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Research article

EVALUATION OF ANALGESIC AND ANTI-INFLAMMATORY ACTIVITIES OF *N*-MANNICH BASES OF SUBSTITUTED 2-MERCAPTO-1*H*-BENZIMIDAZOLES

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ABSTRACT: A series of new [1-(*N*,*N*-disubstituted)aminomethyl-2-(2,4-dinitrophenyl)sulphanyl]-6-substituted-1*H*-benzimidazoles (16a-19f) were synthesized by the Mannich reaction on 2-[(2,4-dinitrophenyl)sulphanyl]-5(6)-substituted-1*H*-benzimidazoles with appropriate secondary amine and paraformaldehyde in presence of concentrated hydrochloric acid in ethanol. The synthesized compounds have been evaluated for analgesic and anti-inflammatory activities. Considerable numbers of them were found to exhibit good activity. 2-(2,4-Dinitrophenylsulphanyl)-6-methoxy-1-pyrrolidin-4-ylmethyl-1*H*-benzimidazole (**18e**) was found to be more potent analgesic than standard pentazocine and almost equivalent in its anti-inflammatory activity in comparison with the working standard diclofenac.

KEY WORDS: 1*H*-Benzimidazole-2-thiol; Mannich reaction; Analgesic; Anti-inflammatory; Carrageenan-induced paw edema model.

INTRODUCTION

The search for non steroidal anti-inflammatory agents used for moderate pain, inflammation and fever devoid of side effects, such as irritation of gastric mucosa, respiratory depression, constipation and physical dependence in an active area of research in medicinal chemistry. Among the various compounds developed, the 2-substituted benzimidazoles (Ersan *et. al*., 1997) and *N*-Mannich bases of various heterocyclic compounds (Preston 1980; Erol *et. al*., 1992; Sridhar *et. al*., 2002) have been reported to exhibit potent anti-inflammatory and analgesic properties (Lazer *et. al*., 1987; Grice *et. al*., 2008; Mader *et. al*., 2008; Jesudason *et. al*., 2009; Sondhi *et. al*., 2002; Kavitha *et. al*., 2010; Monika *et. al*., 2010). Compounds containing benzimidazole skeleton such as 2-phenyl-1*H*-benzimidazole, benzimidazole-2-thiones and their derivatives, N-alkylated and arylated benzimidazole derivatives, have shown prominent DNA binding, anti-diabetic (Bhattacharya *et. al*., 2008; Kamal *et. al*., 2008; Ramya *et. al*., 2009), antimicrobial (Weidner-Well *et. al*., 2001, Bürli *et. al*., 2004; Desai *et. al*., 2006; Huang *et. al*., 2007; Hu L *et. al*., 2009), anthelmintic (Tojo J *et. al*., 1992), antitumor (Abonia *et. al*., 2011), antiulcer (Carcanague *et. al*., 2002), antiviral (Zou R *et. al*., 1996; Luo Y *et. al*., 2010), anti-cancer (Refaat 2010; Yussef *et. al*., 2012), antihistaminic, antioxidant (Kus *et. al*., 2008), and other important inhibitory activities (Shin *et. al*., 2009; Bennamane *et. al*., 2009; Aljourani *et. al*., 2009; Humenyuk *et. al*., 2007 Narkhede *et. al*., 2008). We have reported (Vijaya Kumar *et. al*., 1985; Madhusudhan Rao *et. al*., 1988; Vijaya Kumar and Malla Reddy 1985; Vijaya Kumar and Malla Reddy 1984) several series of benzimidazole Mannich bases and Michael adducts, which have displayed diverse biological activities. In the past many benzimidazole derivatives have shown potent anti-inflammatory and analgesic activities in different animal models (Tsukamoto *et. al*., 1980; Ito K *et. al*., 1982; Ito K *et. al*., 1982; Gilman *et. al*., 1985; Lazer *et. al*., 1987; Taniguchi *et. al*., 1993; Boido *et. al*., 1991; Da Settimo *et. al*., 2001). Introducing nitro substituted phenyl ring increases antibacterial and antifungal activity of heterocyclic systems (Sharma *et. al*., 2012) and the presence of 2,4-dinitrophenyl group was found to enhance the antitumor activity both *in vitro* as well as *in vivo* animal models (Shami *et. al*., 2006).

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Survey of the literature shows that none of the *N*-Mannich bases of 2-[(2,4-dinitrophenyl)sulphanyl]-5(6)-substituted-1*H*-benzimidazoles were screened for analgesic and anti-inflammatory activities. In view of these observations and in continuation of our previous work (Mohan Rao and Vijaya Kumar 2012) on Mannich reactions of mercapto benzimidazoles, we report for the first time, the evaluation of analgesic and anti-inflammatory activities of 1-(*N*,*N*-disubstituted)aminomethyl-2-(2,4-dinitrophenyl)sulphanyl-6-substituted-1*H*-benzimidazoles (Figure 1).

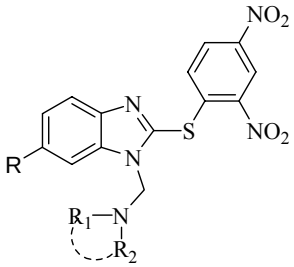


Figure 1: General structure of Mannich bases

MATERIAL AND METHODS

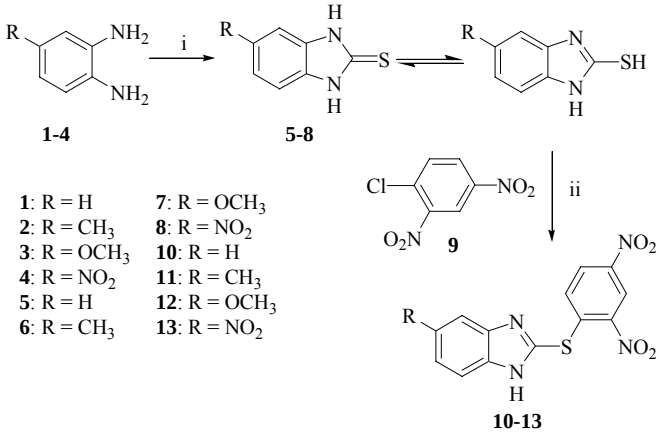
Instrumentation

Melting points of the synthesized Mannich bases were determined with an electro thermal melting point apparatus (Seatal Scientific Ltd.) and are uncorrected. Q Pro-M microwave sample preparation system was used for microwave assisted reactions. Microwaves were generated by magnetron at a frequency of 2450 MHz having an output energy range of 100-500 W and a fiber optic sensor for temperature control. The reactions were monitored by thin layer chromatography (TLC) using silica gel-G coated Al-plates (0.5mm thickness, Merck) and spots were visualized by exposing dry plates to UV light or iodine vapour. Mannich bases were purified by column chromatography using suitable solvents mixture as eluant. IR spectra (υ in cm^{-1}) were recorded on FT-IR spectrometer using KBr pellets, ^1H NMR (δ in ppm) spectra were recorded on 200 MHz / 400 MHz instrument using $CDCl_3$ or DMSO-d_6 as the solvent, and mass spectra were acquired on a Jeol TMS D-300 spectrometer operating at 75 eV. The elemental analysis of compounds was performed, and the analytical data obtained was found to be in good agreement with the calculated values.

Synthesis

1*H*-Benzimidazole-2-thiols were prepared by refluxing respective o-phenylenediamine (1-4) with carbon disulphide in ethanol-water solution of sodium hydroxide (Allan Van *et al.*, 1963). The reaction between 2,4-dinitrochlorobenzene (9) and 5-(un)substituted-1*H*-benzimidazole-2-thiols (5-8) in presence of a base by conventional method and microwave induced method afforded 2-[(2,4-dinitrophenyl)sulphanyl]-5-(un)substituted-1*H*-benzimidazoles (10-13, Scheme-1).

Scheme-1



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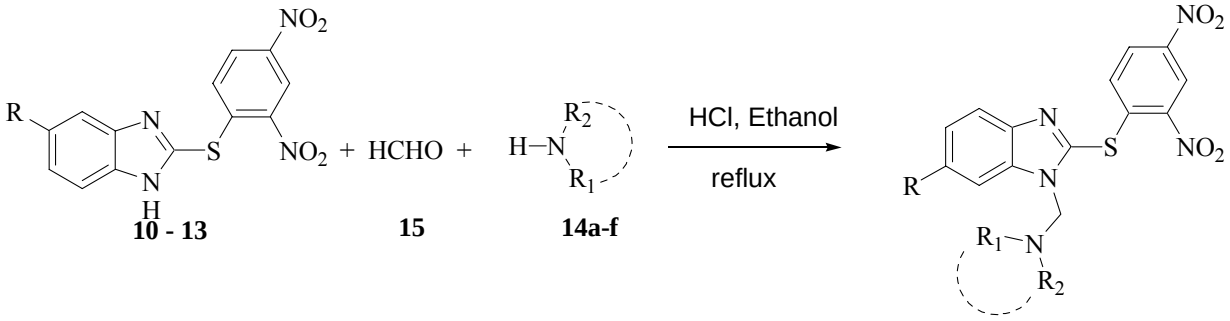
Reagents and conditions: (i) CS_2, NaOH, aq.ethanol, reflux (ii) a) conventional method: Ethanol, reflux, 3 h. b) microwave method: DMF, 2-5 min.

Mannich bases 16a-19f were prepared by the reaction of 10-13 with cyclic/acyclic secondary amines 14a-14f and paraformaldehyde (15) in presence of concentrated hydrochloric acid in alcohol [Scheme-2] (Mohan Rao and Vijaya Kumar 2012). All the synthesized compounds were characterized by elemental analysis, IR, NMR and Mass spectral data.

Scheme-2



10 - 13 **15** **14a-f** **16a - 19f**

16a: R = H, $R_1,R_2 = CH_3$
16b: R = H, $R_1,R_2 = C_2H_5$
16c: R = H, $R_1,R_2 = C_2H_4OH$
16d: R = H, R_1,R_2 = Morpholino
16e: R = H, R_1,R_2 = Pyrrolidino
16f: R = H, R_1,R_2 = Piperidino
17a: R = CH_3, $R_1,R_2 = CH_3$
17b: R = CH_3, $R_1,R_2 = C_2H_5$
17c: R = CH_3, $R_1,R_2 = C_2H_4OH$
17d: R = CH_3, R_1,R_2 = Morpholino
17e: R = CH_3, R_1,R_2 = Pyrrolidino
17f: R = CH_3, R_1,R_2 = Piperidino
18a: R = OCH_3, $R_1,R_2 = CH_3$
18b: R = OCH_3, $R_1,R_2 = C_2H_5$
18c: R = OCH_3, $R_1,R_2 = C_2H_4OH$
18d: R = OCH_3, R_1,R_2 = Morpholino
18e: R = OCH_3, R_1,R_2 = Pyrrolidino
18f: R = OCH_3, R_1,R_2 = Piperidino
19a: R = NO_2, $R_1,R_2 = CH_3$
19b: R = NO_2, $R_1,R_2 = C_2H_5$
19c: R = NO_2, $R_1,R_2 = C_2H_4OH$
19d: R = NO_2, R_1,R_2 = Morpholino
19e: R = NO_2, R_1,R_2 = Pyrrolidino
19f: R = NO_2, R_1,R_2 = Piperidino

PHARMACOLOGICAL ACTIVITIES

Analgesic activity: *In vivo* analgesic activity was carried out by adopting hot plate method (Eddy and Leimbrach 1953) in mice. The mice were placed on an Ugo basile hot plate maintained at 56 °C and the shaking or licking of the paws or jumping was recorded as the hot-plate latency. Swiss albino mice weighing 25-30 gm were used as experimental animals and the test compounds were administered orally in the dose of 100 mg/kg body weight. Pentazocine an analgesic drug was using as working standard. The results are resented in table 1. The reaction time for each individual compound was noted at the end of 30, 60, 90 and 180 min.

Anti-inflammatory activity: Anti-inflammatory activity of the compounds was determined following the technique described by Winter *et. al*., 1962. Swiss albino rats were used as test animals and the phlogistic agent was 0.1 ml of carrageenan suspension (1% carrageenan in Normal saline). A volume of 0.05 ml was injected through a 26 gauge needle into the plantar tissue of the right hind paw of rat. The volume of injected foot was immediately measured by an electronic differentiometer (Mac-lab, Bombay). An oral dose test compounds was fed to the animal in the form suspension using 4% gum acacia in a single dose of 100 mg/kg body weight of the animal. Diclofenac sodium was used as standard anti-inflammatory drug. Carrageenan administration results in inflammation and the effect were measured in 30, 60, 120 and 180 min intervals.

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The percent inhibition of edema between control group and treated group was calculated in comparison with group receiving standard drug using the formula,

$$\text{Percent inhibition of edema} = 100[1-V_t/V_c]$$

Where V_t = volume of paw of the treated animal

V_c = volume of paw of control animal

RESULTS AND DISCUSSION

Pharmacological Activity

Analgesic activity: Examination of Table 1 shows compound 18e exhibited highest analgesic activity and it has transcended the standard drug pentazocine in its action. Compounds 19d and 19f also exhibited marginally higher analgesic activity in comparison with standard drug. It is interesting to note that introducing the substituent at 6th position of benzimidazole nucleus in general contributed for attenuation of analgesic activity. It is observed that presence of electron releasing or withdrawing group on benzene ring of the benzimidazole nucleus did not make much impact on analgesic activity. However, compounds 18e, 19d and 19f showed higher activity in relation to unsubstituted benzimidazoles in benzene skeleton.

Out of six substituents incorporated at nitrogen of benzimidazole nucleus, three were acyclic and the remaining were N-heterocyclic substituents. Diethyl amino substituent was not considered keeping in view of similarity of alkyl side chain. Introduction of acyclic substituents on N^1 of benzimidazole had lesser impact on analgesic activity than heterocyclic amines.

Table 1. Analgesic activity of Mannich bases

Compound	Reaction time in seconds				
	Before	30 min	60 min	90 min	120 min
Control	5.98± 0.19	6.06± 0.18	5.98± 0.18	6.00± 0.18	6.07± 0.14
Pentazocine	6.03± 0.18	8.47±0.39	11.08±0.31	13.40±0.25	13.87±0.23***
16a	6.03±0.18	8.27±0.33	11.08± 0.31	11.48± 0.38	12.17± 0.35***
16c	6.02±0.24	8.27±0.33	11.02±0.24	11.55±0.41	11.50±0.37***
16d	6.05±0.16	8.25±0.19	11.12±0.34	11.78±0.70	11.82±0.21***
16e	6.10±0.11	8.52±0.23	11.08±0.31	12.32±0.39	12.82±0.50***
16f	6.07±0.12	8.40±0.36	11.12±0.31	12.18±0.44	12.78±0.50***
17a	6.08± 0.13	8.25±0.19	11.22 ±0.15	12.35±0.21	12.85±0.33***
17c	6.03±0.18	8.20±0.18	11.10±0.34	11.80±0.31	12.13±0.18***
17d	6.08±0.20	8.30±0.17	11.17±0.39	12.32±0.36	12.92±0.43***
17e	6.07±0.20	8.65±0.31	11.50±0.28	12.27±0.39	13.00±0.26***
17f	6.08±0.20	8.23±0.30	11.07±0.33	12.27±0.45	12.95±0.39***
18a	6.08±0.15	8.45±0.29	11.22±0.30	13.25±0.19	13.28±0.26***
18c	6.08±0.16	8.45± 0.23	11.45±0.26	12.77±0.34	12.78±0.36***
18d	6.13±0.14	8.27±0.33	11.42±0.34	12.97±0.44	13.32±0.42***
18e	6.10±0.13	8.40±0.36	11.53±0.15	13.67±0.28	**14.10±0.09*** **
18f	6.07±0.12	8.43±0.25	11.42±0.15	13.17±0.22	13.60±0.38***
19a	6.07±0.12	8.45± 0.31	11.08± 0.31	13.03± 0.36	13.30±0.21***
19c	6.15±0.12	8.27±0.33	11.25±0.22	12.97±0.37	13.08±0.31***
19d	6.03±0.05	8.30±0.34	11.08±0.31	13.32±0.26	**13.98±0.15*** **
19e	6.12±0.17	8.40±0.11	11.47±0.10	13.23±0.15	13.80±0.15***
19f	6.10±0.11	8.32±0.30	11.15±0.36	13.30±0.17	**13.92±0.23*** **

One-way Analysis of Variance (ANOVA); Values are Mean ± SD (n=6); *** P<0.001

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Among heterocyclic amines, methoxy benzimidazole having pyrrolidino substituent exhibited highest activity followed by nitrobenzimidazole with morpholino and piperidino substituents. It is in general observed that analgesic response gradually increased 30 to 120 min and reached peak at the end of 120 min in all the compounds. Any P value lesser than 0.001 is considered as extremely significant and values between 0.001-0.05 are significant whereas greater than 0.05 are non-significant. It is observed that irrespective of the nature of the substituents on the aromatic ring or N1 nitrogen on benzimidazole ring all the compounds were extremely significant in their analgesic activity. It is therefore concluded that dinitro phenyl sulphanyl substituent with benzimidazole skeleton is an important pharmacophore for showing analgesic activity.

Anti-inflammatory activity: All the compounds that were screened for analgesic activity were also screened for anti inflammatory activity. Perusal of Table 2 presents the anti inflammatory activity of Mannich bases. The results at glance show that the anti inflammatory activity of the compounds is as promising as that of the analgesic activity. Of all the tested compounds 16c, has shown the least percent inhibition followed by 17a. Benzimidazole nucleus having no substituent at 6th position was inferior in its activity in comparison with other substituents. Most of the molecules under investigation have shown 85-91 percentage of inhibition in comparison with standard drug diclofenac sodium. Variation of substituent in the aromatic ring did not produce notable change in percent inhibition but un-substituted benzimidazoles in aromatic nucleus were in general inferior. Compound 18e that bears an electron releasing methoxy substituent and pyrrolidino substituent at the nitrogen has shown comparable anti-inflammatory activity with standard drug. All the five compounds (19a-19f) containing electron withdrawing nitro substituent were more active than other substituents at 6th position.

Table 2. Anti-inflammatory activity of Mannich bases

Compound	Paw volume					Percent inhibition
	Before	30 min	60 min	120min	180 min	
Control	1.63±0.12	2.30±0.11	2.65±0.10	2.93±0.19	3.15±0.14	-
Diclofenac	1.63±0.12	1.82±0.10	1.78±0.08	1.77±0.05	1.70±0.09***	46.0
16a	1.62±0.10	2.33±0.10	2.50±0.13	2.63±0.12	2.87±0.12**	8.8
16c	1.62±0.13	2.10±0.11	2.35±0.12	2.58±0.12	2.97±0.24 ^{ns}	5.7
16d	1.67±0.08	1.87±0.08	1.85±0.05	1.85±0.05	1.85±0.05***	41.2
16e	1.67±0.12	1.90±0.09	1.98±0.15	1.92±0.08	1.82±0.08***	42.2
16f	1.68±0.15	1.90±0.09	1.92±0.08	1.82±0.04	1.80±0.13***	42.9
17a	1.67±0.10	2.37±0.23	2.52±0.15	2.75±0.10	2.92±0.17*	7.3
17c	1.62±0.13	2.32±0.12	2.50±0.23	2.50±0.21	2.38±0.15***	24.4
17d	1.67±0.12	2.15±0.19	2.08±0.08	2.05±0.05	1.90±0.09***	39.7
17e	1.68±0.12	2.07±0.12	2.02±0.12	2.00±0.11	1.90±0.06***	39.7
17f	1.65±0.10	1.83±0.10	1.82±0.12	1.80±0.09	1.82±0.08***	42.2
18a	1.65±0.14	2.30±0.14	2.23±0.08	2.22±0.19	2.15±0.15***	31.7
18c	1.65±0.10	2.13±0.12	2.13±0.21	2.20±0.22	2.25±0.23***	28.6
18d	1.67±0.12	2.07±0.12	2.02±0.15	2.00±0.18	1.92±0.12***	39.0
18e	1.67±0.12	2.02±0.12	1.95±0.05	1.93±0.12	1.78±0.10***	**43.5**
18f	1.67±0.12	2.00±0.14	1.98±0.08	1.97±0.08	1.80±0.09***	42.9
19a	1.67±0.12	2.13±0.14	2.17±0.08	2.02±0.10	2.00±0.09***	36.5
19c	1.68±0.15	2.12±0.15	2.13±0.14	2.07±0.16	2.05±0.16***	34.9
19d	1.65±0.14	2.07±0.08	1.97±0.14	1.85±0.10	1.82±0.10***	42.2
19e	1.65±0.10	2.03±0.16	2.00±0.18	1.93±0.10	1.80±0.09***	42.9
19f	1.67±0.12	2.08±0.12	2.00±0.18	1.98±0.15	1.80±0.09***	42.9

One-way Analysis of Variance (ANOVA)
Values are Mean ± SD (n=6); *** P<0.001; ** P<0.01; * P<0.05; ns P>0.05

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This in contrast with analgesic activity of the Mannich bases which did not discriminate the nature of substituent at 6th position of benzimidazole. It is therefore concluded that substituent present on the benzene nucleus was well tolerated with pyrrolidino substituent on N[1]nitrogen again establishing supremacy among the cyclic secondary amines.

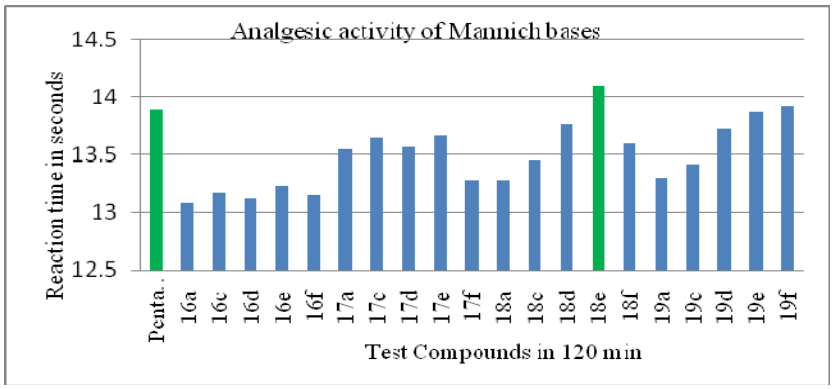

Figure 2. Analgesic activity of Mannich bases

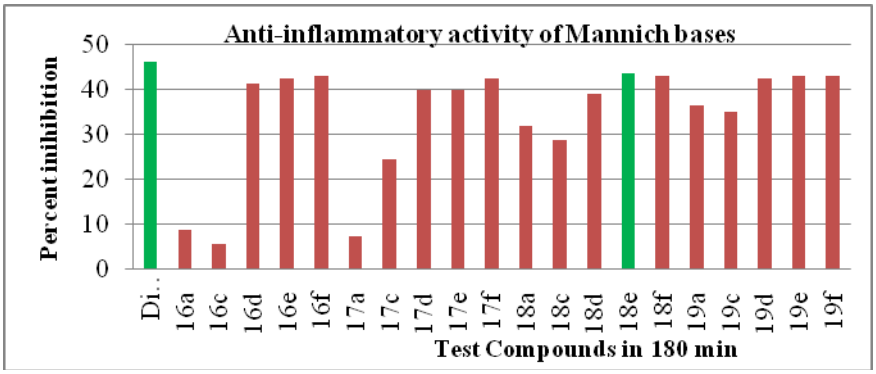

Figure 3. Anti-inflammatory activity of Mannich bases

CONCLUSION

2-[(2,4-dinitrophenyl)sulphanyl]-1*H*-benzimidazoles were synthesized using conventional and microwave induced methods. The microwave induced method offered significant improvement in yield with shorter reaction times. The *N*-Mannich bases synthesized were evaluated for analgesic and anti-inflammatory activity. *N*-Mannich bases 18e, 19d and 19f showed more analgesic activity (Figure 2) than the standard drug pentazocine and 18e emerged as a good anti-inflammatory (Figure 3) compound having above 90% activity in comparison with standard drug diclofenac sodium.

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