8.22 (s, 1H, NH); Anal. Calcd. for C₂₀H₁₇N₅O₂: 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)-one 19d
Yield (73%); DMF (brown crystals); m.p: 304-306°C; ir (potassium bromide, cm⁻¹): 3423 (OH), 3210 (NH), 2974 (CH-aliph.), 1657 (C=O), 1610 (C=N); ¹H-NMR (600 MHz, DMSO-d₆): δ 2.19 (s, 3H, CH₃), 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 C₂₀H₁₅N₅O₂: 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-ajimidazo[2,1-d][1,3,5]triazine 20a**

Yield (64%); dioxane (yellow crystals); m.p: 277-278ºC; ir (potassium bromide, cm⁻¹): 3120 (NH), 2971 (CH-aliph.), 1610 (C=N); ¹H-NMR (600 MHz, DMSO-d₆): δ 6.22 (s, 2H, N(CH₂), 7.19-7.57 (m, 14H, Ar-H), 7.97 (s, 1H, NH); Anal. Calcd. for C₂₃H₁₇N₅: 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-ajimidazo[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); ¹H-NMR (600 MHz, DMSO-d₆): δ 1.92 (s, 6H, 2CH₃), 5.38 (s, 1H, CH), 6.87-7.78 (m, 14H, Ar-H); Anal. Calcd. for C₂₅H₂₁N₅: C, 76.01; H, 4.72; N, 19.27. Found: C, 75.61; H, 4.53; N, 19.15.

**Acute toxicity study**

The acute toxicity study of compound 3c was performed according to OECD/OCDE guidelines No: 423 and a dose of 300 mg/kg body weight was used. 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.

**CONCLUSION**

Several novel fused pyrimidines and imidazoles derived from 2-amino-s-triazino[1,2-benimidazoles 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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