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## AMALGAMATION AND CHARACTERIZATION OF UNUSED HETEROCYCLIC COMPOUNDS DETERMINED FROM 5-BROMO-2, 3-DI (FURAN-2-YL)-1H-INDOLE

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### ABSTRACT

Heterocyclic moiety serve as culminate system on which pharmacophores can be successfully joined to deliver novel drugs. Among different heterocyclic compounds, nitrogen-based heterocycles have been broadly explored as they constitute the center structures of various naturally significant atoms and have been found to be dynamic against distinctive sorts of cancers. Due to the flexibility of indole, it has been a profoundly “privileged motif” for the target-based plan and advancement of anticancer specialists. In addition, it has been utilized as a synthon for the arrangement of huge number of bioactive heterocycles and cleared a way to create successful targets. This survey article presents comprehensive diagram of anticancer possibility of differently substituted indole subsidiaries counting 1H-indole-2, 3-dione subsidiaries. Acid-catalyzed, three-component reaction (Biginelli synthesis) between 5-bromo-2, 3-di (furan-2-yl) 1H-indole, acetylacetone and semicarbazide, thiosemicarbazide, urea, thiourea, guanidine constitutes a rapid and facile synthesis of corresponding tetrahydropyrimidines, which are interesting compounds with a potential for pharmaceutical application.

### KEYWORDS

Heterocyclic compounds, Biginelli synthesis, Indole derivatives and Tetrahydropyrimidines.

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### INTRODUCTON

Heterocyclic compounds have paid hugely to the society within the shape of expansive number of drugs for the treatment of different afflictions and have involved a unmistakable put in restorative chemistry due to their varied biological activities<sup>1</sup>. Indole center has been ceaselessly pulling in the consideration of analysts and has gotten to be a energetic region of inquire about due to its exceptional pharmacological properties<sup>2</sup>. It is assigned as “privileged scaffolds” which tie to different receptors with tall liking, driving to the

advancement of novel bioactive drugs<sup>3</sup>. It is used for the target-based design and development of anticancer agents<sup>4</sup>. In this context, therapeutic effect of multi-target directed indole based hybrid molecules in cancer therapy is recently reviewed by<sup>5</sup>. Indole subsidiaries have been broadly utilized as synthons for the planning of huge number of organically significant heterocycles<sup>6</sup>. In addition, indoles are found in vital manufactured sedate atoms with curiously pharmacological properties like SARS coronavirus 3CL protease inhibitors<sup>7</sup>, anti-HIV movement<sup>8</sup>, antituberculosis activity<sup>9</sup>, anticonvulsant<sup>10</sup> and HIV-TB coinfection<sup>11</sup> including anti-cancer<sup>12</sup>. Indoles are too related with the hindrance of NFkB/mTOR/PI3K/AkT and control of estrogen-mediated action<sup>13</sup>. A few 3-substituted indole subordinates have been found to display surprising antineoplastic properties viz. Inhibition of cell proliferation of human colon carcinoma (HT-29), human ovarian adenocarcinoma (SK-OV-3) and c-Src kinase activity<sup>14</sup>. Together, 3-pyranyl indoles have appeared great anticancer action against MCF-7 breast cancer cell lines in comparison with measures drugs<sup>15</sup>. Biginelli In 1893, the synthesis of functionalized 3, 4-dihydropyrimidin-2(1H)-ones (DHPMs) scheme I via three-component condensation reaction of an aromatic aldehyde, urea and acetyl acetone was reported for the first time by P. Biginelli. Within the past decades, such Biginelli-type dihydropyrimidones have gotten a impressive sum of consideration due to the curiously pharmacological properties related with this heterocyclic plat form. One - pot synthesis may be a methodology to progress the productivity of a chemical response where by a reactant is subjected to progressive chemical responses in fair one reactor. His is often much wanted by chemists since maintaining a strategic distance from a long partition handle and refinement of the middle of the road chemical compounds would spare time and assets whereas expanding chemical abdicate. Numerous dihydropyrimidinones and their derivatives are pharmacologically<sup>16</sup> important as calcium channel blockers, antihypertensive agents and biological activities<sup>17</sup> also contain the

dihydropyrimidinone-5-carboxylate core. Therefore, many synthetic methods for preparing such compounds have been developed<sup>18</sup>.

## MATERIAL AND METHODS

All the chemicals and reagents were purchased from MERCK and Himedia fine chemical companies and are used without further purification. For all the synthesized compounds the melting points were determined in open capillaries and are uncorrected. Thin-layer chromatography (TLC) was used to control the reaction on silica gel 60 F254 aluminium sheets (MERCK). The mobile phase was chloroform and benzene. IR spectra are recorded in KBr on Perkin-Elmer and FTIR Spectrophotometer (cm-1) and 1H NMR spectra on BRUKER AVENE II 400 MHz NMR Spectrometer (Chemical shift in  $\delta$  ppm down field from TMS as an internal.

### Typical procedure of 1, 2-di (furan-2-yl)-2-hydroxyethanone (2)

A solution of sodium cyanide (2mmol, 0.098g) in H<sub>2</sub>O (2ml), was added to a stirred solution of a furfuraldehyde (10mmol) in EtOH (10ml). The mixture was then refluxed. Study the progress of reaction was done by examined TLC using hexane/ethyle acetate (80:20) as eluent. The evaporation technique was used to remove the solvent under reduced pressure. Then, washing with water and diethyl ether to take out residue. Yellow crystals, Yield: 56%, mp: 125-126 0C; FT-IR (KBr, Cm-1):

3420 (OH), 1646 (C=O), 1025(C- O); 1H NMR (DMSO-d<sub>6</sub>, ppm):  $\delta$  5.78 (d, 1H, OH), 5.89 (d, 1H, CH), 6.83 (d, 2H, furyl), 7.52 (d, 1H, furyl), 7.63 (d, 1H, furyl), 7.99 (d, 1H, furyl), 8.24 (d, 1H, furyl).

### 5-bromo-2, 3-di (furan-2-yl) 1H-indole (3)

This product was obtained as a brown crystal, the product was purified by recrystallization (EtOH). IR  $\gamma$  [cm-1] = 3410, 1605, 1516, 1486; 1 H NMR  $\delta$  = 8.2 (br s, 1H, NH), 7.83 (d, 1H), 7.28-7.68 (m, 13H).

### 5-bromo-2, 3-di (furan-2-yl)-1H-indole-6-carbaldehyde (4)

To a cold solution of (3) (20mole) in dimethyl form amide (4.2ml, 0.0542mole) phosphorus oxychloride

(3.5ml, 0.038mole) was added. The reaction mixture was heated on boiling water bath for 2 hrs, there after cool down the mixture until reach to room temperature, the reaction mixture was poured into ice-cold container. Water and neutralized with sodium acetate tri hydrate (100gm /175ml H<sub>2</sub>O) solution the solid so obtained was crystalized from ethanol as yellow wish crystals.

The new heterocyclic compound 5, 6, 7, 8 prepared by the original Biginelli synthesis was reported by P. Biginelli (Bigenilli, 1983) which involves refluxing of compound (4) as aldehyde, acetyl acetone as dike tone and /semecarbazide, thiosemicarbazide/urea/thiourea or guanidine HCl in ethanolic HCl.

To give the corresponding compounds (5), (6), (7), (8) and (9).

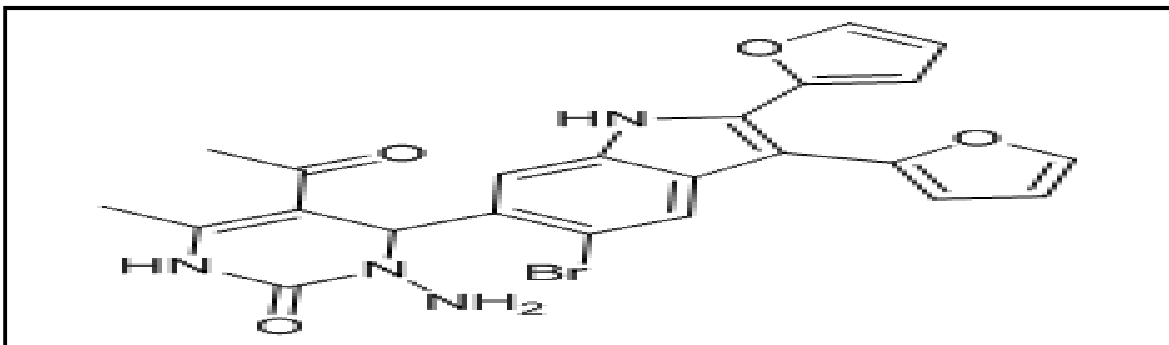
## RESULTS AND DISCUSSION

Avoiding organic solvents during the reactions in organic synthesis leads to a clean, efficient and economical technology (green chemistry). There is an increasing interest in the use of a highly expedient methodology for the synthesis of fine chemicals and heterocyclic compounds of biological importance, we herein report a facile, rapid one pot synthesis of 1, 2-di (furan-2-yl)-2-hydroxyethan-1-one (2) with 4-bromoaniline (1) derivatives to afford 5-bromo-2, 3-di (furan-2-yl) - 1H-indole (3) scheme (I). Derivatives were obtained in good yields .the IR spectrum of compound (2) showed an absorption bond at 1672cm<sup>-1</sup>, 3399cm<sup>-1</sup> characteristic for the carbonyl function and hydroxyl Figure No.1. The IR spectrum of compound (3) don't showed an absorption for the carbonyl function and hydroxyl Figure No.2.

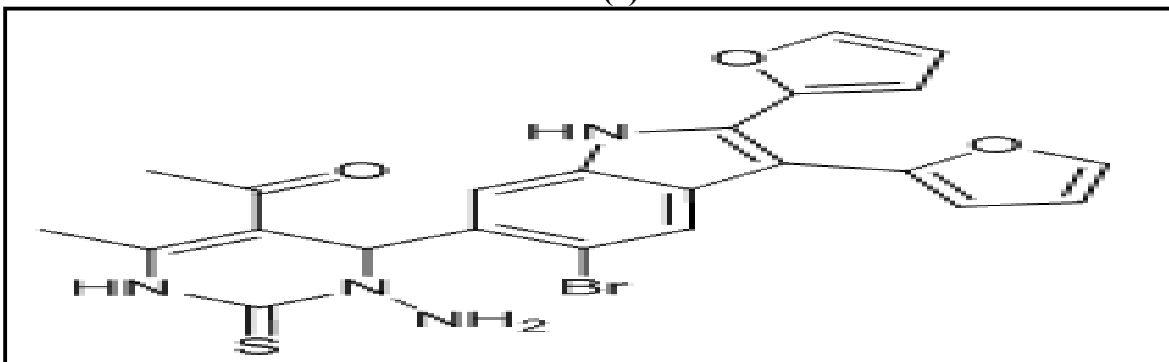
### Discussion

Vilsmeier-Haack formulation of compound (3) with dimethylformamide and phosphorus oxychloride gave 5-bromo- 2, 3-di (furan-2-yl) - 1H-indole-7-carbaldehyde (4). The IR spectrum of compound (4) showed an absorption band at 1730 cm<sup>-1</sup> Figure No.3 characteristic for the carbonyl function of the formyl group.1H NMR spectrum (400 MHz, DMSO) revealed signals at 10.2 (s, 1H, CHO

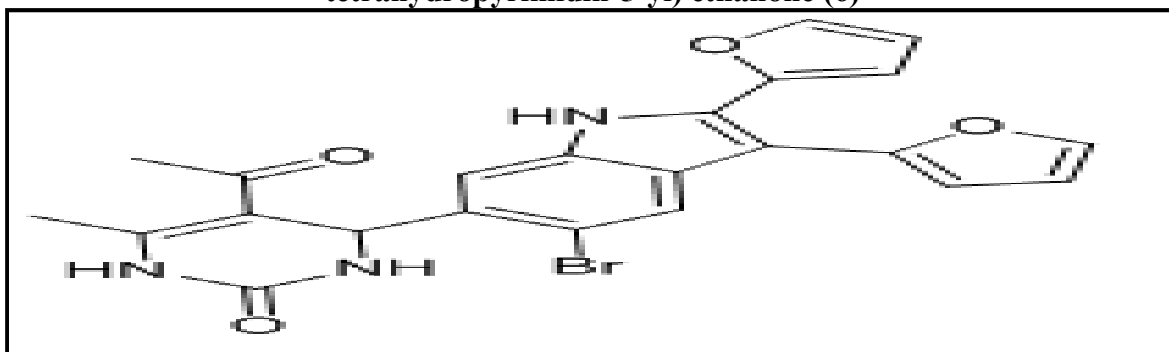
group), 8.21 (s, 1H, = NH indole) Figure No.4. The formulation is directed to position 6 not to any other position since position 6 of compound (3) is the most reactive centre<sup>19</sup>.



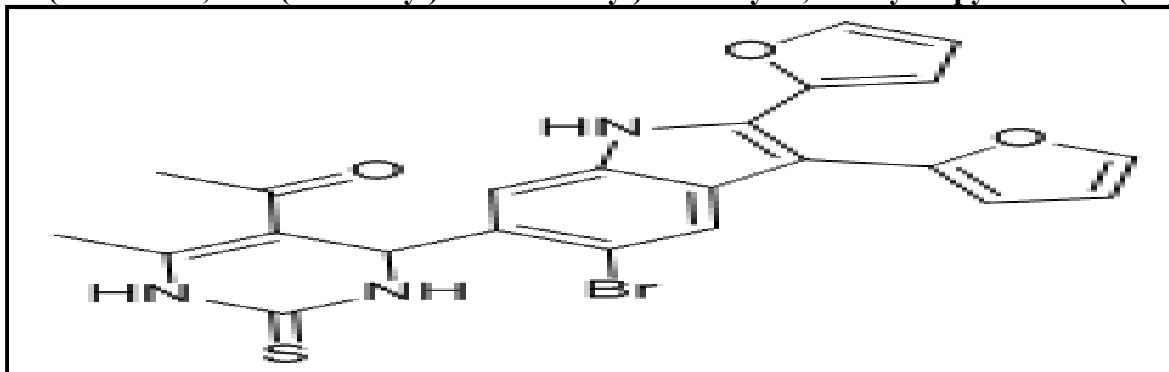
5-acetyl-3-amino-4-(5-bromo-2,3-di(furan-2-yl)-1H-indol-6-yl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (5)



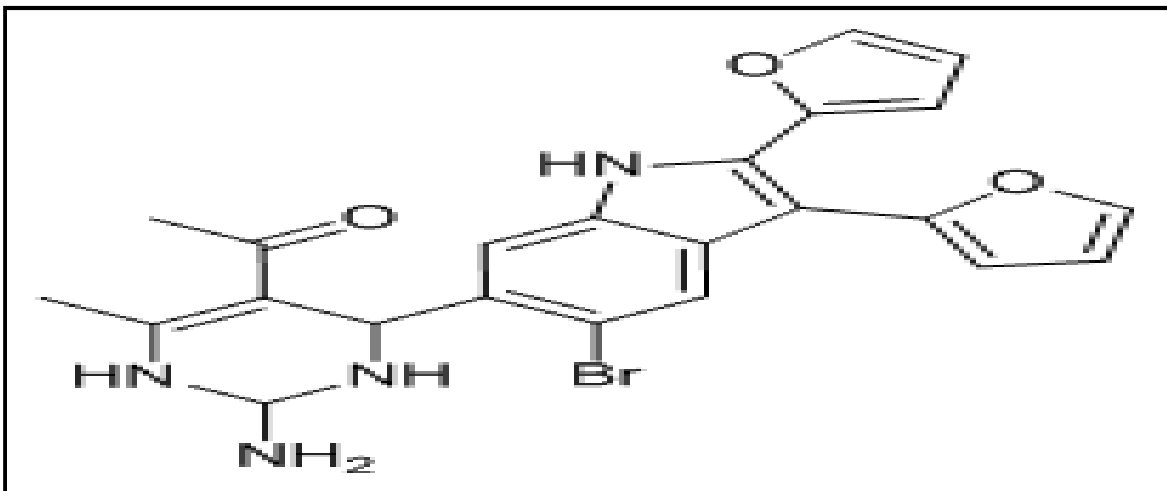
1-(3-amino-4-(5-bromo-2,3-di(furan-2-yl)-1H-indol-6-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethanone (6)



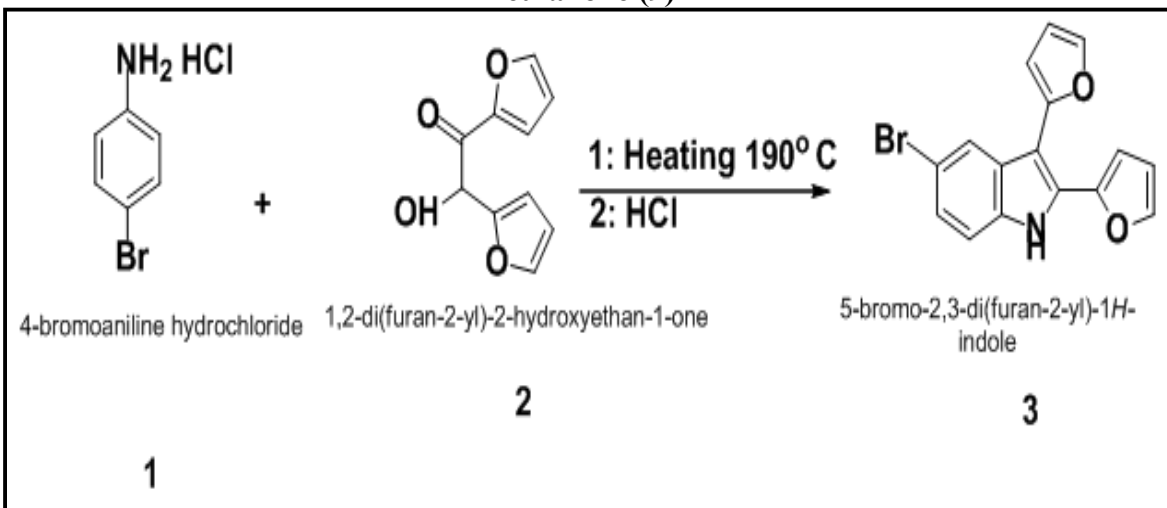
5-acetyl-4-(5-bromo-2,3-di(furan-2-yl)-1H-indol-6-yl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (7)



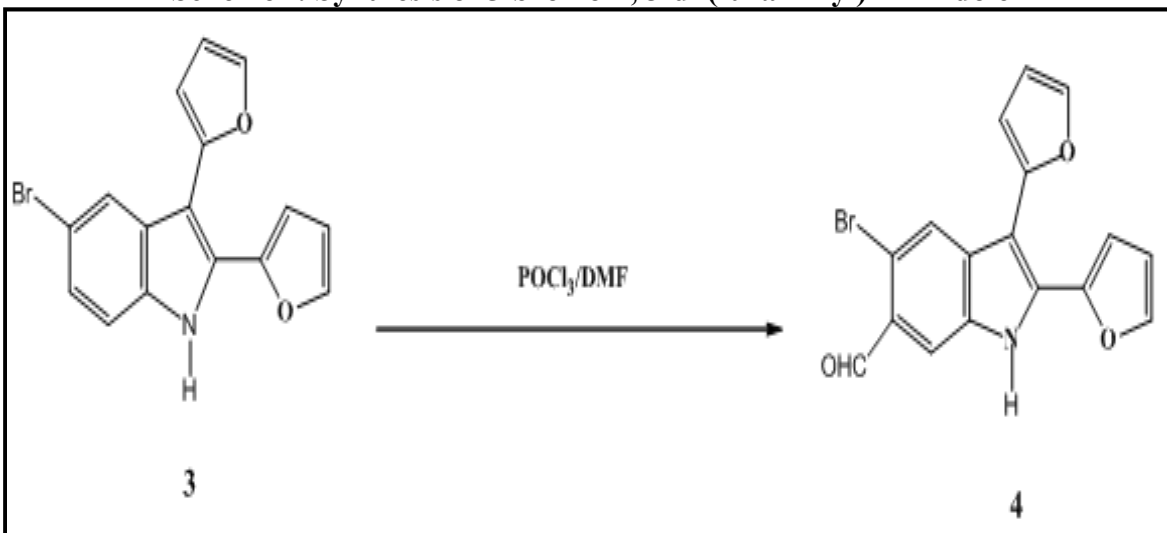
1-(4-(5-bromo-2,3-di(furan-2-yl)-1H-indol-6-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethanone (8)



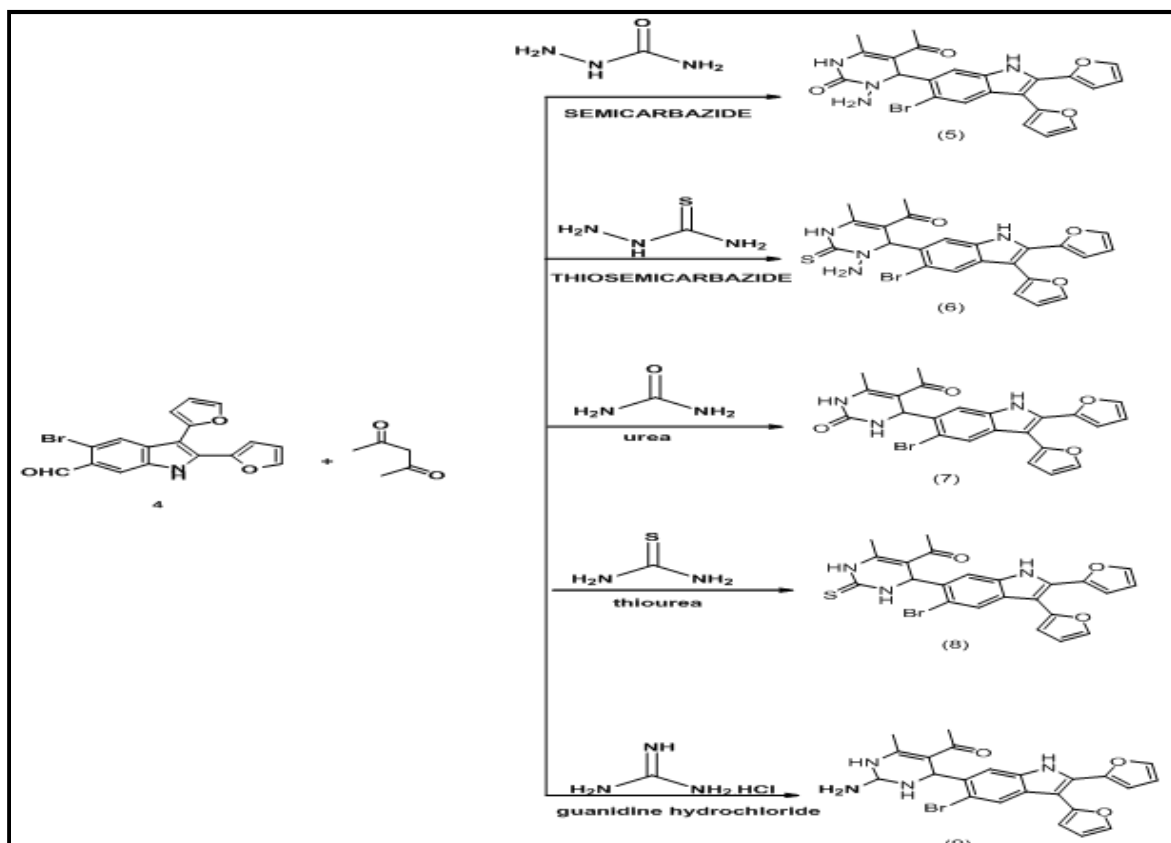
1-(2-amino-4-(5-bromo-2,3-di(furan-2-yl)-1H-indol-6-yl)-6-methyl-1,2,3,4-tetrahydropyrimidin-5-yl)ethanone (9)



Scheme I: Synthesis of 5-bromo-2,3-di(furan-2-yl)-1H-indole



Scheme II: Synthesis of 5-bromo-2,3-di(furan-2-yl)-1H-indole-6-carbaldehyde



Scheme III: Synthesis of tetrahydropyrimidines<sup>5-9</sup>

## CONCLUSION

The synthesis of novel, potentially active dihydropyrimidine derivatives. These derivatives were prepared through biginelli reaction.

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## CONFLICT OF INTEREST

We declare that we have no conflict of interest.

## BIBLIOGRAPHY

1. Chiacchio M A, Iannazzo D, Romeo R, Giofre S V and Legnani L. Pyridine and pyrimidine derivatives as privileged scaffolds in biologically active agents, *Curt Medi Chem*, 26(40), 2019, 7166-7195.
2. Kumari A and Singh R K. Medicinal chemistry of indole derivatives: Current to future therapeutic perspectives, *Bioorganic Chemistry*, 89, 2019, 103021.
3. Dadashpour S and Emami S. Indole in the target-based design of anticancer agents: A versatile scaffold with diverse mechanisms, *EuroJour of Medil Che*, 150, 2018, 9-29.
4. Verma S and Prabhakar S, Y. Target based drug design-a reality in virtual sphere, *Curr Med Chem*, 22(13), 2015, 1603-1630.
5. Sunil D and Kamath P R. Multi-target directed indole based hybrid molecules in cancer therapy: An up-to-date evidence-based review, *Current Topics in Medicinal Chemistry*, 17(9), 2017, 959-985.
6. Suzen S. Recent studies and biological aspects of substantial indole derivatives with anti-cancer activity, *Current Organic Chemistry*, 21(20), 2017, 2068-2076.

7. Chen L R, Wang Y C, Lin Y W, Chou S Y, Chen S F, Liu L T and Juang S H. Synthesis and evaluation of isatin derivatives as effective SARS coronavirus 3CL protease inhibitors, *Bioorganic and Medicinal Chemistry Letters*, 15(12), 2015, 3058-3062.
8. Bal T R, Anand B, Yogeewari P and Sriram D. Synthesis and evaluation of anti-HIV activity of isatin  $\beta$ -thiosemicarbazone derivatives, *Bioorganic and Medicinal Chemistry Letters*, 15(20), 2015, 4451-4455.
9. Guzel O, Karali, N and Salman A. Synthesis and antituberculosis activity of 5 methyl/trifluoromethoxy-1H-indole-2, 3-dione 3-thiosemicarbazone derivatives, *Bioorganic and Medicinal Chemistry*, 16(19), 2018, 8976-8987.
10. Smitha S, Pandeya S N, Stables J P and Ganapathy S. Anticonvulsant and sedative-hypnotic activities of N-acetyl/methyl isatin derivatives, *Sci Phar*, 76(4), 2008, 621-636.
11. Banerjee D, Yogeewari P, Bhat P, Thomas A, Srividya M and Sriram D. Novel isatinyl thiosemicarbazones derivatives as potential molecule to combat HIV-TB co-infection, *European Journal of Medicinal Chemistry*, 46(1), 2011, 106-121.
12. Patel T, Gaikwad R, Jain K, Ganesh R, Bobde Y, Ghosh B Gayen, S. First and report on 3-(3-oxoaryl) indole derivatives as anticancer agents: Microwave assisted synthesis, *in vitro* screening and molecular docking studies, *Chemistry Select*, 4(15), 2019, 4478-4482.
13. Martin T A and Jiang W G. Anti-cancer agents in medicinal chemistry (Formerly current medicinal chemistry-Anti-cancer agents), *Anticancer Agents Med Chem*, 10(1), 2010, 1.
14. Rao V K, Chhikara B S, Shirazi A N, Tiwari R, Parang K and Kumar A. 3-Substitued indoles: One-pot synthesis and evaluation of anticancer and Src kinase inhibitory activities, *Bioorganic and Medicinal Chemistry Letters*, 21(12), 3511-3514.
15. Lakshmi N V, Thirumurugan P, Noorulla K M and Perumal P. T. InCl<sub>3</sub> mediated one-pot multicomponent synthesis, anti-microbial, antioxidant and anticancer evaluation of 3-pyranyl indole derivatives, *Bioorganic and Med Che Let*, 20(17), 2010, 5054-5061.
16. Patil A D, Kumar N V, Kokke W C, Bean M F, Freyer A J, Brosse C D and Carte B. Novel alkaloids from the sponge *Batzella* sp: Inhibitors of HIV gp120-human CD4 binding, *The Journal of Organic Chemistry*, 60(5), 1995, 1182-1188.
17. Kappe C O. 100 years of the Biginelli dihydropyrimidine synthesis, *Tetrahedron*, 49(32), 1993, 6937-6963.
18. Brugier D, Outurquin F and Paulmier C. Studies on the reactivity of N-(3-thienyl) carbamates, *Journal of the Chemical Society, Perkin Transactions*, 1(1), 2001, 37-43.
19. Cho H, Nishimura Y, Yasui Y, Kobayashi S, Yoshida S I, Kwon E and Yamaguchi, M. Synthesis of 4-unsubstituted dihydropyrimidines, Nucleophilic substitution at position-2 of dihydropyrimidines, *Tetrahedron*, 67(14), 2011, 2661-2669.

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