Synergetic synthesis of Pyrrolo [2, 3-d] pyrimidine derivative

Bhaskar Pittala[1], Shashikala Kethireddy[2] and Laxminarayana Eppakayala[3*]

1. Nalla Narasimha Reddy Education Society's Group of Institutions (Autonomous), Chowdariguda, Ghatkesar, Hyderabad-500088.
2. Department of Chemistry, Geethanjali College of Engineering and Technology (Autonomous), Keesara, Rangareddy-501301 Telangana India
3. Department of Chemistry, Sreenidhi Institute of Science and Technology (Autonomous), Ghatkesar, Hyderabad-501 301 Telangana India.

Corresponding Author*

Laxminarayana Eppakayala
Department of Chemistry,
Sreenidhi Institute of Science and Technology (Autonomous),
Ghatkesar, Hyderabad-501 301, Telangana, India.

ABSTRACT

In the present study, presence of DIPEA, a combination of 2, 3-dihydro-1H-inden-2-amine and 4-chloro-2-methyl-7H-pyrrolo [2, 3-d] pyrimidine was transformed into Pyrrolo [2, 3-d] pyrimidine. The safety and convenience was carried out continuously at high temperatures is one of the key benefits of current research. The synthesis has produced good yields and they were identified using spectrum analysis.

Keywords: Synthesis, Heterocyclic compounds, Pyrimidine, Isatin derivatives and Medicinal chemistry.

INTRODUCTION

In medicinal chemistry, heterocyclic compounds with nitrogen are highly important, particularly pyrrolepyramidine derivatives. For the creation of brand-new pharmacological entities, the study of medicinal organic chemistry is fruitful. The field of medicinal chemistry makes use of the pyrrole pyrimidin-4-amine family of biologically active heterocyclics, which is well-known and distinctive and has a structural foundation for drug development. To combat this, new antimicrobial agents must be created. The indole fragment contains a large number of physiologically and pharmacologically active substances.

They have numerous biological activities[1,2] that need to be investigated in order to develop novel molecules with significant medicinal applications. There has been a lot of interest in the development of preparative techniques for making pyrrolepyramidine derivatives. The increasing emergence of multidrug resistance emphasises the urgent need for creating new potentially active antimicrobial agents notwithstanding the abundance of antimicrobial chemotherapeutics now accessible. Several isatin derivatives with substantial biological activities, Due to their biological and chemotherapeutic activities, pyrrolo[2,3-d]pyrimidine scaffolds are a significant draw among other heterocyclic-pyrimidine rings[3] and the large variety of pharmacologically active chemicals that may be synthesized in the lab and isolated from natural sources, fused pyrimidines are a significant family of heterocyclic chemistry that have been studied by medicinal chemists[4]. Because the pyrrolo [2, 3-d] pyrimidine rings resemble purines and pyrimidines, they are known to have a variety of biological activities, including those that inhibit enzymes[5], are antitumor[6] , antimicrobial[7],anticancer[8], antimalarial[9], antiinflammatory[10], antifolates [11], anti-HIV[12], cytotoxic[13], antiviral[14], antifungal[15] , antitubercular[16], antiallergic [17], and anticonvulsant[18], Also, the effectiveness of pyrrolo[2,3-d]pyrimidine derivatives as powerful drugs as inhibitors of the protein kinase Janus Kinase 3 is being thoroughly studied (JAK 3). Several similar chemicals have recently shown promise in the therapy of a variety of immunological diseases [19]. Several medications, including Ruxolitinib[20], Tofacitinib [20], Ribociclib[21], and Baricitinib [22], include pyrrolo[2,3-d]pyrimidine cores in their structures and have received FDA approval. These medications fight cancer by inhibiting tyrosine kinase. Similar to Pemetrexed, a chemotherapeutic agent used to treat non-small cell lung cancer and as an antifolate[23]. As newly employed fluorescent functional materials, however, pyrrolo [2, 3-d] pyrimidine analogues also exhibited high UV-blue fluorescence [24]. The clinical manifestations of BVDV infection can range from very mild symptoms that do not cause the animal to die to few or no symptoms at all. Infection with BVDV most frequently leads to respiratory and reproductive issues. Economically, reproductive diseases caused by BVDV may be the biggest issue. There is some evidence to support the idea that BVDV losses are rising globally. Diarrhea, decreased milk supply, reproductive issues, an increase in other diseases, and death are the losses brought on by transitory infection [25]. Several synthetic approaches have been established to prepare a number of the pyrrolo [2, 3-d] pyrimidine derivatives due to their wide spectrum of pharmacological relevance. These synthetic methods have been appropriately improved to produce compounds with various replacements, high yields, and greater purity. Bovine viral diarrhea is an infectious disease that affects cattle and other ruminants and is brought on by the virus that causes it (BVDV). The bovine viral diarrhoea virus's gene is expressed by the pestivirus through the translation of a fictitious polyprotein, which is then handled by

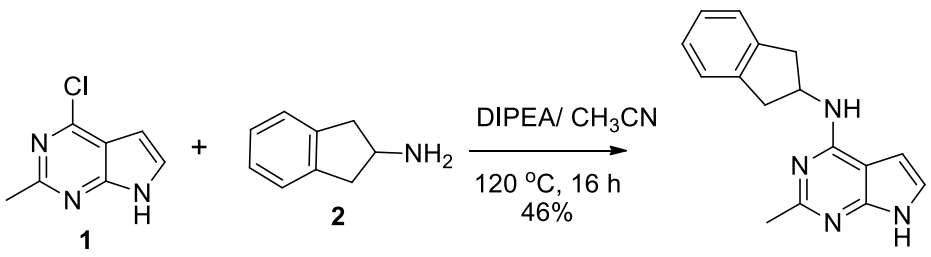
viral and cellular enzymes during cotranslation and posttranslational processing[26]. The cleavages, which result in the release of NS4A, NS4B, NS5A, and NS5B, are catalyzed by a protease found in the N-terminal region of the nonstructural (NS) protein NS3 [26].When creating pharmacologically effective molecules, p-bromobenzene and 2,4-dichloroaniline-containing heterocyclic compounds have drawn a lot of interest [27].

After a thorough analysis of the synthesis of pyrrolpyramidines, it was determined that there were potential to enhance the heterocyclic synthesis by using a new work-up procedure. This reaction is straightforward and low-cost. Following distillation, the solvents are put to new uses, and following efficient processing, we worked with pyrimidine derivatives and reported the novel derivatives. With active inden the reaction can be carried out with a high yield.

EXPERIMENTAL

Purchases were made from Fluka or Merck for chemicals and solvents. All of the chemicals used were analytical calibre. With PerkinElmer spectrum gx FTIR equipment, IR spectra were captured as KBr pellets, and only diagnostic and/or strong peaks are given. Individual 1H NMR spectra were recorded in DMSO-d6 using Varian equipment. The internal standard was provided by signals resulting from leftover protonated solvent. As an internal standard, tetramethylsilane was utilized, and all chemical changes were reported in parts per million (ppm).The 1H NMR chemical shifts and coupling constants were discovered to presumptively display first-order behavior. The order of multiplicity is determined by the list of coupling constants (J).A PE Sciex type API 3000 instrument has been used to record mass spectra. Every reaction was carried out in an argon atmosphere.

Synthesis



N-(2, 3-Dihydro-1H-inden-2-yl)-2-methyl-7H-pyrrolo [2, 3-d] pyrimidin-4-amine

Pyrimidine compound (1), inden amine compound (2), and DIPEA (0.012 MOLE) were mixed in 20 ML of acetonitrile and agitated at 80ºC for 16 hours. TLC began to observe the reaction. Following the completion of the reaction, the liquid was diluted with 3 mL of EtOAc in 100 mL of cold water. The mixed organic layers were concentrated under low stress, washed with water and brine, and yielded 1.8 g of crude product. The unfinished product was loaded onto a silica gel-packed column that measured 30 mm 30 cm in width and height and contained 50 g of 100-200 mesh silica gel after being absorbed on 5 g of this material.

50 percent EtOAc in puppy ether was used to complete the elution, which started with 20 percent EtOAc. All naturally occurring components were gathered and concentrated to produce 1.1 g. (46 percent).

1H NMR: (300 MHz in DMSO-d6): 2.40 (s,3H), 2.97-2.89 (dd, J1= 6.60 Hz, J2=15.9 Hz, 2H), 3.32-3.27 (m, 1H), 3.35 (s, 1H), 4.97-4.90 (m, 1H), 6.51-6.49 (m, 1H), 6.96-6.94 (t, J= 2.7 Hz, 1H), 7.18-7.13 (m, 2H), 7.26-7.21 (m, 2H),7.43-7.41 (d, J= 6.9 Hz ,1H),11.2 (s, 1H).

Mass Spectrocopy: (m/z = 265.0 [M+H] +). HPLC: 99.45% (254 nm) and 99.44% (215 nm).

IR spectrum: (NH) absorption bands appeared at 3434.62, cm-1.

RESULTS AND DISCUSSION

Synthesis details this newly developed chemical. Here, pyrimidine compound(1) is the starting material and is combined with inden amine compound(2) while being stirred at 80ºC for 16 hours while being exposed to DIPEA in acetonitrile. TLC started to watch the response. The liquid was diluted with 3 mL of EtOAc in 100 mL of cold water once the reaction was finished. Under mild stress, the mixed organic layers were concentrated, cleaned with water and brine, and produced 1.8 g of crude product. After being absorbed on 5 g of this substance, the incomplete product was transferred onto a column packed with silica gel that was 30 mm wide and 30 cm tall and contained 50 g of 100-200 mesh silica gel. After starting with 20 percent EtOAc, the elution was finished with 50 percent EtOAc in puppy ether. To create 1.1 g, all naturally occurring components were collected and condensed (46%). the end result is pyrrolopyramidine derivaties (3). This reaction's work-up procedure is easy and reasonably priced. Following distillation, the solvents are put to new uses.

The structure of the compound 3 was confirmed by IR, 1H NMR and mass spectra. In IR spectrum of 3, the (NH) absorption bands appeared at 3434.62, cm-1. The 1HNMR spectrum of the compound 3 showed signals in the range of 11.2 for (s, NH, 1H), 6.96-7.41 (m, 4H, Ar-H) for aromatic ring. The mass spectrum of the same compound 3a showed molecular ion peak at m/z 265 (M+).

CONCLUSION

As part of our ongoing work to create more adaptable, development of an eco-friendly, and efficient technique for the synthesis of heterocyclic compounds, we used a synthetic approach to create isatin. Many benefits of the above-described strategy include more selection, simplicity, and pollution-free settings. Combining all of the targeted Pyrrolo [2, 3-d] derivatives of pyrimidine. The above method has substantial benefits, such as higher selectivity, simplicity, catalyst-free reaction and environmental pollution free conditions over conventional methods. All the derivatives were examined by 1HNMR, IR and Mass spectral data.

REFERENCES

1. Kasa Shiva Raju , Sandeep AnkiReddy , Gowravaram Sabitha , Vagolu Siva Krishna , Dharmarajan Sriram , Kunduru Bharathi Reddy , Someswar Rao Sagurthi,,Bioorg Med Chem Lett; 29(2), 284-290,2019.
2. Jianqing Zhang , Pengqin Chen , Yongli Duan , Hehua Xiong , Hongmin Li , Yao Zeng, Guang Liang, Qidong Tang , Di Wu ;Eur J Med Chem, 215:113273,2021.
3. R. Glushkov, O. Sizova, Pharm. Chem. J. 20 (1986).
4. V.S. Dinakaran, B. Bomma, K.K. Srinivasan, Der Pharma Chem. 4 (2012) 255e265.
5. C.T. Supuran, A. Scozzafava, B.C. Jurca, M.A. Iiies, Eur. J. Med. Chem. 33 (1998).
6. A. Gangiee, S. Kurup, M.A. Ihnat, J.E. Thorpe, S.S. Shenoy, Bioorg. Med. Chem. 18 (2010).
7. S.M. Mosaad, K. Rehab, S.S. Fatahala, Eur. J. Med. Chem, 45 (2010).
8. K. Meenakshi, N. Chandra, M. Sarangapani, N. Raghunandan, N. Gopal. Der Pharmacia Letter, 7(7), 198-203 (2015).
9. P. Selvam, N. Murgesh, M. Chandramohan. E.D. Clercq, E. Keyaerts, L. Vijgen, P. Maes, J. Neyts, M.V. Ranst. Indian J Pharm Sci, 70(1), 91-94 (2008).
10. E. Fernandes, D. Costa, S.A. Toste, J. Lima, S. Reis, Free Radical Biol. Med. 37 (2004).
11. A. Gangjee, Y. Yeng, J.J. McGuire, F. Mehraein, R.L. Kisliuk, J. Med. Chem. 47 (2004).

12. T.R. Bal, B. Anand, P. Yogeeswari, D. Sriram. Bioorg Med Chem Lett, 15(20), 4451-4455 (2005).
13. R. Raj, C. Biot, S. Carrère-Kremer, L. Kremer, Y. Guérardel, J. Gut, P.J. Rosenthal, D. Forge, V. Kumar. Chem Biol Drug Design, 83(5), 622-629 (2014).
14. M. Kumar, B. Narasimhan, P. Kumar, K. Ramasamy, V. Mani, R.K. Mishra, A.B.A. Majeed. Arabian J Chem 7, 436-447 (2014).
15. M.S.A. El-Gaby, A.M. Gaber, A.A. Atalla, K.A. Abd Al-Wahab, Farmaco 57 (2002) 613e617
16. E.M. Flefel, H.S. Abbas, R.A. Mageid, W.A. Zaghary. Molecules, 21(1), 1-15 (2016).
17. S. Nagashima, T. Hondo, H. Nagata, T. Ogiyama, J. Maedo, et al., Bioorg. Med. Chem. 17 (2009) 6926.
18. C. R. Prakash, S. Raja, G. Saravanan, Int J Pharm Sci, 4,177-181 (2010).
19. M.P. Clark, K.M. George, R.G. Bookland, J. Chen, S.K. Laughlin, K.D. Thakur, Bioorg. Med. Chem. Lett 17 (2007).
20. P.K. Singh, H. Singh, O. Silakari, Biochim. Biophys. Acta Rev. Canc. 1866 (2016).
21. S.L. Sammons, D.L. Topping, K.L. Blackwell, Curr. Cancer Drug Targets, 17 (2017).
22. G.R. Burmester, J.W. Bijlsma, M. Cutolo, I.B. McInnes, Nat. Rev. Rheumatol. 13 (2017).
23. M. Hazarika, R.M. White, J.R. Johnson, R. Pazdur, FDA drug approval summaries: pemetrexed (Alimta®), Oncology, 9 (2004).
24. S. Tumkevicius, J. Dodonova, K. Kazlauskas, V. Masevicius, L. Skardziute, S. Jursenas, Tetrahedron Lett. 51 (2010).
25. J. Paeshuyse, J.-M. Chezal, M. Froeyen, P. Leyssen, et al., J. Virol. (2007).
26. N. Tautz, A. Kaiser, H.-J. Thiel, Virology, 273 (2000).
27. M.M. Ghorab, M. Ceruso, M.S. Alsaid, Y.M. Nissan, R.K. Arafa, C.T. Supuran, Eur. J. Med. Chem. 87 (2014).