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RESEARCH ARTICLE

Antidepressant, Analgesic Activity and SAR Studies of Substituted Benzimidazoles

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ABSTRACT:

Purpose. Benzimidazole class of compound is found to have diverse biological properties. From the literature study, it is observed that depression is a severe mental disease affecting a huge population and pain is affecting about 20% of world population. In continuation of our previous research work, we selected benzimidazole pharmacophore to further explore its pharmacological activities. **Methods.** Forced swim test and Thermal stimulus test were used to assess the antidepressant and analgesic activity of synthesized benzimidazole analogs. **Results.** The antidepressant activity results showed that compound **3j** was found most potent having Mean ± SEM value 21.6 ± 0.8 for treated group. Furthermore, in the analgesic test, **3b, 3j,** and **3o** showed Mean ± SEM values; 1.8 ± 0.10, 2.3 ± 0.10 and 2.2 ± 0.10, respectively. The study results suggested that these compounds could be explored further for the development of better antidepressant and analgesic agents. **Conclusion.** From the present study, it may be concluded that these active benzimidazole derivatives have been found to possess potential antidepressant and analgesic activity.

KEY WORDS: Benzimidazole, Antidepressant, Analgesic, Structure activity relationship, Log P.

INTRODUCTION:

In the past years, there has been substantial interest in the development and pharmacological activity of organic compounds possessing hetero aromatic moiety in its structure, such as benzimidazole [1,2]. Structurally, benzimidazole core contains two aromatic *N*-heterocycles that can bind to enzymes or receptors via hydrogen bonds coordinated with metal ions or hydrophobic interactions [3]. Classically, benzimidazoles have been synthesized by the

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condensation of o-phenylenediamine with organic acids or their analogs (nitriles, imidates, or orthoesters). However, benzimidazoles can be synthesized under oxidative cyclization by the cyclocondensation of o-phenylenediamine with the corresponding aldehyde [4]. Benzimidazoles exhibit various pharmacological activities such as antiparasitic, anticancer, antihistaminic, antihypertensive and antiulcer [5]. Benzimidazole has structural similarity to purine, and its analogs could compete with purines [6]. Many benzimidazoles-containing drugs such as thiabendazole (antiparasitic), norastemizole (antihistaminic), telmisartan (antihypertensive) and omeprazole (antiulcer) are used widely to treat the said ailments [7, 8].

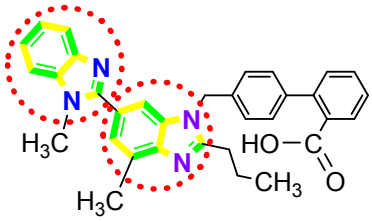
Depression is a state of low mood and the disinclination of activity having a negative effect on a person's psychology, behavior, feelings, world view and physical well-being. According to World Health Organization data depression will be the second most disabling condition in the world by the year 2020 [9]. The major antidepressant drugs include: tricyclics, monoamine oxidase (MAO) inhibitors, selective serotonin re-uptake inhibitors, selective noradrenaline reuptake inhibitors, serotonin modulators and norepinephrine serotonin modulators [10].

Pain is an unpleasant sensation resulting from a harmful sensory stimulation that alerts the body about current or potential spoil to its tissues and organs [11]. Current analgesic medications include opioids, non-steroidal anti-inflammatory drugs (NSAID's) and analgesic adjuvants [12]. A number of new analgesics have been introduced to the market to combat the challenge in the treatment of pain like transient receptor potential vanilloid type 1 (TRPV 1) channel, cannabinoid CB_2 receptors, fatty acid amide hydrolase (FAAH) inhibitors, $GABA_A$ subtype receptors and imidazoline I_2 receptors. These analgesic drugs either provide unsatisfactory pain relief or result in dangerous side-effects [13]. From the literature study, it can be concluded that benzimidazoles act on various therapeutic targets such as cyclooxygenase (COX) enzyme, transient receptor potential vanilloid-1 (TRPV-1) ion channels, cannabinoid receptors, bradykinin receptors, specific cytokines and 5-lipoxygenase activating protein (FLAP) etc [14]. The above-mentioned facts, prompt us to develop the new structural prototype of benzimidazoles for more effective and safer antidepressant and analgesic agents.

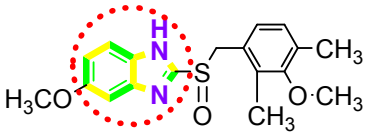
We have earlier reported the anticonvulsant and toxicity evaluation of the newer 1-{(1-(2-substituted benzyl)-1*H*-benzo[*d*]imidazol-2-yl)methyl}-3-arylthioureas [15]. Inspired by the above- mentioned facts, we report herein the antidepressant and analgesic activity of these derivatives. Some of the benzimidazole-containing marketed drugs are shown here (Figure 1).

Thiabendazole (Antiparasitic)

Norastemizole (Antihistaminic)



Telmisartan (Antihypertensive)



Omeprazole (Antiulcer)

Figure 1. Structure of benzimidazole containing marketed drugs

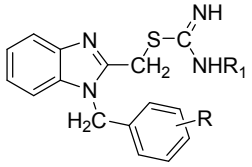
METHODS:

The synthesized benzimidazole analogs (Table 1) were tested for their antidepressant and analgesic activity on Swiss albino mice (20-25 g) of either sex. All the animals used in the experiment were issued by the Central Animal House Facility, Jamia Hamdard, and all the methods used during the experiment were approved by the Institutional Animal Ethics Committee Form no. 502 (173/CPCSEA, 28th Jan-2000). The animals were kept under standard laboratory conditions (12 h light-dark cycles); at an ambient temperature of 25 ± 2^0C and relative humidity 50–60% in groups of six. They were allowed free access to food (standard laboratory pellets) and top water three days prior to the experiment.

Antidepressant Screening

The test compounds were screened by the method described by Porsolt et al. [16]. Albino mice were placed in a chamber (20 cm height; 45 cm in diameter) containing water up to a height of 15 cm maintained at 25 ± 2^0C. The compounds to be tested were dissolved in Tween 80 (0.2% w/v, 0.9% NaCl) and administrated by ip route (100 mg/kg) 30 minutes prior the test session. The period of immobility was measured during the 5-minute test session as passive floating without struggling, with only those movements that are necessary to keep its head above the surface of the water.

Table 1. Chemical structure and Log P of test compounds



Compound	R	R_1	[a]Log P; Found (calc.)
3b	H	2-$CH_3C_6H_5$	6.21(5.04)
3e	H	2-$OCH_3C_6H_5$	5.63(4.46)
3g	H	4-$OCH_3C_6H_5$	5.60(4.46)
3h	H	$C_{10}H_7$	6.70(5.71)
3j	2-Cl	2-$CH_3C_6H_5$	6.73(5.75)
3l	2-Cl	4-$CH_3C_6H_5$	6.68(5.75)
3m	2-Cl	2-$OCH_3C_6H_5$	6.00(5.17)
3o	2-Cl	4-$OCH_3C_6H_5$	5.57(5.17)
3p	2-Cl	$C_{10}H_7$	7.12(6.42)

[a]Log P was determined by octanol: phosphate buffer method; Log P was calculated using software ChemDraw Ultra 8.0.

Analgesic Screening

The synthesized compounds were screened for their analgesic activity by the Thermal stimulus technique [17, 18] using mice. The animals were used in groups of 6 each and kept under standard laboratory conditions. Each compound to be tested was administered orally (20 mg/kg) in the methyl cellulose-water (0.5% w/v) mixture. The tail of mouse was gently dipped in thermostatically controlled water maintained at 55^0C and the analgesic activity was assessed after 4 h interval of administration of the test drug. The end point observed was the time that elapsed between immersion and the attempt to withdraw the tail from hot water for control group as well as the treated group of animals.

RESULT:

Antidepressant Screening:

Compounds (**3b, 3e, 3g, 3h, 3j, 3l, 3m, 3o,** and **3p**) were tested for antidepressant activity against the standard fluoxetine at the dose level of 30 mg/kg. Antidepressant activity was reported as mean average immobility time in seconds. The data was analyzed by using students 't' test and presented as Mean ± SEM data against the individual untreated controls with the treated compounds. Compound **3j** showed an extremely significant decrease in the immobility time (Table 2) and was found potent with Mean ± SEM value 21.6 ± 0.8 comparable to Fluoxetine (23.7 ± 1.1) with extremely significance level ($p < 0.001$). The compounds **3g** and **3m** were also found active with Mean ± SEM values 18.2 ± 0.4 and 23.4 ± 0.6; respectively with high significance level ($p < 0.001$). Moreover, compounds **3e, 3l,** and **3p** also showed activity with Mean ± SEM values 36.4 ± 1.2, 30.5 ± 1.1, and 32.6 ± 1.2; respectively with significance level having value ($p < 0.05$). The change in the immobility time was found non-significant with other compounds.

Table 2- Antidepressant activity of the compounds

Compound	Mean average immobility time (s)[a] Mean ± SEM	
	Control	Treated
3b	38.4 ± 1.1	36.9 ± 1.3
3e	32.6 ± 0.8	36.4 ± 1.2*
3g	42.7 ± 1.0	18.2 ± 0.4**
3h	41.5 ± 0.9	38.8 ± 0.6
3j	30.6 ± 0.9	21.6 ± 0.8***
3l	35.6 ± 0.9	30.5 ± 1.1*
3m	28.6 ± 1.1	23.4 ± 0.6**
3o	42.8 ± 1.3	40.4 ± 1.2
3p	37.5 ± 0.8	32.6 ± 1.2*
Fluoxetine	42.5 ± 1.3	23.7 ± 1.1***

[a]Dose = 30 mg/kg (p.o.); *p < 0.05, **p < 0.01, ***p < 0.001; Data was analyzed by unpaired students 't' test.

Analgesic Screening:

The analgesic study was done on compounds (**3b, 3e, 3g, 3h, 3j, 3l, 3m, 3o,** and **3p**) against the standard drug diclofenac. The readings were noted as mean average reaction time in seconds. The data was presented as Mean ± SEM and the readings were analyzed by students't' test against the individual untreated controls

with the treated compounds. Among the tested compounds, **3b, 3j,** and **3o** were found to be most active analgesics with Mean ± SEM values 1.8 ± 0.10, 2.3 ± 0.10 and 2.2 ± 0.10; respectively with highly significant ($p < 0.01$) level. The compound **3e** was found active with Mean ± SEM value 1.1 ± 0.10 and found to be significant ($p < 0.05$). Increase in the reaction time due to other compounds was found to be non-significant (Table 3).

Table 3 - Analgesic activity of the compounds

Compound	Mean average immobility time (s)[a]	
	Mean ± SEM	
	Control	Treated
3b	1.3 ± 0.10	1.8 ± 0.10**
3e	0.8 ± 0.10	1.1 ± 0.10*
3g	1.3 ± 0.10	1.3 ± 0.15
3h	1.2 ± 0.10	1.3 ± 0.21
3j	1.6 ± 0.15	2.3 ± 0.10**
3l	0.8 ± 0.10	1.0 ± 0.10
3m	1.2 ± 0.06	1.4 ± 0.10
3o	1.8 ± 0.10	2.2 ± 0.10**
3p	1.1 ± 0.06	1.3 ± 0.15
Diclofenac	1.4 ± 0.06	4.7 ± 0.10***

[a]Dose = 20 mg/kg (p.o); *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; Data was analyzed by unpaired students't' test.

LIPOPHILICITY DETERMINATION:

Drugs acting on the central nervous system have to cross the blood-brain barrier (BBB) in order to show potency, therefore, the therapeutic effect of such drugs has to be correlated with optimum Log P which is near 2. Theoretical Log P was calculated by using the software ChemOffice 6.0 (Table 1). The experimental Log P values were determined between octanol and phosphate buffer at room temperature [19]. The theoretical Log P values were compared with experimental values. In our determination, the calculated Log P values were correlated with CNS activity of the titled compounds, showing dependence on biological activity. It was observed that all the compounds are lipophilic in nature; some of the values obtained from the experiment were found to be in good agreement with the theoretical value.

STRUCTURE-ACTIVITY RELATIONSHIP:

The structure-activity relationship study (Figure 2) showed that the chloro group at the second position of benzyl ring with 2-methyl phenyl substitution at arylthioureas was found responsible for enhancing the antidepressant potential. In the analgesic study, it was found that the unsubstitution or the chloro substitution at the second position of benzyl ring and 2-methyl phenyl substitution at arylthioureas as well as the chloro substitution at the second position of benzyl ring with 4-methoxy phenyl substitution at arylthioureas were enhancing the analgesic potential.

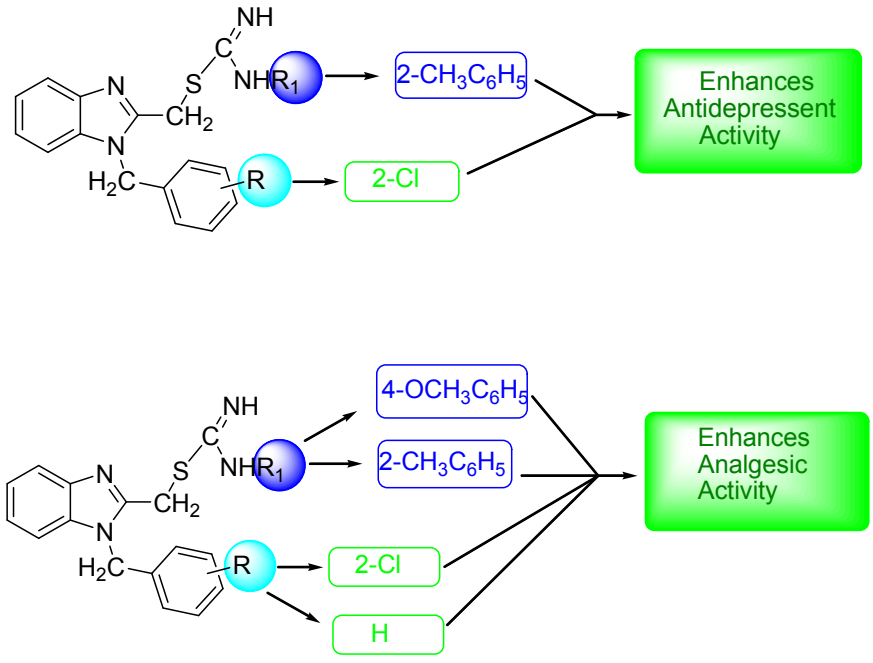


Figure 2. Structure-activity relationship study of the potent compounds

DISCUSSION:

Selected entries from benzimidazole series were evaluated for their antidepressant and analgesic activities. Compounds **3b, 3j,** and **3o** were found to possess better CNS activity against standard drugs. These compounds were found worthy of further investigations aimed at assessing their CNS activity. Currently, investigations are going on in our laboratory in order to improve these findings by creating new selective and potent molecules. Our findings will have a good impact on chemists and biologists for further investigation in search of benzimidazole derived analgesics and antidepressants. Further studies are also required to establish their mechanism of action.

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