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Synthesis and characterization and antifungal screening studies of some novel Imidazole derivatives

Ashok S R, Shivananda M K
Department of Studies & Research in Chemistry, Tumkur University, University College of Science, B H Road, Tumakuru, Karnataka, India.
*Corresponding author Email: shivanmk@yahoo.com

Abstract. Imidazole derivatives are five-mamboed heterocyclic having nitrogen, and oxygen atoms in their ring structure and exhibiting potent as well as wide range of pharmacological activities. Current investigations of imidazole derivatives have provided information that these derivatives may have applications in antimicrobial, antifungal, anti-viral, as well as antidiabitic treatments. Fen bam is an imidazole derivative developed by McNeil Laboratories in the late 1970s as a novel anxiolytic drug with an at-the-time-unidentified molecular target in the brain. The imidazole ring system is present in important biological building blocks such as histamine, and the related hormone histamine. Imidazole can serve as a base and as a weak acid. Many antifungal drugs such as nitroimidazole contain an imidazole ring. Thus, varied pharmacological activities of 2-amino-1-methyl-1H-imidazol-4(5H)-one derivatives have encouraged us to design and synthesize some of new class of heterocycles containing imidazolering and its derivatives. Different isomeric secondary amine containing bicyclical aromatic heterocyclic compounds were treated with 2-amino-1-methyl-1H-imidazol-4(5H)-one in presence of base by using DMF as solvent and HBTU as coupling agent to get target compounds. Pure target compounds were characterized by 1H NMR, 13C NMR and LC-MS. Some of the selected imidazole derivatives were screened for their antifungal activities.

1. Introduction

Hydration (1,3-imidazolidinedione) derivatives display diverse and interesting pharmacological properties. Several such derivatives (phonation, mephenythoin, norantoin, methetoin, ethotoin,fosphenytoin) are well-known anticonvulsive drugs [1,2]. Other 5-substituted hydrations like 5,5-dithienylhydantoin, 5,5-dipyridylhydantoin, spirothiohydantoin, thiohydantoin and dithiohydantoins also possess anticonvulsive activity [3]. Hydration derivatives can also be found as antiarrhythmics (azimilide), antimicrobial agents (nitrofurantoin), skeletal muscle relaxants (dantrolene) and no steroidal ant androgens (nilutamide), while allantoin is used as a keratolytic, astringent, wound remedy, antacid and ant psoriatic drug [2]. Hydantoins also exhibit antidepressant, antiviral and antithrombotic activities, as well as inhibitory activity against some enzymes (human aldose reductase and human leucocyte elastase) [4]. Finally, some herbicides (spirohydantoin, thioxohydantocidin), fungicides (clodantoin) and insecticides also possess the hydantoin skeletons in their structures [5,6]. These observations prompted us to synthesize a series of novel imidazole derivatives in order to assess their antifungal activities. The results of such studies are reported in this paper.

Materials and Methods

Ten new Hydration (1,3-imidazolidinedione) derivatives (**IV**a-**IVj**) containing different substituent's were obtained *via* substituted urea (**II**) by treating R-aminoindan HCl(**I**) with amino acid HCl (IA). The compounds (II) were then treated with NaOH in aqueous MeOH to get compounds (**III)**, which were further reacted with different substituted alkyl chlorides in presence of base to get target compounds (**IV**)(**Scheme-1**). Their structures were confirmed by LC-MS,^{1}H- and ^{13}CNMR and mass spectral studies.

Results and Discussion

The structures of the newly synthesized compounds were deduced from the analysis of their ^{1}H NMR, ^{13}C-NMR and further confirmed by LC-MS analysis. The LC-MS data of the hydration derivatives are tabulated in (**Table 1**) showed characteristic mass with (M+1) and ($M+Na^{+}$). The chemical shifts in ^{1}H NMR, ^{13}C-NMR are in concordance with the proposed structures of the novel compounds and also consistent with previously described analogous hydantoin derivatives. Synthetic route for the synthesis of target compounds is shown in **scheme-1.**

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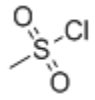
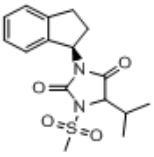
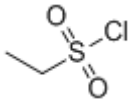
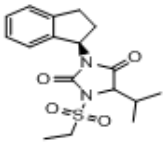
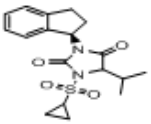
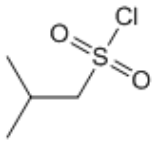
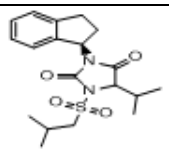
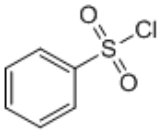
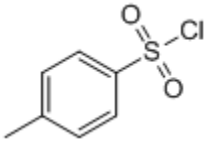
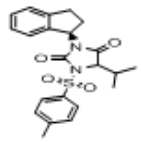
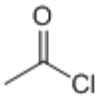
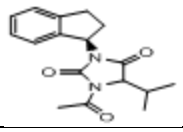
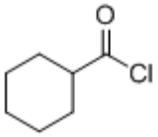
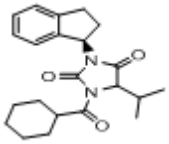
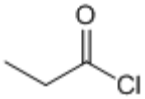
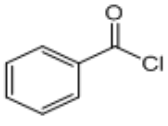
TABLE 1. Characterization data of 3-((R)-2,3-dihydro-1H-inden-1-yl)-5-isopropyl-1-(methylsulfonyl)imidazolidine-2,4-dione(IV)

Sl. No.	Product No.	Substrate	Product	Yield(%)	LCMS
1	IVa			78	359.10 ($M+Na^+$)
2	IVb			81.5	373.10 ($M+Na^+$)
3	IVc			75	385.10 ($M+Na^+$)
4	IVd			84	401.15 ($M+Na^+$)
5	IVe			82.5	421.10 ($M+Na^+$)
6	IVf			78.2	435.10 ($M+Na^+$)
7	IVg			72	301.10 (M+1)
8	IVh			84.5	369.15 (M+1)
9	IVi			91	315.15 (M+1)
10	IVj			82.1	385.15 ($M+Na^+$)

Biological activity studies: Biological activity performed at Community for open Antimicrobial Drug Discovery. (Study Number: P000215, Report Number : SC_0215_01). Primary antimicrobial screening study was carried out by the whole cell growth inhibition assays, using the provided samples at a single concentration, in duplicate (n=2). The inhibition of growth is measured against two fungi, viz., *Candida albicans* and *Cryptococcus neoformans*. Fluconazole was used as the standard drug for comparison.

Antifungal Assay: Procedure Fungi strains were cultured for 3 days on Yeast Extract-Peptone Dextrose (YPD) agar at 30 °C. A yeast suspension of 1 x 106 to 5 x 106 cells/mL (as determined by OD530) was prepared from five colonies. These stock suspensions were diluted with Yeast Nitrogen Base (YNB) broth to a final concentration of 2.5 ×103 CFU/mL. Then, 45 µL of the fungi suspension was added to each well of the compound-containing plates, giving a final concentration of **32 µg/mL** for the tested samples. Plates were covered and incubated at 35 °C for 24 h without shaking. The growth inhibition of *C. albicans* was determined measuring absorbance at 530 nm (OD530),while the growth inhibition of *C. neoformans* was determined measuring the difference in absorbance between 600 and 570 nm (OD600-570), after the addition of reassuring (0.001% final concentration) and incubation at 35 °C for additional 2 h. The absorbance was measured using a Biotek Synergy HTX plate reader. The percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control(fungi without inhibitors) on the same plate. The significance of the inhibition values was determined by Z-scores, calculated using the average and standard deviation of the sample wells (no controls) on the same plate. Samples with inhibition value above 80% and Z-Score above 2.5 for either replicate (n=2 on different plates) were classed as actives. Compounds (**IVa-IVj)** were screened for their antifungal activity and out of ten compounds tested, the compound **IVa** was found to be active for antifungal activity.

Experimental Procedure: All reagents and solvents are commercially available and are used without further purification. 1H NMR spectra were recorded in DMSO using Bruker NMR 300 MHz spectrometer and chemical shifts are reported in δ ppm relative to TMS.

General procedure for the synthesis of methyl 2-(3-((R)-2,3-dihydro-1H-inden-1-yl)ureido)-3-methylbutanoate (II): In a 500mL three neck RB flask, THF (100mL) and R-aminoindan hydrochloride (I) (10g, 0.058mol) kept stirring for 10minutes at 25-35^{o}C. TEA (11.9g, 0.118mol) was added to reaction mass. Stirred the reaction mass for 15mins at 25-35^{o}C. CDI (11.2g, 0.069mol), HOBt (7.6g, 0.058mol) added and stirred the reaction mass for 60 minutes at 25-35^{o}C. Ethyl 2-amino-3-methylbutanoate (IA) (12.6g, 0.087mol) was added slowly along with TEA (11.9g, 0.118mol) and stirred the reaction mass for 4 hours at 25-35^{o}C. The completion of reaction was monitored by TLC. After completion of the reaction, D M water (150ml) added slowly to the reaction mass under stirring and stirred the slurry mass for 30minutes. Off white solid material filtered, washed with 50ml of D M water and dried for 30 minutes. Wet material dried under vacuum for 6 hours at 60^{o}C. (Yield: 15.5g, 90.6%) ; ^{1}H NMR (DMSO-d$_6$) δ: 8.33-8.29 (br s, 1H, N-H), 7.28-7.18 (m, 4H, Ar-H), 6.43-6.40 (d, J= 9Hz, 1H N-H) 6.23-6.20 (d, J= 9Hz, 1H N-H), 5.12-5.04 (q, J = 9 Hz, 1H, -CH), 3.67 (s, 1H, -CH_3), 2.94-2.84 (m, 2H, -CH), 2.45-2.35 (m, 1H, -CH), 2.07-1.97 (m, 1H, -CH),1.73-1.60 (m, 1H, -CH) and 0.91-0.84 (dd, J = 9 Hz, 6H, -CH_3) ; ^{13}C-NMR δ: 173.65 (-*COOCH3*), 158.24 (-CONH); 145.22, 143.10, 127.77,126.77,124.97 and 124.23 (Aromatic C), 58.52 (-CCNH), 54.96 (-NHCCO), 52.03 (-OCH_3), 34.52 (-CCH_2CH_2CN), 30.83 (-CCH_3CH_3), 30.01 (-CCH_2CH_2CN) and 19.54, 18.29 (-CCH_3CH_3) ppm. LC-MS: 291.19 (M+1)

General procedure for the synthesis of 3-((R)-2, 3-dihydro-1H-inden-1-yl)-5-isopropyl imidazolidine-2,4-dione(III): In a 500 mL three neck RB flask, THF (100mL), MeOH (100mL), Purified water (20mL) and methyl 2-(3-((R)-2,3-dihydro-1H-inden-1-yl)ureido)-3-methylbutanoate(10g, 0.038mol) kept stirring for 10minutes at 25-35^{o}C. NaOH (6.19g, 0.154mol) was added to reaction mass. Stirred the reaction mass for90mins at 25-35^{o}C. The completion of reaction was monitored by TLC. After completion of the reaction, reaction mass pH adjusted to 4-5 using 10% HCl at 25-35^{o}C. D M water (100ml) added slowly to the reaction mass under stirring and stirred the slurry mass for 30minutes. Off white solid material was filtered, washed with 50ml of D M water and dried for 30minutes. Wet Material dried under vacuum for 6 hours at 60^{o}C. (Yield: 8.2g, 92.4%) ^{1}H NMR (DMSO-d$_6$) δ: 8.33-8.29 (br s, 1H, N-H), 7.27-6.99 (m, 4H, Ar-H), 5.52-5.45 (q, J = 6, 6 Hz, 1H, -CH), 3.98-3.96 (t, J = 3Hz, 1H, -CH), 3.16-3.06 (m, 1H, -CH), 2.93-2.83 (m, 1H, -CH), 2.38-2.28 (m, 2H, -CH), 2.10-1.97 (m, 1H, -CH), 0.98-0.92 (q, J = 6 Hz, 3H, -CH_3) and 0.85-0.73 (dd, J = 9, 9 Hz, 3H, -CH3); ^{13}C-NMR δ: 173.83-173.73 (-*NCOCH*), 157.37-157.11 (HNCONH), 143.83-143.77, 141.22-141.09, 128.03, 126.85-126.78, 125.08 and 123.29-123.21 (Aromatic C), 61.40-61.22 (-CCNH), 54.63-54.50 (-NHCCO), 30.90 (-CCH_2CH_2), 30.18-30.13 (-CCH_3CH_3), 28.93-28.86(-CH_2CH_2C), 18.96, 16.21-16.09 (-CCH_3CH_3)ppm. LC-MS: 259.10 (M+1)

General procedure for the synthesis of 3-((R)-2,3-dihydro-1H-inden-1-yl)-5-isopropyl-1-(methylsulfonyl)imidazolidine-2,4-diones (IVa-IVj): In a 500mL three neck RB flask, MDC (200mL) and 3-((R)-2, 3-dihydro-1H-inden-1-yl)-5-isopropylimidazolidine-2, 4-dione (1g, 0.0029mol) kept stirring for 10minutes at 2-10^{o}C. NaOH powder (0.29g, 0.00725mol) was added to reaction mass. Stirred the reaction mass for 15mins at 5-10^{o}C. R = Alkylsulfonyl, Arylsulfonyl, alkyl carbonyl and Aryl carbonyl added slowly to the reaction mass at 5-10 ^{o}C under nitrogen atmosphere and the reaction mass was stirred for 60 minutes at 5-10 ^{o}C. The completion of reaction was monitored by TLC. After reaction completion, reaction mass filtered through celite and the filtrate was washed with D M water (10ml). MDC layer concentrated under vacuum completely. Crude material was purified using column chromatography employing Stationary phase: Silica 60-120 mesh and Mobile Phase: Ethyl acetate: n-heptane.

3-((R)-2,3-dihydro-1H-inden-1-yl)-5-isopropyl-1-(methylsulfonyl)imidazolidine-2,4-dione (IVa): White crystalline powder, Yield = 78%**,** ^{1}H NMR (DMSO-d$_6$) δ: 7.28-7.07 (m, 4H, Ar-H), 5.65-5.54 (m, 1H, -CH), 4.60-4.55 (dd, J = 3Hz,

1H, -CH), 3.45 (s, 3H, -CH3), 3.37-3.11 (m, 1H, -CH), 2.97-2.87 (m, 1H, -CH), 2.44-2.30 (m, 3H, -CH), 1.16-1.04 (dd, J = 6, 6 Hz, 3H, $-CH_3$) and 0.93-0.80 (dd, J = 6, 6 Hz, 3H, $-CH_3$); ^{13}C-NMR δ: 169.78-169.68 (-*NCOCH*), 153.58-153.23 (HNCONH), 144.24-144.16, 139.77-139.67, 128.54-128.49, 127.05-126.89, 125.19-127.17 and 123.74-123.58 (Aromatic C), 65.89-65.48 (-CCNH), 55.83-55.43 (-NHCCO), 41.45-41.15 ($-SCH_3$), 31.05 ($-CCH_2CH_2$), 30.99-30.93 ($-CCH_3CH_3$), 28.69-28.63($-CH_2CH_2C$), 18.16-18.06, 15.62-15.52 ($-CCH_3CH_3$)ppm.LC-MS: 359.10 ($M+Na^+$).

3-((R)-2,3-dihydro-1H-inden-1-yl)-5-isopropyl-1-(ethylsulfonyl)imidazolidine-2,4-dione(IVa): hite crystalline powder, Yield = 81.5%**,** ^{1}H NMR (DMSO-d_6) δ: 7.28-7.07 (m, 4H, Ar-H), 5.65-5.54 (m, 1H, -CH), 4.60-4.55 (dd, J = 3Hz, 1H, -CH), 3.45 (s, 3H, $-CH_3$), 3.37-3.11 (m, 1H, -CH), 2.97-2.87 (m, 1H, -CH), 2.44-2.30 (m, 3H, -CH), 1.16-1.04 (dd, J = 6, 6 Hz, 3H, $-CH_3$) and 0.93-0.80 (dd, J = 6, 6 Hz, 3H, $-CH_3$); ^{13}C-NMR δ: 169.78-169.68 (-*NCOCH*), 153.58-153.23 (HNCONH), 144.24-144.16, 139.77-139.67, 128.54-128.49, 127.05-126.89, 125.19-127.17 and 123.74-123.58 (Aromatic C), 65.89-65.48 (-CCNH), 55.83-55.43 (-NHCCO), 41.45-41.15 ($-SCH_3$), 31.05 ($-CCH_2CH_2$), 30.99-30.93 ($-CCH_3CH_3$), 28.69-28.63($-CH_2CH_2C$), 18.16-18.06, 15.62-15.52 ($-CCH_3CH_3$)ppm.LC-MS: 359.10 ($M+Na^+$).

Conclusion

Ten new Hydantoin (1,3-imidazolidinedione) derivatives (**IV**a-**IVj**) were synthesized and their structures were confirmed by LC-MS,^{1}H- and ^{13}CNMR and mass spectral studies. The antifungal screening studies showed that the compound (**IVa)** was found to be active and hence needs further in depth pharmacological investigations.Acknowledgement: The authors acknowledge the Community for open Antimicrobial Drug Discovery for Antifungal screening studies of the compounds reported herein, Alkem Laboratories for analytical studies and Tumkur University, Tumakuru for the encouragement and providing necessary facilities to carry out research work.

References

[1]. Williams, D.A.; Lemke, T.L. Foye's Principles of Medicinal Chemistry, 5th ed.; Lippincott Williams & Wilkins: Philadelphia, **2002**.

[2]. Kleemann, A.; Engel, J.; Kutscher, B.; Reichert D. Pharmaceutical Substances, Synthesis, Patents, Applications, 4th ed.; Thieme: Stuttgart, **2001**.

[3]. Malawska, B. New anticonvulsant agents. Curr. Topics Med. Chem. **2005**, 5, 69-85.

[4]. Fiallo, M.M.L.; Kozlowski, H.; Garnier-Suillerot, A. Mitomycin antitumor compounds. Part 1. CD studies on their molecular structure. Eur. J. Pharm. Sci. **2001**, 12, 487-494.

[5]. Gregoriou, M.; Noble, M.E.M.; Watson, K.A.; Garman, E.F.; Krulle, T.M.; Delafuente, C.;Fleet,G.W.J.; Oikonomakos, N.G.; Johnson, L.N. The structure of a glycogen phosphorylase glucopyranose spirohydantoin complex at 1.8 angstrom resolution and 100 k – the role of the water structure and its contribution to binding. Protein Sci. **1998**, 7, 915-927.

[6]. Shiozaki, M. Syntheses of hydantocidin and C-2 thioxohydantocidin. Carbohyd. Res. **2002**, 337,2077-2088.

[7]. Iqbal Z, Ali S, Iqbal J, Abbas Q, Qureshi IZ. Dual action spirobicycloimidazolidine-2,4-diones: Antidiabetic agents and inhibitors of aldose reductase-an enzyme involved in diabetic complications.Bio & Med Chem Lett **2013**;23: 488.

[8]. Kurobuchi S. 2-Oxochromene derivatives. EP2248811B1, **2012; Nov 14**.

[9]. 19- Hsu ACT, Michelotti EL, Shaber SH. N-iodopropargyl hydantoin compounds, compositions, preparation, and use as antimicrobial agents, EP0572191A1,**1993; Dec 1**.

[10]. Porter RH; Jaeschke G; Spooren W; et al. (**November 2005**). "Fenobam: a clinically validated nonbenzodiazepine anxiolytic is a potent, selective, and noncompetitive mGlu5 receptor antagonist with inverse agonist activity". J. Pharmacol. Exp. Ther. **315** (2): 711–21. doi:10.1124/jpet.105.089839. PMID 16040814.

[11]. Marino, MJ; Conn, PJ (**2006**). "Glutamate-based therapeutic approaches: Allosteric modulators of metabotropic glutamate receptors". Current Opinion in Pharmacology. **6** (1): 98–102. doi:10.1016/j.coph.2005.09.006. PMID 16368268.

[12]. Wållberg, A; Nilsson, K; Osterlund, K; Peterson, A; Elg, S; Raboisson, P; Bauer, U; Hammerland, LG; Mattsson, JP (2006). "Phenyl ureas of creatinine as mGluR5 antagonists. A structure-activity relationship study of fenobam analogues". Bioorganic & Medicinal Chemistry Letters. **16** (5): 1142–5. doi:10.1016/j.bmcl.**2005.11.092**. PMID 16380255.

[13]. Ceccarelli, SM; Jaeschke, G; Buettelmann, B; Huwyler, J; Kolczewski, S; Peters, JU; Prinssen, E; Porter, R; et al. (**2007**). "Rational design, synthesis, and structure-activity relationship of benzoxazolones: New potent mglu5 receptor antagonists based on the fenobam structure". Bioorganic & Medicinal Chemistry Letters. **17** (5): 1302–6.doi:10.1016/j.bmcl.**2006.12**.006. PMID 17189691.

[14]. Jaeschke, G; Porter, R; Büttelmann, B; Ceccarelli, SM; Guba, W; Kuhn, B; Kolczewski, S; Huwyler, J; et al. (**2007**). "Synthesis and biological evaluation of fenobam analogs as mGlu5 receptor antagonists". Bioorganic & Medicinal Chemistry Letters. **17** (5): 1307–11. doi:10.1016/j.bmcl.**2006.12**.033. PMID 17196387.

[15]. Gichinga, Moses G.; Olson, Jeremy P.; Butala, Elizabeth; Navarro, Hernán A.; Gilmour, Brian P.; Mascarella, S. Wayne; Carroll, F. Ivy (**2011**). "Synthesis and Evaluation of Metabotropic Glutamate Receptor Subtype 5

Antagonists Based on Fenobam". ACS Medicinal Chemistry Letters. **2** (12): 882–884. doi:10.1021/ml200162f. PMC 3328804 .PMID 22523618.

[16]. Pecknold, JC; McClure, DJ; Appeltauer, L; Wrzesinski, L; Allan, T (**1982**). "Treatment of anxiety using fenobam (a nonbenzodiazepine) in a double-blind standard (diazepam) placebo-controlled study". Journal of Clinical Psychopharmacology.**2** (2): 129–33. doi:10.1097/00004714-198204000-00010. PMID 7042771.