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Analgesic and antidepressant activities of benzothiazole-benzamides

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ABSTRACT

Various benzothiazole-benzamides synthesized were evaluated for their analgesic and antidepressant activities. Interestingly, all the compounds showed promising activities against the two screenings. Some displayed highly significant activities when compared to the standard.

Key words: Analgesic, antidepressant activities of benzothiazole-benzamides.

INTRODUCTION

Benzothiazole derivatives in recent years have acquired conspicuous significance due to their wide spectrum of biological activities including anticonvulsant, analgesic, and antidepressant activities.[1,2] Benzamides on the other hand had also been found to show a wide range of pharmacological activities such as anticonvulsant[3], anti-inflammatory[4], analgesic[5], and antidepressant activity[6].

The present series was designed previously by combining the two pharmacologically active pharmacophores to get benzothiazole-benzamide derivatives and their anticonvulsant activity of them has been reported[7].

Since the results were found very encouraging, we intended to test these compounds for other pharmacological activities. This paper presents the analgesic and antidepressant activities of the synthesized benzothiazole-benzamides (Fig. 1).

MATERIAL AND METHODS

Analgesic activity

The analgesic activity was assessed by using Thermal stimulus technique[8]. The investigations were done on albino mice in groups of 6 each which were kept under standard laboratory conditions. The test compounds were suspended in methyl cellulose-water (0.5 %) mixture. Each compound was administered orally at a dose of 20 mg/kg. The analgesic activity was assessed after 4 h interval of the administration. Tail of each mice was gently immersed into thermostatically controlled water at 55 °C. The parameter measured in test samples was time that elapsed between immersion and the attempt to withdraw the tail from hot water for control as well as treated group of animals.

Antidepressant activity

The antidepressant activity was studied on albino rats of either sex (110-140 g) in group of 6 each by forced swimming test/despair swim test.[9] The forced swimming test consisted of placing rats,

individually in plexiglass cylinders (40 cm high, 20 cm in diameter) containing water (24-26 °C, 30 cm deep) for two swimming sessions: an initial 15 min training session, which was followed 24 h later, by a 5 min test session after 1 h of drug administration, the animals were removed from the cylinder dried with paper towels, placed in an individual cage to rest and recover for 15 min and was noted. Immobility time is the time spent by rat floating in water without struggling, making those movements necessary to keep the head above the water.

RESULTS AND DISCUSSION

Computational parameters

Various computational parameters were calculated by using software ACD labs version 8.0 and the values are presented in Table 1. All the values were found to be in acceptable range. Fig 2 depicts the 3D optimized general structure of the synthesized compounds.

Analgesic activity

All the compounds showed promising

Table 1: Computational data of compounds (1-6)

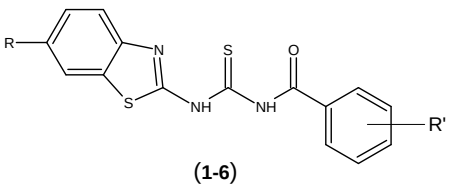
Compound	[a]Molar Refractivity (cm^3)	[b]Molar Volume (cm^3)	[c]Index of Refraction	[d]Surface Tension (dyne/cm)	[e]Density (g/cm^3)	[f]Polarizability (cm^3)
1	90.65	219.6	1.763	76.4	1.508	35.93
2	100.23	243.5	1.790	80.1	1.752	40.93
3	95.55	231.5	1.762	76.6	1.579	37.87
4	100.24	243.5	1.790	80.1	1.752	40.93
5	95.55	231.5	1.762	76.6	1.579	37.83
6	104.02	263.4	1.719	67.7	1.417	41.23

All properties are calculated from ACD labs version 8.0.[a]Molar refractivity within ± 0.3 cm^3 range; [b]Molar volume within ± 0.3 cm^3 range; [c]Index of refraction within ± 0.02 range; [d]Surface tension within ± 0.3 dyne/cm range; [e]Density within ± 0.06g/ cm^3 range; [f]Polarizabilty within ± 0.5 × 10^{-24} cm^3 range.

Table 2: Analgesic and antidepressant activities of compounds (1-6)

Compound	Analgesic activity[a] Mean ± SEM[c]		Antidepressant activity[b] Mean ± SEM[d]	
	Control	Treated	Control	Treated
1	11 ± 1.40	19.0 ± 1.840**	34.4 ± 1.490	24.0 ± 1.640
2	2.9 ± 0.341	4.4 ± 0.461**	42.0 ± 1.267	22.6 ± 1.002***
3	3.6 ± 0.477	7.7 ± 0.470***	34.6 ± 1.670	25.0 ± 1.433*
4	2.2 ± 0.177	5.4 ± 0.481***	48.2 ± 2.504	38.0 ± 2.378**
5	2.7 ± 0.524	6.1 ± 0.663**	39.8 ± 1.332	24.6 ± 1.484**
6	2.7 ± 0.521	6.8 ± 0.660**	23.2 ± 0.827	16.8 ± 0.942***
Diclofenac	1.8 ± 0.20	19.6 ± 0.890***	-	-
Fluoxetine		-	193.6 ± 0.640	24.2 ± 4.99***

n = 6; [a]Dose = 20 mg/kg (p.o.); [b]Dose = 30 mg/kg (p.o.) [c]Mean average reaction time (sec.); [d]Mean average immobility time (sec). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Data was analyzed by student's unpaired 't' test.



(1-6)

	R	R'
1	F	H
2	Br	2-Cl
3	F	2-Cl
4	Br	4-Cl
5	F	4-Cl
6	OCH_3	4-OCH_3

Fig. 1: General structure for the synthesized compounds (1-6)

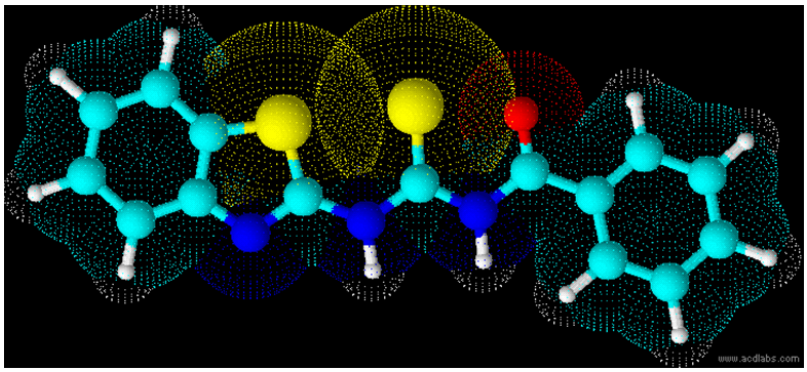


Fig. 2: Three dimensional optimized general structure of the synthesized *N*-(6-substituted-1,3-benzothiazol-2-ylcarbamothioyl)-2/4-substituted benzamides (1-6)

analgesic activity when tested and compared with the standard drug diclofenac and the results are presented in Table 2. Compounds 3 and 4 were found to be highly potent with $p < 0.001$, whereas, compounds 1, 2, 5 and 6 showed significant analgesic activity with $p < 0.01$.

Antidepressant activity

Antidepressant activity of all the titled compounds was evaluated and the results are shown in Table 2. Compounds 2 and 6 showed significant decrease in the immobility time and were found to be highly potent ($p < 0.001$) comparable with the standard drug fluoxetine. Compounds 4 and 5 were also found to be having significant antidepressant activity with $p < 0.01$. Results of the rest of the compounds were not significant.

CONCLUSION

A newer series of compounds were synthesized and evaluated as analgesics and antidepressant agents. Some compounds have shown encouraging activities and are needed to be investigated further to get better agents that can have strong future commitments.

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REFERENCES

1. Sawhney, S. N., Bhutani, S. and Dharamvir. "Synthesis of some 2-(2-benzothiazolyl) and 2-(2-benzimidazolyl)-6-aryl-4,5-dihydro-3(2*H*)-pyridazinones as potential anti-inflammatory agents." *Ind. J. Chem.* **26**B: 348-350 (1987).
2. Singh, S. P. and Vaid, R. K. “Synthesis and anti-inflammatory activity of some 2-(4’-butyl-3’,5’-dimethylpyrazol-1’yl)-6-substituted benzothiazoles and 4-butyl-1-(6’-substituted-2’-benzothiazolyl)-3-methylpyrazol-5-ones.” *Ind. J. Chem*. **25**B: 288-291 (1986).
3. Foster, J. E., Nicholson, J. M., Butcher, R., Stables, J. P. and Edafiogho, I. O. "Synthesis, characterization and anticonvulsant activity of enaminones part 6: Synthesis of substituted vinylic benzamides as potential anticonvulsants." *Bioorg. Med. Chem*. **7**: 2415-2425 (1999).
4. Caliendo, G., Santagada, V., Perissuti, E., Severino, B., Fiorino, F. and Warner, T. D. “Synthesis of substituted benzamides as anti-inflammatory agents that inhibit preferentially cyclooxygenase-I but do not cause gastric damage.” *Eur. J. Med. Chem*. **36**: 517-530 (2001).
5. Coats, S. J., Schulz, M. J., Carson, J. R., Codd, E. E. Hlasta, D. J. and Pitis, P. M. "Dax, Parellel methods for the preparation and SAR exploration of N-ethyl-4-[(8-alkyl)-8-aza-bicyclo[3.2.1]-oct-3-ylidene) aryl-methyl]-benzamides, powerful μ and Ä opioid agonists." *Bioorg. Med. Chem. Lett*. **14**: 2109-2112 (2004).
6. Sonda, S., Kawahara, T., Katayama, K., Sato, N. and Asano, K. "Synthesis and pharmacological evaluation of benzamide derivatives as selective 5-HT_4 receptor agonists." *Bioorg. Med. Chem*. **13**, 3295-3308 (2005).
7. Rana, A., Siddiqui, N., Khan, S. A., Haque, S. E. and Bhat, M. A. "N-{[(6-Substituted-1,3-benzothiazole-2-yl)amino]carbonothioyl}-2/4-substituted benzamides: synthesis and pharmacological evaluation." *Eur. J. Med. Chem*. **43**: 1114-1122 (2008).
8. Kendall, D. A., Browner, M. and Enna, S. J. “Comparison of antinociceptive effect og gamma-aminobutyric acid (GABA) agonists: evidence for a cholinergic involvement.” *J. Pharmacol. Exp. Ther*. **220**: 482-487 (1982).
9. Porsolt, R. D., Le Pichon, M., and Jalfre, M. "A new animal model sensitive to antidepressant treatments.” *Nature* **266**: 730-732 (1977).
10. Winter, C. A., Risley, E. A. and Nus, G. N. "Carrageenan induced edema in hind paw of the rat as an assay for anti-inflammatory drugs." *Proc. Soc. Exp. Biol*. **111**: 544-546 (1962).