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Synthesis and analgesic/anti-inflammatory evaluation of fused heterocyclic ring systems incorporating phenylsulfonyl moiety

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ABSTRACT

A series of pyrazolo[1,5-*a*]pyrimidine, triazolo[1,5-*a*]pyrimidine, and pyrimido[1,2-*a*]benzimidazole ring systems incorporating phenylsulfonyl moiety were synthesized via the reaction of 3-(*N*,*N*-dimethylamino)-1-aryl-2-(phenylsulfonyl)prop-2-en-1-one derivatives **2a**,**b** with appropriate nitrogen nucleophiles. The analgesic and anti-inflammatory activities of the newly synthesized compound were investigated in vivo. 3-Bromo-2-phenyl-6-(phenylsulfonyl)-7-(4-methylphenyl)pyrazolo[1,5-*a*]pyrimidine (**5e**) was found to have an excellent analgesic activity in comparison with indomethacin as a reference drug, while the highest anti-inflammatory effect was observed in the case of 2-(4-bromophenyl)-6-(phenylsulfonyl)-5-(4-methylphenyl)pyrazolo[1,5-*a*]pyrimidine (**5d**). From the structure–activity relationship (SAR) point of view, the analgesic/anti-inflammatory activity of pyrazolo[1,5-*a*]pyrimidine derivatives was found to be much higher than triazolo[1,5-*a*]pyrimidine and pyrimido[1,2-*a*]benzimidazole derivatives.

1. Introduction

Inflammation is a natural and beneficial reaction in response to infections and trauma. The inflammation process begins when unknown antigen gains access to the patient's tissue and combines with an antibody in the joint. This activates an antigen complement–antibody immune complex which precipitates in the synovium and joint fluid. This in turn leads to release of chemical mediators that cause migration of polymorphonuclear leukocytes, phagotizing the immune complex. Lysosomal membrane discharges protease and collagenase causing continued inflammation, tissue destruction, and loss of physical properties of the connective tissue and joints.[1]

Management of inflammatory disorders involves a stepwise approach to the use of therapeutic agents. Relieving of pain and reduction of inflammation are urgent goals to reduce the severity of symptoms.[1] A generally accepted stepwise approach to treat the inflammation disorders includes physical therapy, non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying anti-rheumatic drugs (DMARDs), corticosteroids and finally, immunosuppressive agents.

Among different types of NSAIDs, pyrazoles,[2–12] and fused pyrazole with six-membered rings[13–19] occupy central position among those compounds that are used as analgesic and anti-inflammatory agents. On the other hand, sulfone moiety is usually incorporated as an active part in many analgesic anti-inflammatory molecules available as drugs in market such as celecoxib,[2,20] valdecoxib,[21] rofecoxib,[22] parecoxib,[23] etoricoxib,[24] tenoxicam,[25] piroxicam,[26] meloxicam,[27] lornoxicam,[28] ampiroxicam,[29] and nimesulide.[30]

In continuation of our recent work aiming at the synthesis of heterocyclic systems with remarkable biological importances,[31–41] we report here on the utility of β-keto-β-sulfonylenamines as building blocks for the synthesis of phenylsulfonylpyrazoles, 1*H*-pyrazolo[1,5-*a*]pyrimidines, 1,2,4-triazolo[1,5-*a*]pyrimidines, and pyrimido[1,2-*a*]benzimidazole and study their analgesic and anti-inflammatory activities in order to get a new compounds that could be optimized for potent analgesic anti-inflammatory agents.

2. Results and discussion

2.1. Chemistry

Heating of the 1-aryl-2-(phenylsulfonyl)ethanones **1a**,**b** with *N*,*N*-dimethylformamide–dimethylacetal (DMF–DMA) under moisture free conditions, afforded a single product identified as the corresponding 3-(*N*,*N*-dimethylamino)-1-aryl-2-(phenylsulfo-

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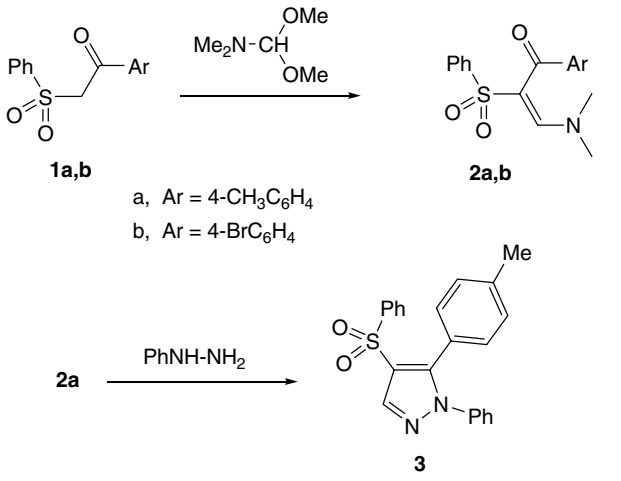
nyl)prop-2-en-1-one derivatives **2a**,**b**, respectively, in high yields (Scheme 1). The structures of isolated products were established on the bases of their elemental and spectral data. For example, the ^{1}H NMR spectrum of compound **2a** displayed a singlet signal at δ 2.42 due to 4-methyl protons, a singlet signal at δ 2.98 due to *N*,*N*-dimethyl protons, a singlet signal at δ 7.75 due to ethylenic proton, in addition to an aromatic multiplets in the region δ 7.25–7.62.

When compound **2a** was treated with phenylhydrazine, in refluxing ethanol, it afforded a single product that was analyzed correctly for $C_{22}H_{18}N_2O_2S$. The structure of the isolated product was identified as 1,5-diphenyl-4-(phenylsulfonyl)-*1H*-pyrazoles (**3**), based on its spectral data (Scheme 1). For example, its ^{1}H NMR spectrum revealed a singlet signal at δ 8.20 characteristic for a pyrazole CH proton. Moreover, the mass spectrum of the same product showed a peak at *m*/*z* 374 corresponding to its molecular ion.

The behavior of compounds **2** toward some heterocyclic amines is also investigated. Thus, when compounds **2a**,**b** were treated with substituted 5-aminopyrazole derivatives **4a**–**g** in the presence of a catalytic amount of piperidine, they afforded the corresponding 1*H*-pyrazolo[1,5-*a*]pyrimidines derivatives **5a**–**g** (Scheme 2). The other possible structure **6** was ruled out on the basis of the ^{1}H NMR spectra of the isolated products. For example, the ^{1}H NMR spectrum of compound **5a**, taken as atypical example, which revealed a singlet signal δ 9.11 which was assigned for the pyrimidine CH-2 in structure **5** and not CH-4 in structure **6**. Although spectral data seemed of no help in distinguishing between structures **5** and **6**.[42] However, structure **5** was firmly established for the reaction products by an alternate synthesis. For example, the reaction of 5-aminopyrazole **4a** with DMF–DMA and subsequent condensation of the formed amidine, 5-*N*-(*N*,*N*-dimethylaminomethylene)amino-3-methyl-1*H*-pyrazole[43] (**7**) with 1-(4-methylphenyl)-2-(phenylsulfonyl)ethanone (**1a**) afforded a product identical in all respects (mp, mixed mp, and spectra) with those of compound 2-methyl-6-(phenylsulfonyl)-5-*p*-tolylpyrazolo[1,5-*a*]pyrimidine (**5a**) (Scheme 2).

Treatment of the enaminone derivatives **2a,b** with 2-aminobenzimidazole (**8**) in pyridine under reflux gave, in each case, only one isolable product. The isolated products were identified as 2-aryl-3-(phenylsulfonyl)pyrimido[1,2-*a*]benzimidazole derivatives **11a,b** (Scheme 3). The IR spectrum of the reaction products revealed, in each case, no bands due to amino or carbonyl functions. Moreover, the ^{1}H NMR spectrum of compound **11a**, taken as an example, revealed two singlet signals at δ 2.42 and 9.24 due to methyl and pyrimidine protons, respectively. The formation of products **11a,b** is assumed to take place via the addition of the exocyclic amino group in 2-aminobenzimidazole to the activated double bond in the enaminone **2** to give the acyclic non-isolable intermediates **10a,b**, which undergo intramolecular cyclization and subsequent aromatization via the loss of dimethylamine and water molecules under the reaction conditions to afford the final products **11a,b** as depicted in Scheme 3.



Scheme 1.

The structures of the pyrimido[1,2-*a*]benzimidazole derivatives **11a,b** were further confirmed by their alternate synthesis via the reactions of 1-aryl-2-(phenylsulfonyl)ethanones **1a**,**b** with *N*′-(*1H*-benzimidazol-2-yl)-*N*,*N*-dimethylformamidine (**9**) which afforded products identical in all respects (mp, mixed mp, TLC, IR, and mass spectra) with those obtained from the reaction of the enaminone derivatives **2a,b** with 2-aminobenzimidazole (**8**) as shown in Scheme 3.

The enaminone derivatives **2a,b** react also with 3-amino-1,2,4-triazole (**12**) and afforded a high yield of a 7-aryl-6-(phenylsulfonyl)[1,2,4]triazolo[1,5-*a*]pyrimidine **13a,b**. The structures of the reaction products were assigned based on their elemental analyses and spectral data (cf. experimental part). The latter products are assumed to be formed via an initial addition of the amino group of 3-amino-1,2,4-triazole to the activated double bond in the enaminones **2a**,**b** followed by elimination of dimethylamine and water to afford the final products **13a**,**b**.

2.2. Pharmacology

2.2.1. Anti-inflammatory activity

The effect of the tested compounds and indomethacin, as a reference, was measured before and 1, 2, 3, 4, 5, and 6 h after carrageenan injection. Percent edema inhibition was calculated as a regard to saline control group, as depicted in Table 1 and Figure 1. Most of the tested compounds showed a reasonable inhibition of edema size in comparison with indomethacin. As shown in Table 1, 2-(4-bromophenyl)-6-(phenylsulfonyl)7-(4-methylphenyl)pyrazolo [1,5-*a*]pyrimidine (**5d**) was found to be the most potent anti-inflammatory compound, whereas compounds **11a**, **13a**, and **13b** showed the least inhibitory effect.

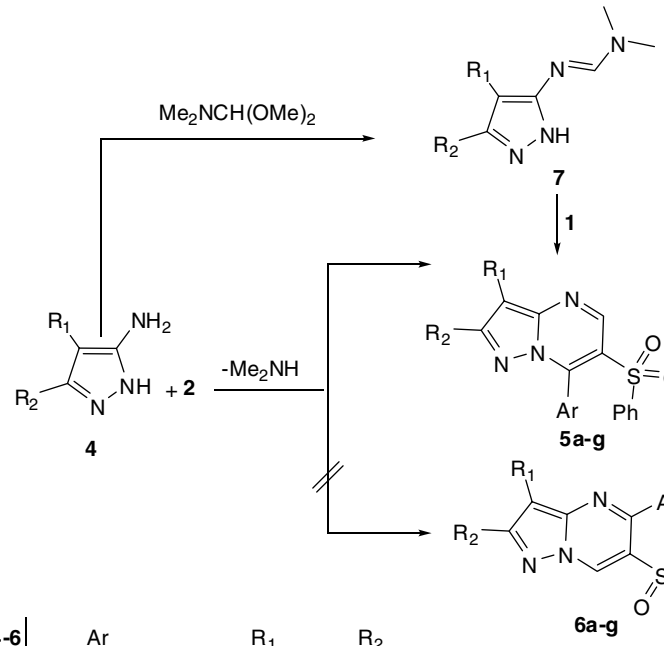
From the structure–activity relationship (SAR) viewpoint, the anti-inflammatory activity of pyrazolo[1,5-*a*]pyrimidine derivatives **5b–d** showed higher activity than the pyrimido[1,2-*a*]benzimidazole **11a** and triazolo[1,5-*a*]pyrimidine **13a,b** (Table 1 and Fig. 1).

The electronic effect of bromine atom on pyrazole ring decreases the anti-inflammatory effect as in the case of compound **5e**. On the other hand, the electronic effect of bromine atom on phenyl moiety attached to pyrazole ring increases the anti-inflammatory effect as in the case of compound **5d**. Replacement of bromine atom with methyl group also decreases the anti-inflammatory effect as in the case of compound **5c** (Table 1 and Fig. 1).

2.2.2. Analgesic activity

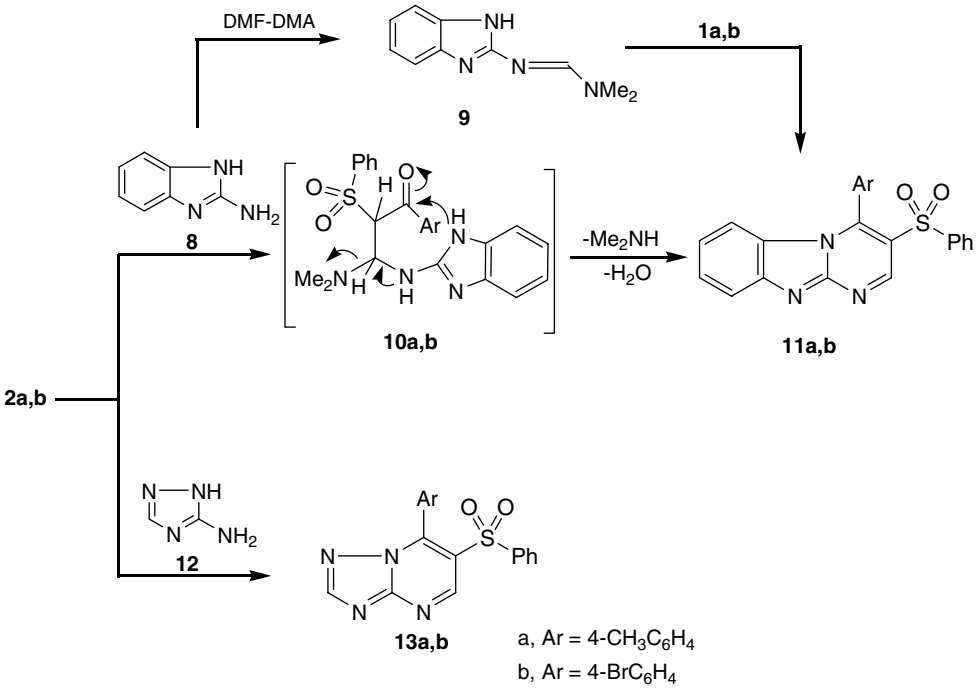
The analgesic activity of the synthesized compounds was also investigated. It was assessed by two different models: the acetic acid-induced writhing test and hot-plate test. Some of the pyrazolo[1,5-*a*]pyrimidine derivatives exhibited analgesic effects as shown in Tables 2, 3 and Figures 2–4.

Compared with the control, the analgesic potency of compound **5e** was found to be the highest. According to the structure–activity relationship (SAR), it is clear that the pyrazolo[1,5-*a*]pyrimidine ring system is more active than both pyrimido[1,2-*a*]benzimidazole and triazolo[1,5-*a*]pyrimidine ring systems. Among the same ring system (i.e., pyrazolo[1,5-*a*]pyrimidine), it was noticed that attachment of bromine atom to pyrazole moiety enhances the analgesic effect as in the case of compound **5e** (cf. anti-inflammatory effect in Table 2 and Figs. 2 and 3).



4-6	Ar	R_1	R_2
a	4-$CH_3C_6H_4$	H	CH_3
b	4-$CH_3C_6H_4$	H	C_6H_5
c	4-$CH_3C_6H_4$	H	4-$CH_3C_6H_4$
d	4-$CH_3C_6H_4$	H	4-BrC_6H_4
e	4-$CH_3C_6H_4$	Br	C_6H_5
f	4-BrC_6H_4	H	4-ClC_6H_4
g	4-BrC_6H_4	H	CH_3

Scheme 2.



Scheme 3.

3. Conclusion

From Tables 1–3, it is clear that the highest anti-inflammatory and analgesic activities were observed in the case of compounds **5d**,**e**, respectively. Therefore, it can be concluded that such compounds exert their pharmacological effects by more than one mechanism, either via inhibition of certain enzyme or intermediate incorporated in inflammatory reaction, and/or direct action on pain

Table 1
The anti-inflammatory activity of oral administration of the tested compounds (50 mg/kg) and indomethacin (50 mg/kg)

Compound	Paw edema thickness (mm)											
	1 h (X ± SE)	% Edema inhibition	2 h (X ± SE)	% Edema inhibition	3 h (X ± SE)	% Edema inhibition	4 h (X ± SE)	% Edema inhibition	5 h (X ± SE)	% Edema inhibition	6 h (X ± SE)	% Edema inhibition
Control	0.174± 0.0035	–	0.190± 0.0040	–	0.250± 0.0052	–	0.150± 0.0011	–	0.123± 0.0011	–	0.103± 0.0010	–
5a	0.129 ± 0.0025*	25.8	0.142 ± 0.0033*	25.2	0.190 ± 0.0045*	23.2	0.129 ± 0.0019*	14.0	0.113 ± 0.0017*	8.1	0.094 ± 0.0010*	8.7
5b	0.100 ± 0.0026*	42.5	0.112 ± 0.0030*	41.0	0.159 ± 0.0030*	36.4	0.116 ± 0.010*	22.6	0.088 ± 0.0027*	28.2	0.087 ± 0. 0026*	15.5
5c	0.09 ± 0.0023*	54.59	0.109 ± 0.0032*	42.6	0.172 ± 0.0036*	31.2	0.120 ± 0.0020*	20	0.102 ± 0.0018*	17.0	0.091 ± 0.0016*	11.6
5d	0.045 ± 0.0029*	74.1	0.052 ± 0.0030*	72.6	0.077 ± 0.0120*	69.2	0.110 ± 0.0020*	26.6	0.084 ± 0.0019*	31.7	0.047 ± 0.0018*	54.3
5e	0.060 ± 0.0010*	65.5	0.074 ± 0.0012*	61.0	0.113 ± 0.0015*	54.8	0.140 ± 0.0033*	12.5	0.125 ± 0.0029*	0	0.098 ± 0.0022*	6.6
5f	0.130 ± 0.0031*	24.2	0.143 ± 0.0040*	24.7	0.188 ± 0.0054*	24.8	0.122 ± 0.0050*	18.6	0.106 ± 0.0029*	13.8	0.089 ± 0.0030*	13.2
5g	0.161 ± 0.0032*	7.4	0.180 ± 0.0032*	5.2	0.239 ± 0.0046*	4.4	0.151 ± 0.0029*	0	0.123 ± 0.0010*	0	0.105 ± 0.0010*	0
11a	0.160 ± 0.0032*	7.3	0.176 ± 0.0033*	5.0	0.236 ± 0.0044*	4.2	0.150 ± 0.0043*	0	0.124 ± 0.0024*	0	0.105 ± 0.0024*	0
13a	0.163 ± 0.0033*	7.5	0.180 ± 0.0031*	5.2	0.240 ± 0.0045*	4.4	0.145 ± 0.0048*	3.3	0.120 ± 0.0028*	2.4	0.101 ± 0.0028*	1.9
13b	0.170 ± 0.0035*	2.2	0.182 ± 0.0032*	4.2	0.246 ± 0.0047*	1.6	0.148 ± 0.0051*	1.3	0.122 ± 0.0029*	0.8	0.102 ± 0.0030*	0.9
Ind.	0.040 ± 0.0018*	77	0.090 ± 0.0026*	56	0.140 ± 0.0048*	44	0.114 ± 0.0035*	28.7	0.088 ± 0.0015*	28.4	0.052 ± 0.0013*	50

Data represent mean values ± SE of six mice per group and the percent changes versus basel (zero min) values and 1, 2, 3, 4, 5, and 6 h post-carrageenan injection.
Data were analyzed using one-way ANOVA and Duncan's multiple comparison test $^{*}P < 0.05$.
Percent edema inhibition was calculated as regards saline control group.
Potency was calculated as regards the percentage change of the indomethacin treated group.
*Significant difference from the control value at $P < 0.05$.
SE, standard error; Ind., indomethacin.

regulating receptors. To confirm this suggestion, further studies are now in progress based on molecular modeling.

4. Experimental

4.1. Chemistry

4.1.1. General

All melting points were measured on a Gallenkamp melting point apparatus. The infrared spectra were recorded in potassium bromide disks on a pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometers. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H spectra were run at 300 MHz and ^{13}C spectra were run at 75.46 MHz in deuterated chloroform ($CDCl_3$) or dimethyl sulfoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt.

Aminopyrazoles **6a–c**,[44–46] **7**,[43] and phenylsulfones **1a,b**[47] were prepared according to procedures in the literature.

4.1.2. 3-(Dimethylamino)-2-(phenylsulfonyl)-1-*p*-tolylprop-2-en-1-one and 1-(4-bromophenyl)-3-(dimethylamino)-2-(phenylsulfonyl)prop-2-en-1-one (2a,b)

A mixture of 1-aryl-2-(phenylsulfonyl)ethanone **1a,b** (20 mmol) and dimethylformamide–dimethylacetal (DMF–DMA) (20 mmol) in dry xylene (20 mL) was refluxed for 8 h, then left to cool to room temperature. The reddish-brown precipitated product was filtered off, washed with light petroleum (40–60 °C), and dried. Recrystallization from benzene afforded **2a,b**. The physical and spectral data of compounds **2a–c** are listed below.

4.1.2.1. 3-(Dimethylamino)-2-(phenylsulfonyl)-1-*p*-tolylprop-2-en-1-one (2a). Yield (78%); mp 135 °C; IR (KBr) υ_{max}/cm^{-1}: 1644 (conjugated C=O), 1551 (C=C); ^{1}H NMR ($CDCl_3$): δ 2.42 (s, 3H), 2.98 (s, 6H), 7.25–7.62 (m, 9H, ArH's), 7.75 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 21.20, 62.55, 106.56, 122.26, 125.25, 128.16, 129.33, 133.80, 138.90, 140.71, 142.23, 153.48, 187.29; MS (*m/z*, %): 329 (M^+, 23.7). Anal. Calcd for $C_{18}H_{19}NO_3S$ (329.41): C, 65.63; H, 5.81; N, 4.25; S, 9.73%. Found: C, 65.61; H, 5.82; N, 4.28; S, 9.70%.

4.1.2.2. 1-(4-Bromophenyl)-3-(dimethylamino)-2-(phenylsulfonyl)-prop-2-en-1-one (2b). Yield (70%); mp 161–162 °C; IR (KBr) υ_{max}/cm^{-1}: 1644 (conjugated C=O), 1551 (C=C); ^{1}H NMR ($CDCl_3$): δ 2.88 (s, 6H), 7.25–7.45 (m, 9H, ArH's), 7.81 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 62.54, 106.73, 126.26, 127.25, 127.93, 128.16, 128.81, 129.38, 130.90, 133.5, 143.71, 153.23, 152.48, 188.01; MS (*m/z*, %): 395 (M^{+2}, 30.2), 393 (M^+, 31.1). Anal. Calcd for $C_{17}H_{16}BrNO_3S$ (394.28): C, 51.79; H, 4.09; Br, 20.27; N, 3.55; S, 8.13%. Found: C, 51.76; H, 4.11; Br, 20.30; N, 3.56; S, 8.10%.

4.1.3. 1-Phenyl-4-(phenylsulfonyl)-5-*p*-tolyl-1*H*-pyrazole (3)

Phenylhydrazine (1.5 mL) was added to a stirred solution of the enaminone **2a** (10 mmol) dissolved in AcOH (30 mL). Stirring was lasted for 12 h at room temperature. The solid product obtained was filtered off dried, and recrystallized from DMF. Yield (69%); mp 175 °C; IR (KBr) υ_{max}/cm^{-1}: 1597 (C=N); ^{1}H NMR (DMSO-d_6): δ 2.35 (s, 3H, CH_3), 7.00–7.55 (m, 14H, ArH's), 8.20 (s, 1H, pyrazole-3-CH); ^{13}C NMR (DMSO-d_6): δ 21.30, 123.57, 123.79, 124.91, 127.04, 128.12, 128.53, 128.75, 128.88, 130.23, 132.67, 138.57, 139.84, 140.44, 142.05, 143.61; MS (*m/z*, %): 374 (M^+, 42.6). Anal. Calcd for $C_{22}H_{18}N_2O_2S$ (374.46): C, 70.57; H, 4.85; N, 7.48; S, 8.56%. Found: C, 70.54; H, 4.86; N, 7.51; S, 8.53%.

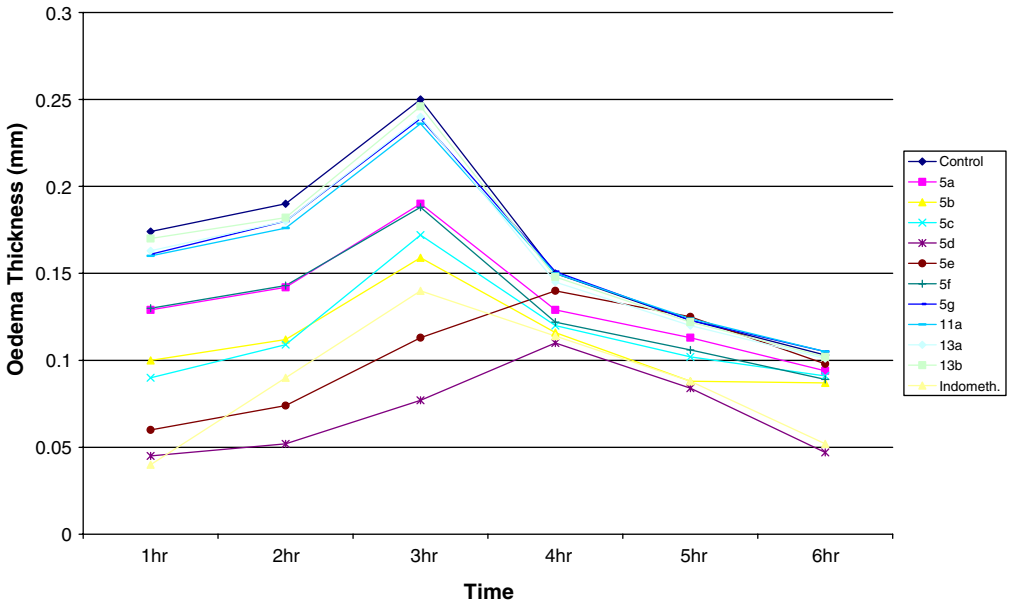


Figure 1. Anti-inflammatory potency of the tested compounds (50 mg/kg) and indomethacin (50 mg/kg).

Table 2
Analgesic activity of oral administration of tested compounds (50 mg/kg) and indomethacin (50 mg/kg)

Compound	Reaction time (*S*)									
	0 (*X* ± SE)	30 min (*X* ± SE)	Change (%)	Pot.	1 h (*X* ± SE)	Change (%)	Pot.	2 h (X ± SE)	Change (%)	Pot.
Control	5.3 ± 0.3	5.4 ± 0.3	1.8	—	5.4 ± 0.3	1.8	—	5.4 ±0.3	1.8	—
5a	5.6 ± 0.2*	6.5 ± 0.4*	16.0	0.37	6.5 ± 0.3*	16.0	0.21	5.9 ± 0.3*	5.3	0.07
5b	5.9 ± 0.4*	6.8 ± 0.5*	15.2	0.35	7.0 ± 0.5*	18.6	0.24	6.8 ± 0.4*	15.2	0.19
5c	7.3 ± 0.8*	9.1 ± 0.7*	25	0.58	12.2 ± 1.0*	67.1	0.87	11.5 ± 0.9*	57.5	0.71
5d	6.2 ± 0.6*	8.0 ± 0.4*	29	0.67	9.7 ± 0.4*	56.4	0.73	9.7 ± 0.4*	56.4	0.70
5e	7.3 ± 0.4*	10.5 ± 0.7*	43.8	1.02	13.0 ± 0.3*	78.0	1.02	12.3 ± 1.0*	68.4	0.84
5f	5.4 ± 0.3*	7.2 ± 0.5*	33	0.77	9.3 ± 0.4*	72.2	0.93	8.2 ± 0.6*	51.8	0.63
5g	6.8 ± 0.4	8.7 ± 0.4*	27	0.63	9.8 ± 0.8	44.1	0.57	9.5 ± 0.5	39.7	0.49
11a	6.5 ± 0.3*	7.1 ± 0.2*	9.2	0.21	8.0 ± 0.4*	23.0	0.30	7.9 ± 0.3*	21.5	0.26
13a	5.6 ± 0.2*	6.0 ± 0.9*	7.1	0.16	5.9 ± 0.8*	5.3	0.06	5.6 ± 0.8*	0	0
13b	7.3 ± 0.3	7.7 ± 0.6*	5.4	0.12	7.8 ± 0.7	6.8	0.08	7.7 ± 0.6*	5.4	0.06
Ind.	7.9 ± 0.4*	11.3 ± 0.4*	43.0	1	14 ± 0.3	77.2	1	14.3 ± 0.4	81.0	1

Data represent mean values ± SE of six mice per group, shown at the basal (zero time) and three values for each group (saline, indomethacin, and tested compounds) after 0.5, 1, and 2 h. Statistical comparisons between basal (pre-drug values) and post-drug values.
Data were analyzed using one-way ANOVA and Duncan's multiple comparison test $^{*}P < 0.05$.
Percentage change was calculated from basal (pre-drug) values and post-drug values.
Potency was calculated as regards the percentage change of the indomethacin.
Values between parentheses represent on increase of reaction time compared to zero time.
Pot., potency; SE, standard error; Ind., indomethacin.

4.1.4. Pyrazolo[1,5-*a*]pyrimidine derivatives (5a–g)

Method A: To a mixture of the enaminone **2a,b** (10 mmol) and appropriate aminopyrazole derivatives **3** (10 mmol) in absolute EtOH (25 mL) was added few drops of piperidine and the reaction mixture was refluxed for 3 h, then left to cool. The formed solid product was filtered off and recrystallized from EtOH/DMF to afford the pyrazol[1,5-*a*]pyrimidine derivatives **5a–g** in 75–87% yield. The physical and spectral data of compounds **5a–g** are listed below.

Method B: A solution of 1-(4-methylphenyl)-2-(phenylsulfonyl)ethanone (**1a**) (10 mmol) and an equivalent molar ratio of 5-*N*-(*N*,*N*-dimethylaminomethylene)amino-3-methyl-1*H*-pyrazol (**7**) in ethanol (20 mL), in the presence of 0.3 mL piperidine, was heated under reflux for 6 h. The solvent was removed by distillation under reduced pressure and the remainder was left to cool. The precipitated solid product was collected by filtration. Recrystallization from DMF afforded product identical in all respects (mp, mixed mp, TLC, IR, and mass spectra with **5a**).

4.1.4.1. 2-Methyl-6-(phenylsulfonyl)7-*p*-tolylpyrazolo[1,5-*a*]pyrimidine (5a). Yield (85%); mp 160 °C; IR (KBr) υ_{max}/cm^{-1}: 1596 (C=N); ^{1}H NMR (DMSO-d_6): δ 2.37 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 6.77 (s, 1H, pyrazole-4-CH), 7.14–7.42 (m, 9H, ArH's), 9.11 (s, 1H, pyrimidine-6-CH); ^{13}C NMR (DMSO-d_6): δ 12.69, 22.28, 95.38, 120.69, 121.01, 121.86, 123.32, 126.26, 128.57, 131.55, 133.60, 135.32, 140.48, 146.25, 150.28, 158.61; MS (*m*/*z*, %): 363 (M^+, 7.7), 222 (100). Anal. Calcd for $C_{20}H_{17}N_3O_2S$ (363.43): C, 66.10; H, 4.71; N, 11.56; S, 8.82%. Found: C, 66.18; H, 4.70; N, 11.53; S, 8.85%.

4.1.4.2. 2-Phenyl-6-(phenylsulfonyl)7-(4-methylphenyl) pyrazolo[1,5-*a*]pyrimidine (5b). Yield (76%); mp 214 °C; IR (KBr) υ_{max}/cm^{-1}: 1594 (C=N); ^{1}H NMR (DMSO-d_6): δ 2.43 (s, 3H, CH_3), 6.78 (s, 1H, pyrazole-4-CH), 7.14–7.84 (m, 14H, ArH's), 9.17 (s, 1H, pyrimidine-6-CH); ^{13}C NMR (DMSO-d_6): δ 21.12, 95.14, 120.99, 121.04, 121.91, 124.36, 126.48, 127.26, 128.73, 128.97, 129.66, 131.58, 133.54, 140.36, 140.62, 147.47, 148.96, 150.37, 158.18;

Table 3
Analgesic effect of oral administration of tested compounds (50 mg/kg), and indomethacin (50 mg/kg) on visceral pain by using writhing test in race

Compound	Number of writhing		
	30 min ($X \pm SE$)	Change (%)	Potency
Control	85 ± 4.4*	—	—
5a	59.5 ± 2.2*	30.0	0.35
5b	61.2 ± 2.0*	28.0	0.32
5c	21.7 ± 0.9*	74.4	0.86
5d	29.5 ± 1.4*	65.2	0.76
5e	12.2 ± 1.1*	85.6	0.99
5f	28.3 ± 1.6*	66.7	0.77
5g	37 ± 1.5*	56.4	0.65
11a	77.2 ± 4.5*	9.1	0.10
13a	85.5 ± 4.8*	—	0.0
13b	75.8 ± 3.9*	10.8	0.12
Ind.	12 ± 1.0*	85.8	1

Data represent mean values ± SE of six mice per group and percentage inhibition of number of writhing/30 min. Statistical comparison of the difference between saline control group and treated groups was done by one-way ANOVA and Duncan's multiple comparison test *$P < 0.05$.
Potency was calculated as regards the percentage change of the indomethacine.
SE, Standard error; Ind, indomethacin.

MS (m/z, %): 425 (M^+, 3.8), 248 (100). Anal. Calcd for $C_{25}H_{19}N_3O_2S$ (425.50): C, 70.57; H, 4.50; N, 9.88; S, 7.54%. Found: C, 70.81; H, 4.51; N, 9.85; S, 7.50%.

4.1.4.3. 6-(Phenylsulfonyl)-2,7-di(4-methylphenyl)pyrazolo-[1,5-*a*]pyrimidine (5c). Yield (82%); mp 240 °C; IR (KBr) υ_{max}/cm^{-1}: 1596 (C=N); ^{1}H NMR (DMSO-d_6): δ 2.42 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 6.78 (s, 1H, pyrazole-4-CH), 7.15-7.85 (m, 13H, ArH's), 9.17 (s, 1H, pyrimidine-6-CH); ^{13}C NMR (DMSO-d_6): δ 21.12, 21.13, 95.58, 120.99, 121.05, 121.96, 124.32, 126.76, 127.36, 128.99, 129.67, 131.64, 133.72, 135.52, 141.68, 147.25, 150.38, 156.42, 158.22, 159.32; MS (m/z, %): 439 (M^+, 4.1), 298 (100). Anal. Calcd for $C_{26}H_{21}N_3O_2S$ (439.53): C, 71.05; H, 4.82; N, 9.56; S, 7.30%. Found: C, 71.09; H, 4.85; N, 9.53; S, 7.26%.

4.1.4.4. 2-(4-Bromophenyl)-6-(phenylsulfonyl)-7-(4-methylphenyl)-pyrazolo[1,5-*a*]pyrimidine (5d). Yield (87%); mp 242 °C; IR (KBr) υ_{max}/cm^{-1}: 1596 (C=N); ^{1}H NMR (DMSO-d_6): δ 2.32 (s, 3H, CH_3), 6.95 (s, 1H, pyrazole-4-CH), 7.33–7.77 (m, 13H, ArH's), 9.12 (s, 1H, pyrimidine-6-CH); ^{13}C NMR (DMSO-d_6): δ 21.12, 55.58, 95.58, 120.99, 121.03, 121.96, 124.32, 127.26, 128.99, 129.57,

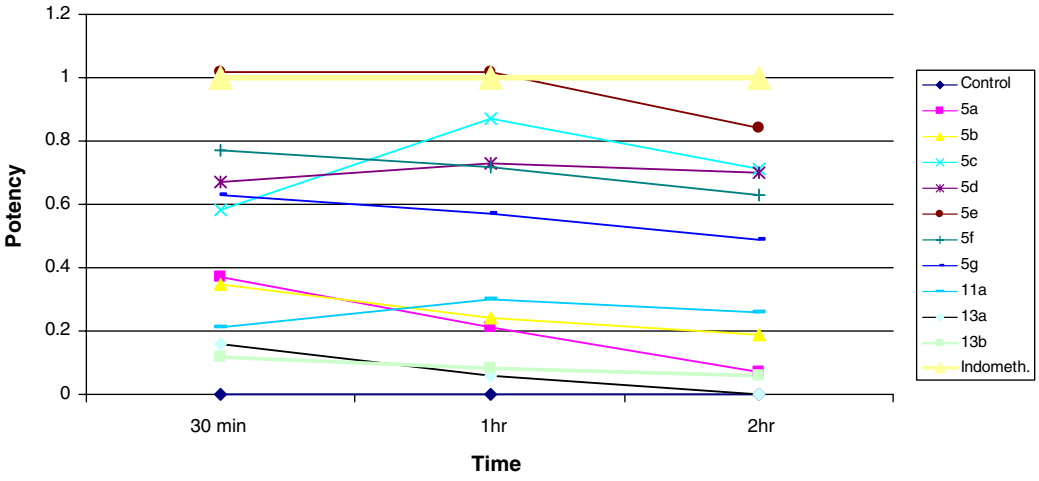


Figure 2. Analgesic activity of tested compounds (50 mg/kg) and indomethacin (50 mg/kg).

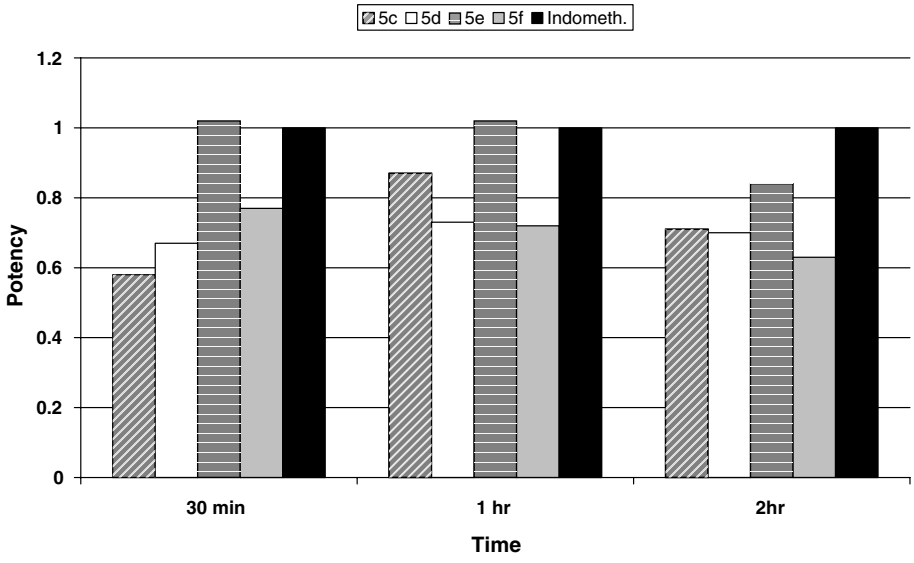


Figure 3. Analgesic activity of the highest potent tested compounds (50 mg/kg) and indomethacin (50 mg/kg).

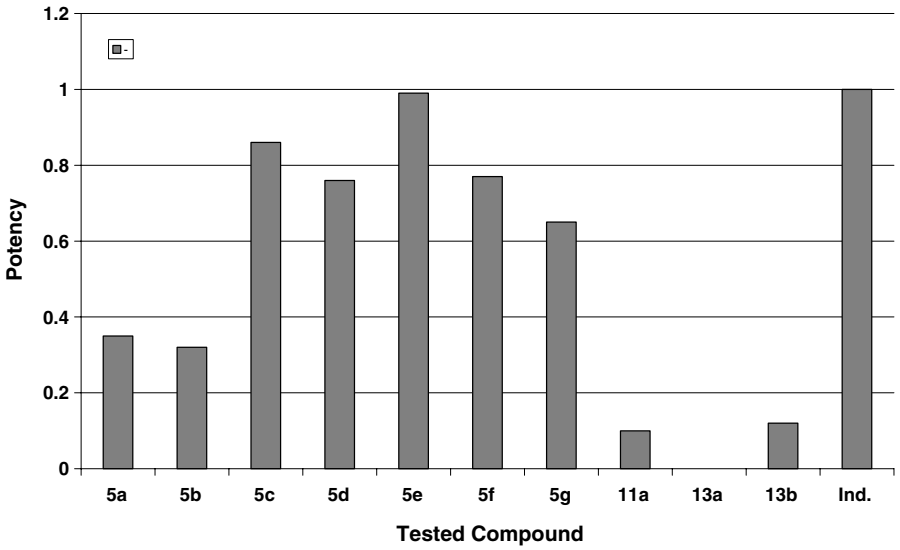


Figure 4. Analgesic activity of tested compounds (50 mg/kg) and indomethacin (50 mg/kg) for on visceral pain by using writhing test in race.

131.64, 133.70, 135.52, 140.68, 147.25, 150.38, 159.32, 162.61; MS (*m/z*, %): 505 (M^{+2}, 3.0), 503 (M^{+}, 2.9), 264 (100). Anal. Calcd for $C_{25}H_{18}BrN_3O_2S$ (504.40): C, 59.53; H, 3.60; N, 8.33; S, 6.36%. Found: C, 59.47; H, 3.59; N, 8.35; S, 6.35%.

4.1.4.5. 3-Bromo-2-phenyl-6-(phenylsulfonyl)7-(4-methylphenyl) pyrazolo[1,5-*a*]pyrimidine (5e). Yield (78%); mp 268 °C; IR (KBr) υ_{max}/cm^{-1}: 1596 (C═N); ^{1}H NMR (DMSO-d_6): δ 2.41 (s, 3H, CH_3), 7.13–7.80 (m, 14H, ArH's), 9.27 (s, 1H, pyrimidine-6-CH); ^{13}C NMR (DMSO-d_6): δ 21.12, 95.14, 95.58, 120.99, 121.03, 121.96, 124.32, 127.26, 128.99, 129.57, 131.64, 133.70, 135.52, 140.68, 147.25, 150.38, 159.32, 162.61; MS (*mz*, %): 505 (M^{+2}, 5.1), 503 (M^{+}, 5.3), 262 (100). Anal. Calcd for $C_{25}H_{18}BrN_3O_2S$ (504.40): C, 59.53; H, 3.60; N, 8.33; S, 6.36%. Found: C, 59.54; H, 3.62; N, 8.30; S, 6.32%.

4.1.4.6. 7-(4-Bromophenyl)-2-(4-chlorophenyl)-6-(phenylsulfonyl)-pyrazolo[1,5-*a*]pyrimidine (5f). Yield (78%); mp 250 °C; IR (KBr) υ_{max}/cm^{-1}: 1596 (C═N); ^{1}H NMR (DMSO-d_6): δ 6.75 (s, 1H, pyrazole-4-CH), 7.44–7.78 (m, 13H, ArH's), 9.13 (s, 1H, pyrimidine-6-CH); ^{13}C NMR (DMSO-d_6): δ 94.58, 114.28, 121.32, 123.96, 126.32, 127.22, 127.99, 129.13, 131.64, 133.70, 135.52, 140.68, 141.85, 147.25, 150.38, 158.32, 158.76, 160.61; MS (*m/z*, %): 526 (M^{+4},3.3), 524 (M^{+2}, 4.0), 522 (M^{+}, 1.2), 284 (100). Anal. Calcd for $C_{24}H_{15}BrClN_3O_2S$ (524.82): C, 54.93; H, 2.88; N, 8.01; S, 6.11%. Found: C, 54.99; H, 2.88; N, 8.00; S, 6.15%.

4.1.4.7. 7-(4-Bromophenyl)-2-methyl-6-(phenylsulfonyl)pyrazolo-[1,5-*a*]pyrimidine (5g). Yield (85%); mp 200 °C; IR (KBr) υ_{max}/cm^{-1}: 1596 (C═N); ^{1}H NMR (DMSO-d_6): δ 2.31 (s, 3H, CH_3), 6.80 (s, 1H, pyrazole-4-CH), 7.24–7.32 (m, 9H, ArH's), 9.12 (s, 1H, pyrimidine-6-CH); ^{13}C NMR (DMSO-d_6): δ 12.88, 95.58, 120.99, 121.03, 121.96, 124.32, 127.26, 129.57, 133.70, 135.52, 140.68, 147.25, 150.38, 159.32, 162.61; MS (*m/z*, %): 429 (M^{+}, 13.7); 427 (M^{+}, 13.5), 286 (100). Anal. Calcd for $C_{19}H_{14}BrN_3O_2S$ (428.30): C, 53.28; H, 3.29; N, 9.81; S, 7.49%. Found: C, 53.24; H, 3.28; N, 9.80; S, 7.46%.

4.1.5. *N′*-(*1H*-Benzimidazol-2-yl)-*N,N*-dimethylformamidine (9)

A mixture of 2-aminobenzimidazole (**8**) (20 mmol) and dimethylformamide–dimethylacetal (DMF–DMA) (20 mmol) in dry xylene (20 mL) was refluxed for 1/2 h, then left to cool to room temperature. The white precipitated product was filtered off, washed with light petroleum (40–60 °C), and dried. Recrystallization from benzene afforded **9**; mp 248–250 °C; IR (KBr) υ_{max}/cm^{-1}: 3460 (NH) 1631 (C═N), 1551 (C═C); ^{1}H NMR ($CDCl_3$): δ 3.13 (s, 6H), 6.98–7.34 (m, 4H, ArH's), 8.78 (s, 1H), 11.51 (br, NH); MS (*m/z*, %): 188.11 (M^{+}, 25.7). Anal. Calcd for $C_{10}H_{12}N_4$ (188.23): C, 63.81; H, 6.43; N, 29.77%. Found: C, 63.95; H, 6.32; N, 29.88; S, 9.70%.

4.1.6. Synthesis of pyrimido[1,2-*a*]benzimidazole derivatives (11a,b)

Method A. A mixture of 3-(dimethylamino)-2-(phenylsulfonyl)-1-(4-methylphenyl)prop-2-en-1-one (**2a**) or 1-(4-bromophenyl)-3-(dimethylamino)-2-(phenylsulfonyl)prop-2-en-1-one (**2b**) (10 mmol) and 2-aminobenzimidazole (**8**) (1.33 g, 10 mmol) in pyridine (25 mL) was refluxed for 12 h, then left to cool. The solvent was evaporated in vacuo and the residual solid was taken in EtOH, then collected by filtration, washed with water, dried, and finally recrystallized from DMF/H_2O to afford the corresponding pyrimido[1,2-*a*]benzimidazole derivatives **11a,b**, respectively.

Method B. A solution of the appropriate compound **1** (10 mmol) and *N′*-(*1H*-benzimidazol-2-yl)-*N,N*-dimethylformamidine (**9**) (1.88 g, 10 mmol) in ethanol (20 mL) and piperidine (0.3 mL) was heated under reflux for 10 h, then left to cool. The precipitated solid product was collected by filtration, washed with ethanol, and finally recrystallized from DMF/H_2O to afford products identical in all respects (mp, mixed mp, TLC, IR, and mass spectra) with compounds **11a,b** prepared by Method A above.

4.1.6.1. 2-(4-Methylphenyl)-3-(phenylsulfonyl)pyrimido[1,2-*a*]benzimidazole (11a). Yield (88%); mp 270 °C; IR (KBr) υ_{max}/cm^{-1}: 1611 (C═N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.42 (s, 3H, CH_3), 7.15–7.95 (m, 13H, ArH's), 9.24 (s, 1H, pyrimidine-4-CH); ^{13}C NMR (DMSO-d_6): δ 21.12, 114.03, 119.50, 120.66, 120.96, 122.917, 127.33, 127.42, 127.62, 127.92, 128.92, 130.64, 133.65, 134.35, 135.47, 139.98, 141.32, 144.84, 160.17; MS (*m/z* %): 399 (M^{+}, 31.8), 258 (100). Anal. Calcd for $C_{23}H_{17}N_3O_2S$ (399.46): C, 69.15; H, 4.29; N, 10.52; S, 8.03%. Found: C, 69.12; H, 4.28; N, 10.50; S, 8.01%.

4.1.6.2. 2-(4-Bromophenyl)-3-(phenylsulfonyl)pyrimido[1,2-*a*]-benzimidazole (11b). Yield (86%); mp > 300 °C; IR (KBr) υ_{max}/cm^{-1}: 1611 (C═N); ^{1}H NMR (DMSO-d_6): *δ 7.15–8.65 (m, 13H, ArH's), 10.34 (s, 1H, pyrimidine-4-CH);* ^{13}*C NMR (DMSO-d_6)*: δ 114.06, 119.60, 120.66, 120.96, 122.917, 127.33, 127.42, 127.62, 127.92,

128.92, 130.64, 133.65, 134.45, 135.47, 139.98, 141.32, 144.94, 160.27; MS (*m/z*, %): 465 (M^+, 28.9); 463 (M^+, 29.2), 322 (100). Anal. Calcd for $C_{22}H_{14}BrN_3O_2S$ (464.33): C, 56.91; H, 3.04; N, 9.05; S, 6.91%. Found: C, 56.86; H, 3.03; N, 9.05; S, 6.93%.

4.1.7. Synthesis of triazolo[1,5-*a*]pyrimidine derivatives (13a,b)

General procedure. To a mixture of 3-(dimethylamino)-2-(phenylsulfonyl)-1-(4-methylphenyl)prop-2-en-1-one (**2a**) and 1-(4-bromophenyl)-3-(dimethylamino)-2-(phenylsulfonyl)prop-2-en-1-one (**2b**) (10 mmol) and the appropriate 3-amino-l,2,4-triazole (**12**) (0.84 g, 10 mmol) in pyridine (25 mL) was refluxed for 12 h, then left to cool. The solvent was evaporated in vacuo and the residual solid was taken in EtOH, then collected by filtration, washed with water, dried, and finally recrystallized from DMF/H_2O to afford the corresponding triazolo[1,5-*a*]pyrimidine derivatives **13a,b**, respectively. The physical and spectral data of compounds **13a,b** are listed below.

4.1.7.1. 7-(4-Methylphenyl)-6-(phenylsulfonyl)-[1,2,4]triazolo-[1,5-*a*]pyrimidine (13a). Yield (81%); mp 266 °C; IR (KBr) υ_{max}/cm^{-1}: 1621 (C=N); ^{1}H NMR (DMSO-d_6): δ 2.41 (s, 3H, CH_3), 7.36–7.73 (m, 9H, ArH's), 8.62 (s, 1H, triazole-3-CH), 9.16 (s, 1H, pyrimidine-4-CH); ^{13}C NMR (DMSO-d_6): δ 21.12, 124.36, 125.77, 127.49, 127.97, 129.20, 131.44, 134.08, 135.94, 139.94, 149.35, 153.37, 155.70, 157.74; MS (*m/z*, %): 350 (M^+, 34.1), 209 (100). Anal. Calcd for $C_{18}H_{14}N_4O_2S$ (350.39): C, 61.70; H, 4.03; N, 15.99; S, 9.15%. Found: C, 61.69; H, 4.03; N, 15.97; S, 9.11%.

4.1.7.2. 7-(4-Bromophenyl)-6-(phenylsulfonyl)-[1,2,4]-triazolo[1,5-*a*]pyrimidine (13b). Yield (79%); mp 291 °C; IR (KBr) υ_{max}/cm^{-1}: 1620 (C=N); ^{1}H NMR (DMSO-d_6): δ *7.26–8.60 (m, 9H, ArH's), 8.69 (s, 1H, triazole-3-CH), 9.54 (s, 1H, pyrimidine-4-CH);* ^{13}*C NMR (DMSO-*d_6): δ 124.28, 126.38, 126.77, 127.47, 127.77, 129.01, 130.80, 133.91, 139.92, 150.50, 153.37, 155.76, 157.73; MS (*m/z*, %): 415 (M^+, 22.5); 413 (M^+, 22.5), 273 (100). Anal. Calcd for $C_{17}H_{11}BrN_4O_2S$ (415.26): C, 49.17; H, 2.67; N, 13.49; S, 7.72%. Found: C, 49.16; H, 2.66; N, 13.51; S, 7.70%.

4.2. Pharmacology

4.2.1. Animals

Eighty adult albino rats of both sexes weighing 120–150 g and 80 mice weighing 20–25 g were obtained from animal house laboratory Nile company, Cairo, Egypt and acclimatized for 1 week in the animal facility that has 12 h light/dark cycles with the temperature controlled at 21–23 °C. Normal rat chow and water were made available.

4.2.2. Equipment

Dial micrometer model (120-1206 Baty, Sussex, England).

4.2.3. Chemical

Carrageenan sodium (1%) (Sigma, USA), Tween 80, saline, distilled water, indomethacin capsule, Batch No. 0.40604, MUB (Egypt).

4.2.4. Preparation of samples

The test compounds and the reference standard were prepared as suspensions in Tween 80 (2%). The administered oral dose of the tested compounds was 50 mg/kg body weight with analogy of a reported procedure.[48] The negative control group received 1 mL of water suspended in Tween 80.

4.2.5. Anti-inflammatory test

The anti-inflammatory testing was assessed according to the method described by Winter et al.[49] and Obukowic et al.[50] Thus, rats were divided into 13 groups, each of six animals. One group received the reference standard; 11 groups received the tested compound and one group left as a control group. The reference drug, indomethacin, and the tested compounds were given by oral route at doses of 5 and 50 mg/kg body weight, respectively. One hour later, 0.05 mL of carrageenan sodium (1%) was sublunary injected in the right hind paw. The thickness of the paw was measured after administration of the compounds at time intervals 1, 2, 3, 4, 5, and 6 h by using micrometer. The results were expressed as the percentage inhibition of edema thickness at each time interval versus that of the standard drug.

4.2.6. Anti-nociceptive activity

This activity was determined by measuring the responses of animals to the thermal and chemical stimuli.

4.2.6.1. Thermal test. Hot-plate test was conducted according to Eddy and Leimback[51] using an electronically controlled hot-plate (Ugo Basile, Italy) adjusted at 52 °C ±0.1 °C and the cut-off time was 60 s. Nine groups of mice each of six were used. The mice were divided and received the same doses of tested compounds and indomethacin as mentioned before. The time taken from introducing the animal in the hot cylinder till it licked its feet or jumped out of the glass jar was measured and recorded at time interval 0.5, 1, and 2 h.

4.2.6.2. Chemical test. Acetic acid-induced writhing in mice was performed according to the convenient published methods.[52,53] The mice were divided and received the tested compounds at dose of 50 mg/kg, and indomethacin at dose of 50 mg/kg. After 30 min interval, the mice received 0.6% acetic acid ip (0.2 mL/mice). The number of writhes in 30 min period was counted and compared.

4.2.7. Statistical analysis

Data are expressed as means ± SE. In anti-inflammatory study, data are expressed as means ± SE. The results of carrageenan-induced paw edema experiments are also expressed as percentage of change from control (pre-drug) values. Differences between vehicle control and treatment groups were tested using one-way ANOVA followed by multiple comparisons by the Duncan's multiple rang test. A probability value less than 0.05 was considered statistically significant.

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