Facile synthesis of \(N'\)-(anthracen-9(10H)-ylidene)-4-(4-hydrophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide and other derivatives

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Abstract. Pyrimidine as vital constituents of nucleic acid is recognized for its role in the chemotherapy of AIDS. Hydrazide-hydrazone is important moieties with notable biological diversity in drug design. Thus, the aim of this present study is to synthetically couple these two frameworks together in order to achieve small molecular targets for possible development of improved therapeutic candidates. This was achieved in a domino reaction starting with one-pot three-component reaction to afford ethyl-4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 7 which upon treatment with hydrazine hydrate under acid-mediated condition gave 8, as an essential precursor and reactive intermediate. The expedient condensation of intermediate 8 with various cyclic and straight chain ketones furnished \(N'\)-(anthracen-9(10H)-ylidene)-4-(4-hydrophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide 9a and other 9b-i scaffolds as envisaged. The reaction progress was monitored by thin layer chromatography (TLC) and upon reaction completion, the purification process was carried out with recrystallization and/or column chromatography. The authenticity of the prepared products 9a-i was confirmed by spectroscopic means including IR, UV, \(^1\)H-NMR, \(^1\)C-NMR and DEPT-135 as well as analytical data. These final products are good candidates for further study as regards anti-plasmodial activity which are been developed and examined.

1. INTRODUCTION
Over the years, heterocyclic compounds have attracted great attention in the advancement of medicinal chemistry [1] and they have been used as crucial scaffolds in the development of numerous therapeutic agents [2]. Heterocycles are known to be one of the largest areas of research in organic chemistry [1]. Pyrimidine templates, as profitable heterocycles, have pulled in multiple considerations because of their vast applications in the progress of medicinal chemistry [3]. Pyrimidines were initially identified as a product obtained from the degradation of uric acid. The genesis of pyrimidine derivatives is ascribed to the isolation of alloxan in 1818, which was done by the oxidation of uric acid in the presence of nitric acid by Brugnatelli[4]. Pyrimidine skeleton also occur in many natural substance e.g vitamin B1 (thiamine), uracil and cytosine respectively. Pyrimidine and their pyrimidine containing compounds are known to be significant in drug and agrochemical production. Several pyrimidine compounds have fascinating biological and pharmacological activities such as anti-HIV [5], anticancer [6], anti-inflammatory [7], antimicrobial [8], antitumor [9], antioxidant [10], antituberculosis[11] and antimalarial [12] activities.
Furthermore, pyrimidine derivatives have played an important role in drug discovery and development. For instance, some of commercially available drugs bearing pyrimidine derivatives are 5-fluorouracil 1 as anticancer, pyrimethamine 2 as antimalarial, minoxidil 3 as vasodilator, complera 4 as antihypertensive, etravirine 5 as anticancer and rilpivirine 6 as anti-HIV [5,13] as shown in Fig. 1. In similar manner, compounds containing hydrazide-hydrazone linkages have been reported as bioactive molecules also showing a wide range of biological activities including antiviral, antifungal, antibacterial, antitubercular, antiprotozoal, anti-inflammatory, anticonvulsant and anticancer action [14]. It is envisaged that incorporation of hydrazide-hydrazone in pyrimidine moieties will lead to synergistic effect and enhancement of biological activities of such hybrid. Therefore, the purpose of this present work is to synthesize, purify and effectively characterize novel pyrimidine-based hydrazide-hydrazone derivatives which might be of significance in future drug development.

Fig. 1: Commercially available drug bearing pyrimidine moieties as active ingredient

2. MATERIAL AND METHODS
2.1. General Conditions
Reagents used for this work were of analytical grade and were used as supplied by the manufacturer (Sigma-Aldrich, USA) without purification. The products purity was determined using thin layer chromatography. Determination of melting points was carried out with Stuart melting point machine SMP10 (UK). Infrared data were generated with the Bruker FT-IR spectrophotometer (Germany) whereas the ultraviolet-visible analysis was obtained for the ethanolic solution of the synthesized compounds with the aid of Genesys™ 10S UV-Vis. spectrophotometer (Thermo Scientific, USA). Both 1H and 13C nuclear magnetic resonance of the products were analyzed in DMSO-d6 using Bruker NMR machine (Germany). Carlo Erba-1108 elemental analyzer manufactured in Germany was used for C, H, N microanalysis.
2.2. Synthetic Procedure

2.2.1. Preparation of ethyl 4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7).

4-Hydroxybenzaldehyde (0.49 g, 4.00 mmol), ethyl acetoacetate (0.51 mL, 4.00 mmol) and urea (0.24 g, 4.00 mmol), was added in a consecutive manner to 15.00 mL of ethanol with 3 drops concentrated HCl in a quick-fit round bottom flask. Refluxing of the reacting mixture was carried out for 12 h and the product formation was constantly authenticated using TLC to ascertain if the desired product has been formed. At the completion of the reaction, the mixture was allowed to cool under atmospheric conditions and further transferred into chilled water. The solid mass obtained was worked up and re-crystallized in ethanol to afford 7 which was stored in sample bottle for further analysis.

2.2.2. Procedure for the synthesis 4-(4-hydrophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxyhydrazide (8).

Precursor 7 (1.00 g, 3.60 mmol) was stirred in 15.00 mL of ethanol and hydrazine hydrate (0.17 mL, 3.80 mmol) was cautiously tipped into it drop-wise. The produced mixture was then subjected to conventional heating under reflux for 5 h to give a crude product. The reacting mixture was monitored with TLC plate until the product formed. Upon total consumption of the starting material, solid mass obtained was cooled and further transferred into cold water, the product was filtered, re-crystallized from ethanol, and air-dried to afford 8. This product served as precursor for accessing 9a-i.

2.2.3. General Procedure for the synthesis of N’-(alkanilydene)-4-(4-hydrophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxyhydrazide derivatives (9a-i).

Precursor 8 (1.50 g., 5.70 mmol) was stirred in DMF (5 mL) until total dissolution. The required ketone a-i (5.70 mmol) was added per run under the influence of catalytic amount of acetic acid. The resulting mixture was heated under reflux until the starting material was totally consumed (6 h as shown by TLC monitoring) and reacted with ketone derivatives (a-i) under the catalytic amount of acetic acids and reflux for 6 h to give compounds (9a-i) respectively. The solution formed, allowed to cool, poured onto water to collect the crude products which were purified from ethanol to obtained pure compounds 9a-i.

2.2.3.1. Synthesis ofN’-(anthracen-9(10H)-ylidene)-4-(4-hydrophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxyhydrazide, 9a. When a = anthrone, 9a was obtained with percentage yield of 92.50%, melting point 209-210°C, UV analyses, \( \lambda_{\text{max}} \) in nm (log \( \varepsilon_{\text{max}} \)): 202 (3.25), 280 (4.15), IR determination: 3509 (OH of phenol), 3277 (N-H aromatic), 2954 (C-H aromatic), 2850 (C-H of aliphatic), 1689 (C=O of amide), 1626 (C=C aromatic), 1570 (C=N), 1519 (C-N), 1368 (C=O of phenol), 1295 (C-N aromatic amine), 764 (Ar-H) cm\(^{-1}\). \(^1\)H-NMR (400 MHz, DMSO-d\(_6\) ) \( \delta \): 8.40 (s, 1H, N-H), 7.94-7.92 (d, \( J = 8.00 \) Hz, 2H, Ar-H), 7.85-7.83 (d, \( J = 7.44 \) Hz, 2H, Ar-H), 7.50-7.45 (m, 4H, Ar-H), 7.33-7.31 (d, \( J = 8.04 \) Hz, 2H, Ar-H), 7.08-7.06 (d, \( J = 7.82 \) Hz, 2H, Ar-H), 6.44 (s, 1H, NH), 6.22 (d, \( J = 4.84 \) Hz, 1H, NH-CH), 5.13-5.11 (d, \( J = 4.84 \) Hz, 1H, CH-NH), 3.77 (s, 2H, CH\(_2\)), 2.38 (s, 3H, CH\(_3\)). \(^13\)C-NMR (100 MHz, DMSO-d\(_6\) ) \( \delta \): 172.5, 171.2, 150.4, 146.3, 139.7 (2 \( \times \) C), 135.9, 133.8 (2 \( \times \) C), 131.3 (2 \( \times \) CH), 129.7 (2 \( \times \) CH), 128.3 (2 \( \times \) CH), 127.2, 126.5 (2 \( \times \) CH), 125.2 (2 \( \times \) CH), 115.9 (2 \( \times \) CH), 108.3, 54.1 (CH), 32.2 (CH\(_2\)), 18.1 (CH\(_3\)) ppm (See Fig. 2 for signal labelling).

2.2.3.2. Synthesis of (E)-6-(4-hydroxyphenyl)-4-methyl-2-oxo-N’-(2-oxoindolin-3-ylidene)-1,2-dihydropyrimidine-3-carboxyhydrazide, 9b. when \( b = \) isatin, 9b was obtained with percentage yield of 53.00%, melting point 220-221°C, UV analyses, \( \lambda_{\text{max}} \) in nm (log \( \varepsilon_{\text{max}} \)): 283 (3.55), 325 (3.35), 196 (3.25). IR determination: 3512 (O-H), 3455 (N-H), 3362 (N-H), 3115 (C-H aromatic), 2920 (C-H aliphatic), 2854 (C-H aliphatic), 1687 (C=O of amide), 1646 (C=C aromatic), 1599 (C-N), 1368 (O-H of phenol), 1295 (C-N aromatic amine), 764 (Ar-H) cm\(^{-1}\).
2.2.3.3. Synthesis of (E)-4-(4-hydroxyphenyl)-6-methyl-N'-(5-nitro-3-oxoindolin-2-ylidene)-1,2-dihydropyrimidine-5-carboxyhydrazide 9c. When e = 5-nitrosatin, 9e was obtained with percentage yield of 84.50%, melting point 216-219°C, UV analyses, \( \lambda_{\text{max}} \) in nm (log \( \varepsilon_{\text{max}} \)): 205 (4.53), 280 (4.44), 244 (4.32), 355 (2.62), IR determination: 3511 (OH), 3362 (N-H), 3277 (N-H), 3237 (N-H), 3119 (C-H aromatic), 2924 (C-H aliphatic of CH\(_2\)), 2854 (C-H of aliphatic), 1682 (C=O of amide), 1646 (C=C aromatic), 1599 (C-N), 1518 (NO\(_2\) asym), 1365 (O-H of phenol), 1345 (NO\(_2\)sym) 1295 (C-N aromatic amine), 764 (Ar-H) cm\(^{-1}\).

2.2.3.4. Procedure for the synthesis of (E)-6-(4-hydroxyphenyl)-4-methyl-2-oxo-N'-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)-2-dihydropyrimidine-5-carboxyhydrazide 9d, when d = camphor, 9d was obtained with percentage yield of 66.20%, melting point 213-217°C, 3509 (O-H of phenol), 3362 (N-H), 3277 (N-H), 3237 (N-H), 3119 (C-H aromatic), 2924 (C-H aliphatic of CH\(_2\)), 2854 (C-H of aliphatic), 1682 (C=O of amide), 1646 (C=C aromatic), 1599 (C-N), 1364 (O-H of phenol), 1295 (C-N aromatic amine), 764 (Ar-H) cm\(^{-1}\).

2.2.3.5. Synthesis of (N')-cyclopentyliedene-6-(4-hydroxyphenyl)-4-methyl-2-oxo-1,2-dihydropyrimidine-5-carboxyhydrazide 9e, when e = cyclopentanone, 9e was obtained with percentage yield of 75.24%, melting point 226-229°C, UV analyses, \( \lambda_{\text{max}} \) in nm (log \( \varepsilon_{\text{max}} \)): 202 (4.39), 280 (4.35), IR determination: 3515 (O-H), 3302 (N-H), 3278 (N-H), 3107 (C-H aromatic), 2912 (C-H aliphatic), 2844 (C-H aliphatic), 1672 (C=O of amide), 1647 (C=C aromatic), 1601 (C=C), 1366 (C-O phenol), 1285 (C-N), 764 (Ar-H) cm\(^{-1}\).

2.2.3.6. Synthesis of (N')-cyclohexyliedene-6-(4-hydroxyphenyl)-4-methyl-2-oxo-1,2-dihydropyrimidine-5-carboxyhydrazide 9f, when f = cyclohexanone, 9f was obtained with percentage yield of 72.19%, melting point >239°C, UV analyses, \( \lambda_{\text{max}} \) in nm (log \( \varepsilon_{\text{max}} \)): 202 (4.19), 286 (4.29), IR determination: when g = pentan-2-one, the yield was 73.03%, melting point 239 °C (sharp), IR 3510 (O-H),3362 (N-H),3277 (N-H), 3237 (N-H), 3117 (C-H aromatic), 2924 (C-H aliphatic of CH\(_2\)), 2844 (C-H aliphatic), 1672 (C=O of amide), 1644 (C=C aromatic), 1598 (C=N), 1295 (C-N), 764 (Ar-H) cm\(^{-1}\).

2.2.3.7. Synthesis of (E)-6-(4-hydroxyphenyl)-4-methyl-2-oxo-N'-(pentan-2-yldiene)-1,2-dihydropyrimidine-5-carboxyhydrazide 9g, when g = pentan-2-one, 9g was obtained with percentage yield of 73.03%, melting point 237-239°C, UV analyses, \( \lambda_{\text{max}} \) in nm (log \( \varepsilon_{\text{max}} \)): 205 (4.11), 286 (4.29), IR determination: 3512 (O-H),3362 (N-H), 3312 (N-H), 3277 (N-H), 3237 (N-H), 3119 (C-H aromatic), 2924 (C-H aliphatic), 2854 (C-H aliphatic), 1682 (C=O of amide), 1646 (C=C aromatic), 1599 (C=N), 1368 (C-O phenol), 1295 (C-N), 764 (Ar-H) cm\(^{-1}\).

2.2.3.8. Synthesis of (E)-6-(4-hydroxyphenyl)-4-methyl-N'-(4-methylpentan-2-yldiene)-2-oxo-1,2-dihydropyrimidine-5-carboxyhydrazide 9h, when h = 4-methyl pentan-2-one, 9h was obtained with percentage yield of 85.88%, melting point 238-240°C, UV analyses, \( \lambda_{\text{max}} \) in nm (log \( \varepsilon_{\text{max}} \)): 202 (4.09), 280 (4.11), IR determination: 3362 (N-H), 3277 (N-H), 3237 (N-H), 3119 (C-H aromatic), 2924 (C-H aliphatic), 2854 (C-H aliphatic), 1682 (C=O amide), 1646 (C=C aromatic), 1599 (C=N), 1365 (C-O phenol), 1295 (C-N), 764 (Ar-H) cm\(^{-1}\).

2.2.3.9. Synthesis of (E)-N'-(heptan-2-yldiene)-6-(4-hydroxyphenyl)-4-methyl-2-oxo-1,2-dihydropyrimidine-5-carboxyhydrazide 9i, when i = 2-heptanone, 9i was obtained with percentage yield of 71.44%, melting point 222-224°C, UV analyses, \( \lambda_{\text{max}} \) in nm (log \( \varepsilon_{\text{max}} \)): 205 (5.45), 277 (4.51), IR determination: IR, 3511 (O-H),3362 (N-H) 3277 (N-H), 3237 (N-H), 3119 (C-H aromatic), 2924 (C-H aliphatic), 2854 (C-H aliphatic), 1680 (C=O amide), 1648 (C=C aromatic), 1597 (C=N), 1368 (C-O phenol), 1295 (C-N), 764 (Ar-H) cm\(^{-1}\).
3. RESULT AND DISCUSSION

3.1. Chemistry
Promoting the research work regarding identification and preparation of bioactive heterocycles[1,15], we herein aimed to incorporate alkanylidene in pyrimidine framework via hydrazide-hydrazone linker. This three-step reaction sequence was initiated by acid-catalyzed reactive coupling of urea and acetoacetate ester as well as 4-hydroxybenzaldehyde using Biginelli approach to furnish carboxylate 7 in 91% yield. Treatment of ester 7 by freshly distilled hydrazine hydrate led to the formation of carbohydrazide 8 in 87.00% yield (Scheme 1). The last stage of this synthetic adventure dealt with eco-friendly synthesis of pyrimidine-based hydrazide-hydrazones otherwise known as 4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2-dihydropyrimidine-5-carbohydrazide derivatives 9a-i (Scheme 2) in diverse yield varied from 92.50% to 53.00%. The physico-chemical properties of the titled products were measured and are as documented in Table 1. The colour of the compounds varied from red for compounds 9a-c; to brown for compounds 9d, 9f and 9h; while the remaining compounds 9e, 9g and 9i were ash, yellow and white respectively. The targeted products 9a-i were synthesized under the same condition and it was observed that 9a had the highest yield of 92.50% followed by 9h which has 85.88% and compound 9b had the lowest yield which was 53.00%. The melting points of the compounds varied from 209-210°C for compound 9a to 238-240°C for compound 9h. The high melting point observed in all 9a-i might be due to consistent appearance of hydrazide in all the targeted products and probable existence of hydrogen bonding. This agreed with the finding from our earlier study [15]. The reaction progress, completion and product purity were confirmed with thin layer chromatographic (TLC) technique using two different set of eluents depending on polarity variation. These solvent systems were DCM:MeOH → (9.8:0.2, v/v) denoted as x and pure DCM (dichloromethane) denoted as y and the \( R_f \) values ranged from 0.50 for 9d to 0.85 for 9h(Table 1).

Scheme 1: Synthetic route to carboxylate 7 and pyrimidin-2-one hydrazide 8
Scheme 2: Synthetic route to pyrimidin-2-one based hydrazide-hydrazones 9a-i

Table 1: Physicochemical properties of the synthesized hydrazide-hydrazones 9a-i

| Comp No | Molecular Formula (Molecular Weight) | Colour | R f value | Melting point/°C | Yield % | Elemental analytical data | Comp No = Compound Number. S= sharp melting point. |
|---------|-----------------------------------|--------|-----------|-------------------|---------|----------------------------|--------------------------------------------------|
| 9a      | C 26 H 22 N 4 O 3 (438.48) Red    | 0.83   | 209-210   | 92.50            | 71.22(71.37) | 5.06(4.93)                 | 12.78(12.95)                                      |
| 9b      | C 26 H 22 N 4 O 3 (391.38) Red    | 0.72   | 220-221   | 53.00            | 61.38(61.24) | 4.38(4.49)                 | 17.89(18.01)                                      |
| 9c      | C 20 H 17 N 5 O 4 (436.38) Wine   | 0.60   | 216-219   | 84.50            | 55.05(54.89) | 3.70(3.81)                 | 19.26(19.09)                                      |
| 9d      | C 22 H 23 N 4 O 3 (396.48) Brown  | 0.50   | 214-217   | 66.20            | 66.64(66.81) | 7.12(6.99)                 | 14.13(14.02)                                      |
| 9e      | C 17 H 20 N 4 O 3 (436.38) Ash    | 0.70   | 226-229   | 75.24            | 62.18(62.33) | 6.14(5.98)                 | 17.06(16.91)                                      |
| 9f      | C 18 H 22 N 4 O 3 (342.39) Brown  | 0.83   | 239 (s)   | 72.19            | 63.14(63.31) | 6.48(6.71)                 | 16.36(16.49)                                      |
| 9g      | C 17 H 22 N 4 O 3 (330.38) Yellow | 0.78   | 237-239   | 73.03            | 61.80(61.72) | 6.71(6.92)                 | 16.96(17.15)                                      |
| 9h      | C 18 H 24 N 4 O 3 (344.41) Brown  | 0.85   | 238-240   | 85.88            | 62.77(62.94) | 7.02(6.85)                 | 16.27(16.44)                                      |
| 9i      | C 19 H 26 N 4 O 3 (358.43) White  | 0.66   | 222-224   | 71.44            | 63.67(63.86) | 7.31(7.50)                 | 15.63(15.81)                                      |

Reagents Used: (a) anthrone (b) isatin (c) 5-nitroisatin (d) camphor (e) cyclopentanone (f) cyclohexanone (g) pentan-2-one (h) 4-methylpentan-2-one (i) heptan-2-one. Reaction Condition: MW or Reflux, DCM, cat. Acetic acid
3.2. Spectroscopic Characterization

Synthesized compound structures were established spectroscopically using IR, UV, NMR, and elemental analysis. KBr pellet was used for running infrared analysis and the frequencies were measured in wavenumber. The phenolic OH was found in all the compounds as envisaged at 3515-3509 cm\(^{-1}\) while the presence of three NH functionalities were observed at 3455-3437 cm\(^{-1}\). The stretching absorption bands of C-H aromatic, C-H aliphatic, C=O amide, C=C unsaturation, and C=N imino were found at 3119-3107 cm\(^{-1}\), 2954-2844 cm\(^{-1}\), 1689-1672 cm\(^{-1}\), 1648-1601 cm\(^{-1}\) and 1599-1570 cm\(^{-1}\) respectively. This was in concordance with the IR data values within the earlier work of Tageldin and co-workers who synthesized and characterized pyrazolo[3,4-d]pyrimidines and screened them for anti-inflammatory properties [7].

The ultraviolet-visible spectra were run in DMF and the absorbance was used to determine the Log \(\varepsilon_{\text{max}}\) using Beer-Lambert law. All synthesized compounds 9a-i had the first wavelength (\(\lambda_{\text{max}}\)) at 202-205 nm. This was due to the occurrence of \(\pi\rightarrow\pi^*\) transition peculiar to C=C. This implies the presence of aromatic ring in the core structure of compounds 9a-i. Other \(\lambda_{\text{max}}\) experienced at higher values were as a result of bathochromic shift which were informed by the presence of auxochrome and extensive conjugation. These higher values are ascribable to the additional transition from the non-bonding electrons of the auxochrome which was \(n\rightarrow\pi^*\) transition; characteristic of K bands of C=N functional group [8]. The \(^1\)H NMR spectrum of 9a ran in deuterated DMSO showed the most downfield signal at 8.40 ppm to be a singlet of NH while other two NH protons resonated as a singlet and a doublet at 6.44 and 6.22 respectively. The aromatic proton of phenolic were experienced as 2H doublet at 7.94-7.92 ppm and 2H doublet at 7.08-7.06 ppm. The rest of the signals in the aromatic region between 7.85-7.83 ppm and 7.33-7.31 ppm were accountable for anthracene nucleus. This was supported by the recent finding from El-Naggar and co-workers who reported that the aromatic protons resonated between 6.50 ppm to 8.50 ppm [9]. CH of pyrimidine nucleus was observed as a 1H doublet at 5.13-5.11 ppm with a coupling constant of 4.84 ppm indication its neighborhood effect from NH proton of pyrimidine. The upfield singlet at 3.77 ppm and 2.38 ppm depicted the presence of CH\(_2\) and CH\(_3\) protons respectively (Fig. 2). The \(^{13}\)C NMR spectrum of 9a was used as the representative for the series of products reported herein. The \(^{13}\)C NMR spectrum of Compound 9a identified twenty-six carbon atoms which agreed with the molecular formula of compound 9a (C\(_{26}\)H\(_{22}\)N\(_4\)O\(_3\)). The two most downfield signals at 172.5 ppm and 171.2 ppm depicted the presence of carbonyl C=O of hydrazide and pyrimidin-2-one. All the aromatic carbon atoms were noticed from 150.4 to 108.3 ppm. It the upfield region, the methine (CH), methylene (CH\(_2\)) and methyl (CH\(_3\)) carbon atoms resonated at 54.1, 32.2 and 18.2 ppm respectively. These signals were in conformity with the proposed structure of 9a.
4. CONCLUSION

The synthesis of the targeted pyrimidine-base hydrazide-hyrazones 9a-i were successfully achieved in this present work via both conventional using acid catalyzed synthetic approach. The characterization of the compounds was done using physico-chemical properties and spectroscopic data. Further studies of toxicity effect and Structural Activity Relationship (SAR) would prove very advantageous for the improvement of the biological and pharmacological activities of the potent pyrimidinones synthesized therein for possible drug development.

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